Abstracts

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# Drug Discovery and Therapy World Congress 2016

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Welcome Note

The “Drug Discovery & Therapy World Congress 2016”, scheduled to be held from 22nd - 25th July, 2016 will bring together the world's leading scientists in the field of drug discovery and therapy to present their latest researches in the exciting setting of Boston.

Four Nobel Laureates and leading researchers will participate in this conference. The conference will provide a platform for the participating scientists to interact with eminent colleagues and enjoy the intellectually stimulating environment of Boston.

We would like to welcome the participants including a large number of students to DDTWC 2016. We hope that this would be an exciting event as the leading authorities in their respective fields will present their latest and outstanding researches during the conference.
PL-168

NOVEL DRUG DESIGN

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Drug resistance of bacteria and other microbes is a world-wide medical problem in the human population. A new technology is needed to provide drugs that can easily attack several targets in bacteria and other microbes and will be stable for longer periods of time in humans than currently available drugs. Such a technology can be provided immediately and potential therapeutic compounds are very active in laboratory cultures against several bacteria and the malaria parasite, Plasmodium falciparum. The molecular structure of the new compounds contains a RNA-like molecule and is much larger than traditional drugs.

PL-169

Track: Pharmaceutical Biotechnology

BIOCATALYSIS AND DRUG REPOSITIONING- A WAY FORWARD FOR COST EFFECTIVE LEAD DISCOVERY

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Microbial transformation is an effective tool for structural derivatizations that are difficult to achieve by conventional chemical methods. Microbial systems are also extensively employed in the study of drug metabolism and bioremediation. The process is the best tool in medicinal chemistry for the introduction or modification of specific functionalities at the positions difficult to access by conventional chemical methods. In last two decades, this methodology has become an indispensable tool for asymmetric synthesis, not only in academic research but also at the industrial scale. There is a need to fully exploit the potential of biotransformation in creating new and novel chemical space for the discovery of lead molecules against prevalent diseases.

During our studies we structurally modified a number of existing drugs into their structural analogues by microbial and plant cell suspension cultures. The resulting metabolites have exhibited interesting biological activities, different from their precursor drugs. Medrysone (11β-hydroxy-6a-methylpregn-4-ene-3,20-dione) is an anti-inflammatory agent used in ophthalmic treatments. The microbial transformation of medrysone with the filamentous fungi, C. blakesleeanus (ATCC 8688a), N. crassa (ATCC 18419) and R. stolonifer (TSY 0471). Fermentation of medrysone with these fungi yielded seven new metabolites. Various cellular assays, such as phagocyte oxidative burst, T-cell proliferation, and cytokines analysis, were performed on the drugs and metabolites to evaluate their anti-inflammatory potential. Oxymetholone which is marketed as anadrol, a synthetic anabolic steroid developed in 1960 by Zoltan ‘Anadrol Z’ F. It has been approved by the US Food and Drug Administration for the treatment of anemias caused by deficient red cell production. Its biotransformation was carried out with various fungi resulted in the production of various new and a known metabolites. Oxymetholone and some of its metabolites showed anti-inflammatory activity. Similarly, Exemestane (trade name aromasin) is a steroidal aromatase inhibitor, used for the treatment of breast cancer. Aromatase inhibitors block the synthesis of estrogen. This lowers the estrogen level, and slows the growth of cancers. Exemestane was invented and synthesized by the Italian company using commercially available boldenone (androsta-1,4-diene-17β-ol-3-one) FDA approved it in October 2005. After biotransformation cytotoxicity was checked, which showed that new metabolite of exemestane showed activity against HeLa and PC3 cancer cell lines. Similarly melengestrol acetate is used as a feed additive for feedlot heifers, was found to be a potent anti-inflammatory agent along with its new transformed product. Tibolone is a synthetic steroid hormone drug, used for the treatment of endometriosis and hormone replacement therapy in post menopausal women, we have successfully biotransformed the drug into its new derivatives and find our
their potent activity as alpha glucosidase inhibitors. These results showed that resulted new and known compounds can fasten the process of drug development.

During this presentation, underlying philosophy and approach of our research on cost-effective discovery of lead molecules by using drug repositioning and biotransformation strategies will be discussed.

**PL-2**

**THYMOSINS: FROM DISCOVERY TO CLINICAL APPLICATION**

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The Thymosins are a family of small peptides with hormonal-like properties first isolated from calf thymus glands. They are biological response modifiers (BRMs) and belong to a large class of molecules that modulate the immune system and are important to the repair and regeneration of tissue following injury. The first account of the isolation and partial characterization of the active peptide components of the thymus, collectively called "Thymosins" was reported in 1966. Over the next several years, a partially purified and standardized heat stable preparation termed Thymosin fraction 5 (TF5) was developed which was amenable for scale-up and suitable for clinical trials. In April 1974, the first clinical trial with TF5 began under the clinical direction of Arthur Amman, the Director of Pediatric Immunology at the University of California San Francisco Medical School. His first patient treated with TF5 was a 5 year old girl with DiGeorge Syndrome, presenting with a body weight of 26 lbs. She had extremely low numbers of T-cells and was critically ill with overwhelming infections. In a landmark paper published in 1975 in the New England Journal of Medicine, the results of the use of TF5 to treat children with a variety of primary immune deficiencies were published.

Since the early pre-clinical and clinical studies with TF5, in patients with PIDs, cancer, infectious diseases and autoimmune diseases, the major research interests of our laboratory has been in purifying and characterizing the biologically active components in TF5 and translating these studies from the lab bench to the clinic. Two of these molecules, Thymosin A1 (Ta1) and Thymosin B4 (Tb4) have been synthesized and have reached the clinic.

Ta1, the acetylated N-terminal 28 amino acid fragment of prothymosin a (113 amino acids), is now approved in 35 countries for the treatment of hepatitis B and C, and as an immune stimulant and adjuvant under the commercial name of Zadaxin. In addition to its recognized efficacy in the broad areas of infectious diseases, immune deficiency diseases and cancer, the most event reports of clinical trials with Ta1, are pointing to important, hitherto unrecognized, applications in a number of other diseases and disorders, including septic shock, acute respiratory distress syndrome, peritonitis, acute cytomegalovirus infections, TB and lung infections in critically ill patients. It is also emerging as a promising chemoprotective agent in patients undergoing chemotherapy.

Tb4 is also acetylated at the N-terminal serine position. It is a peptide of 43 amino acids and is the first of the synthesized beta-Thymosins to reach the clinic. Many of its activities directly affect the repair and regeneration cascade following injury. Tb4's pleiotropic biological activities centering around accelerating wound healing and repair have provided the scientific foundation for ongoing and projected Phase 2/3 human trials. Indications for treatment include dermal wounds, eye injuries, including severe dry eye and neurotrophic keratitis, and repair of the heart following a heart attack. Recently reported animal studies indicate that Tb4 may also be useful in treating brain injuries follow stroke, trauma or neurological diseases such as multiple sclerosis as well as a number of peripheral neuropathies. The ability of Tb4 to reduce scarring and to down-regulate NFkB and a large number of inflammatory chemokines and cytokines point to a number of additional activities in treating other autoimmune diseases, fibrosis and diseases associated with the aging process. Now, 50 years after the original discovery of the Thymosins, advances in genomics, proteomics, and gene therapy are rapidly amplifying our understanding of the important role of these thymus-derived peptides in both health and disease and their future potential. From these studies has come the real promise that synthetic versions of several of the Thymosin peptides isolated from TF5 will be useful in the treatment of a number of difficult to treat life threatening acute and chronic diseases and to promote the healing and remodeling of wounds following injury and trauma.
EPIGENETICS OF ALZHEIMER'S DISEASE AND DEMENTIA: POTENTIAL DRUG TARGETS

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Epigenetic mechanisms contribute to several neurodegenerative diseases, including Alzheimer's disease (AD). Over time, environmentally induced epigenomic changes can result in an increased risk of dementia, yet individually these changes are essentially latent. Should sufficient alterations to the genome accrue, gene regulation becomes sufficiently perturbed, resulting in dementia. Such disruption is biochemical (epigenomic tags). AD and other idiopathic dementias are associated with epigenetic transformations. These transformations connect the environment and genes to pathogenesis and have led to the investigation of epigenetic-based targets. The epigenome-based latent early-life associated regulation (LEARn) hypothesis states that accumulated environmental 'hits' produce latent epigenetic changes. This process can occur across generations via transgenerational LEARn (tLEARn). In the case of tLEARn, each person is a 'unit' accumulating preclinical or subclinical 'hits' as in the original model. These changes can then be epigenomically passed along to offspring.

These hits can alter biochemical pathways until a pathological threshold is reached, which appears clinically as the onset of dementia. This leads to a novel remedial possibility: Since epigenetic changes occur over time in response to environmental effects, impending dementia of a high-risk individual could be averted through environmental changes, including explicit pharmaceutical intervention, healthy lifestyle choices, and other environmental adjustments. We posit that LEARn-based drug design could lead to effective treatments by identifying potential epigenetic marker-based therapeutic strategies. In short, the epigenetic evidence suggests that dementia is not an abruptly occurring and harshly delineated state, but rather a gradual change in critical biochemical and cellular pathways that transforms an otherwise healthy individual to a dysfunctional one, following neurodegeneration. Thus, evidence from epigenetics could lead to ways to detect and reverse such processes before clinical dementia ensues.

We sincerely thank grant supports from the National Institute on Aging (US NIH) R01-AG051086, and Indiana Clinical & Translational Sciences Institute (ICTSI) and ISDH Spinal Cord and Brain Injury Board Fund.

APPLICATION OF NITRIC OXIDE RESEARCH TO DRUG DEVELOPMENT

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The role of nitric oxide in cellular signaling in the past three decades has become one of the most rapidly growing areas in biology. Nitric oxide (NO) is a gas and a free radical with an unshared electron that can regulate an ever-growing list of biological processes. Nitric oxide is formed from L-arginine by a family of enzymes called nitric oxide synthases. These enzymes have a complex requirement for a number of co-factors and regulators including NADPH, tetrahydrobiopterin, flavins, calmodulin and heme. The enzymes are present in most cells and tissues. In many instances, nitric oxide mediates its biological effects by activating the soluble isoform of guanylyl cyclase (SGC) and increasing cyclic GMP synthesis from GTP Cyclic GMP, in turn, can activate cyclic GMP-dependent protein kinase (PKG) and can cause smooth muscles and blood vessels to relax, decrease platelet aggregation, alter neuron function, etc. These effects can decrease blood pressure, increase blood flow to tissues, alter memory and behavior, decrease blood clotting, etc. The list of effects of nitric oxide that are independent of cyclic GMP formation is also growing at a rapid rate. For example, nitric oxide can interact with transition metals such as iron, thiol groups, other free radicals, oxygen, superoxide anion, unsaturated fatty
acids, and other molecules. Some of these reactions result in the oxidation of nitric oxide to nitrite and nitrate to terminate the effect and perhaps act as NO reservoir for future NO formations; while other reactions can lead to altered protein structure function and/or catalytic capacity. These effects of (NO) probably regulate bacterial infections, inflammation of tissues, tumor growth, and other disorders. These diverse effects of nitric oxide that are cyclic GMP dependent or independent can alter and regulate numerous important physiological events in cell regulation and function. Nitric oxide can function as an intracellular messenger, an autacoid, a paracrine substance, a neurotransmitter, or as a hormone that can be carried to distant sites for effects. Thus, it is a unique molecule with an array of signaling functions. However, with any messenger molecule, there can be too little or too much of the substance, resulting in pathological events. Some of the methods to regulate either nitric oxide formation, metabolism, or function have been in clinical use for more than a century as with the use of organic nitrates and nitroglycerin in angina pectoris that was initiated in the 1870’s. Inhalation of low concentrations of nitric oxide can be beneficial in premature infants with pulmonary hypertension and increase survival rates. Ongoing clinical trials with nitric oxide synthase inhibitors and nitric oxide scavengers are examining the effects of these agents in septic shock, hypotension with dialysis, inflammatory disorders, cancer therapy, etc. Recognition of additional molecular targets in the areas of nitric oxide and cyclic GMP research will continue to promote drug discovery and development programs in this field. Current and future research will undoubtedly expand the clinician's therapeutic armamentarium to manage a number of important diseases by perturbing nitric oxide formation and metabolism. Such promise and expectations have obviously fueled the interests in nitric oxide research for a growing list of potential therapeutic applications. There have been and will continue to be many opportunities from nitric oxide and cyclic GMP research to develop novel and important therapeutic agents. There are presently more than 150,000 publications in the areas of nitric oxide research. The lecture will discuss our discovery of the first biological effects of nitric oxide and how the field has evolved since our original reports in 1977. The possible utility of this signaling pathway to facilitate novel drug development and the creation of numerous projects in the Pharmaceutical and Biotechnology industries will also be discussed.

REFERENCES

PL-117

TRANSITION METAL CATALYSIS FOR A SUSTAINABLE AND PROSPEROUS WORLD

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Until recently, most of the 24 d-block transition metals had been used primarily as useful materials for (i) construction and also as tools and containers, etc., (Ti, Zr, Fe and their alloys with V, Cr, Mn, Co, Ni, etc.), (ii) precious and ornamental items (Au, Pt, Ir, Os, Ag, etc.), and (iii) electromagnetic applications (Cu, Nb, Ta, W, Re, etc.). Over the past several decades, their superb properties as chemically useful substances, especially as catalysts for chemical reactions, have been increasingly recognized. “Why are they so useful as catalysts?”

In most cases, their superb catalytic properties may be attributed to one or both of the following two: (1) ability to provide simultaneously both filled nonbonding valence-shell orbitals (one or more) and empty valence-shell orbitals (one or more) within thermally stable species and (2) ability to undergo simultaneously both reduction and oxidation under one set of reaction conditions in one reaction vessel.

A combination of these two properties can be exploited in devising a wide variety of useful catalytic reactions for formation and cleavage of C–C, C–H, C–O and other bonds.

For critically important C–C bond formation, a) reductive elimination, b) carbometalation, and c) migratory insertion may be exploited. As representative examples of reductive elimination and carbometalation, the Pd-catalyzed cross-
coupling proceeding via reductive elimination and Zr-catalyzed asymmetric carboalumination of alkenes (ZACA) proceeding via carbometalation will be discussed.

**PL-1**

ELUCIDATION OF NOVEL MEDIATORS IN RESOLUTION OF INFECTIOUS INFLAMMATION

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Uncontrolled inflammation is now known to be a component of many widely occurring chronic diseases such as arthritis, periodontal disease, asthma, cardiovascular diseases and neurodegenerative diseases. Using a systems approach with self-limited inflammatory infectious exudates to map tissue events, cell traffic and identification of protein and chemical mediators, we identified 3 structurally separate families of potent n-3 essential fatty acid-derived (EPA, DPA, DHA) novel mediators, termed resolvins, protectins and maresins. Complete structural elucidation and total organic synthesis of these new molecules demonstrated their functions in vivo in the resolution of acute inflammation in many animal models. Each family member is chemically distinct and functions as a pro-resolving local mediator that controls the duration and magnitude of acute inflammatory responses with actions in pico- to nanogram concentration range in vivo in animal disease models. The biosynthetic pathways and potent mediators from the resolvins, protectin and maresin bioactive metabolomes are coined specialized pro-resolving mediators (SPM). Mapping of these resolution circuits provides new avenues to probe the molecular basis of many widely occurring diseases (CN Serhan Nature 2014) [1]. This presentation focuses on our recent advances on the biosynthesis and functions of specialized pro-resolving mediators (SPM), stereochemical assignments, total organic synthesis of new resolvins D4 and their actions in counter-regulation of pro-inflammatory cytokines (TNF, IL-6) and pro-inflammatory eicosanoids. SPM possess potent multi-pronged anti-inflammatory, pro-resolving, and anti-microbial actions in animal models. We use LC-MS-MS mediator-metabololipidomics to profile SPM in human tissues (serum, plasma [2], breast milk [3], adipose and brain) which uncovered new pathways that stimulate tissue regeneration and bacterial clearance [4, 5]. Several SPM are in clinical development and in ongoing clinical trials in humans. Identification of SPM during inflammation-resolution indicates that resolution is an active programmed process challenging the old concept that resolution is a passive process where chemotactic molecules dilute and simply wane to resolve the local leukocyte exudates. Together these findings indicate that endogenous resolution pathways may underlie prevalent diseases associated with uncontrolled inflammation and open the potential for resolution-based pharmacology. The author acknowledges support of NIH grant P01 GM095467.

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**PL-170**

*Track: Genomics*

**ENTPRISE: AN ALGORITHM FOR PREDICTING HUMAN DISEASE-ASSOCIATED AMINO ACID SUBSTITUTIONS FROM SEQUENCE ENTROPY AND PREDICTED PROTEIN STRUCTURES**

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The advance of next-generation sequencing technologies has made exome sequencing rapid and relatively inexpensive. A major application of exome sequencing is in the identification of genetic variations likely to cause a Mendelian diseases. This requires processing large amounts of sequence information. Therefore computational approaches that can accurately and efficiently identify the subset of disease-associated variations are needed. The accuracy and high false positive rates of existing computational tools leave much room for improvement. Here, we develop a boosted tree regression machine-learning approach to predict human disease-associated amino acid variations by utilizing a comprehensive combination of protein sequence and structure features. On comparing our method, ENTPRISE, to the state-of-the-art methods SIFT, PolyPhen-2, MUTATIONASSESSOR, MUTATIONTASTER, FATHMM, ENTPRISE exhibits significant improvement. In particular, on a testing dataset consisting of only proteins with balanced disease-associated and neutral variations, the Matthews Correlation Coefficient by ENTPRISE is 0.493 as compared to 0.432 by PPH2-HumVar, 0.406 by SIFT, 0.403 by MUTATIONASSESSOR, 0.402 by PPH2-HumDiv, 0.305 by MUTATIONTASTER, and 0.181 by FATHMM. ENTPRISE is then applied to nucleic acid binding proteins in the human proteome. Disease-associated predictions are shown to be highly correlated with the number of protein-protein interactions. Both these predictions and the ENTPRISE server are freely available for academic users as a web service at http://cssb.biology.gatech.edu/entprise/.

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**PL-116**

*Track: Pharmaceutical Biotechnology*

**DISCOVERY OF HIGHLY MODIFIED MACROCYCLIC PEPTIDES THROUGH mRNA-DISPLAY**

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The mRNA-display method results in the covalent attachment of a nascent protein or peptide to its own mRNA. In this way extremely large libraries of random sequence peptides can be generated, and subjected to cycles of selection and amplification. We have used this approach to generate very high affinity ligands to protein and small molecule targets. We have extended this approach to the in vitro selection of highly modified cyclic peptides, a promising class of therapeutic agents.
One of the most vexing problems in life science is that of “undruggability,” the difficulty of targeting certain biological macromolecules in vivo using existing drug or ligand discovery technologies. It has been estimated that as many as 80-90% of all potential targets, including many that have been extensively validated in humans and in animal models, are undruggable. The Verdine laboratory is developing powerful new chemistry-based platform technologies to address these undruggable targets. Specifically, the lab is developing cell-penetrating mini-proteins, molecules that, like protein therapeutics, possess the ability to target large flat surfaces, but that, like small molecules, are fully synthetic and hence can be modified at will. Progress on the development of one class of cell-penetrating mini-proteins – hydrocarbon-stapled alpha-helical peptides – will be reviewed in this talk.

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KEYNOTE LECTURES
**γ-AMINOBUTYRIC ACID-A BIOLOGICALLY ACTIVE SUBSTANCE IS SYNTHESIZED AND RELEASED BY THE ENDOTHELIUM: PHYSIOLOGICAL IMPLICATIONS**

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**Rationale:** γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter of the central nervous system and is found in the systemic circulation of humans at a concentration between 0.5 to 3μM. Apart from the neuronal organs, GABA has also been detected in some peripheral tissues including the intestine and pancreas. However, the potential source of circulating GABA and its significance on the vascular system remains largely unknown. Since endothelium of the blood vessels is in direct contact with the circulation, we hypothesized that endothelial cells may synthesize and release GABA to modulate some functions in the endothelium as well as following its release into the circulation.

**Objective:** To assess whether GABA is synthesized and released by the endothelial cells and some of its physiological implications.

**Methods and Results:** Utilizing the human umbilical vein endothelial cells (HUVEC) and aortic endothelial cells (HAEC), we demonstrated for the first time that human endothelial cells synthesize and release GABA from [1-14C]glutamate. Localization of GABA and the presence of the GABA synthesizing enzyme, Glutamic acid decarboxylase (GAD) in endothelial cells were confirmed by immunostaining and immunoblot analysis respectively. Presence of GABA was further confirmed by immunohistochemistry in the endothelium lining of the human coronary vessel. Endothelium derived GABA regulated the key mechanisms of ATP synthesis including fatty acid and pyruvate oxidation in endothelial cells. In addition, GABA protected endothelial cells by inhibiting the reactive oxygen species (ROS) generation and prevented monocyte adhesion by attenuating the inflammatory adhesion molecules, VCAM-1 and MCP-1 expression. GABA had no relaxing effect *in vitro* on either endothelial intact or endothelial denuded rat aortic rings. When injected intravenously to anesthetized rats, GABA exhibited a dose-dependent fall in blood pressure (BP) and this fall still occurred in animals pretreated with NG L-arginine methyl ester (L-NAME) an inhibitor of nitric oxide (NO) synthesis. However, the fall in BP was abolished following pretreatment of the animals following blockade of the autonomic ganglia by pentolinium.

**Conclusion:** In summary, our findings indicate another novel source of circulating GABA. GABA has profound effects on the endothelium homeostasis and modulates BP by an action on the autonomic ganglia.

**KNL-89**

*Track: Drug Discovery in Pre-clinical Research*

**MEDICINAL PLANTS AS SOURCE OF NEW PHARMACOPHORES**

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Modern drug development is a lengthy and expensive process, which requires an investment of over $1.8-2.0 billion, a large interdisciplinary team of researchers, and years of studies. Unfortunately this situation has out-resourced and out-numbered the pharmaceutical R&D and academic institutions of developing nations. As a result, several diseases, affecting the lives of poor population remain untreated. This situation demands a major re-emphasis on natural products using the indigenous knowledge. During this presentation, results of
our studies on discovery of bioactive natural products and their synthetic derivatives as potential drug candidates at low cost will be presented.

Urolithiasis is the most common disease of urinary tract affecting up to 15% of world population. To explore the possible antiurolithic effect of natural products, we have evaluated the ethanolic extract Bryophyllum pinnatum and its constituent (caffeic acid) in in vitro calcium oxalate crystallization and in vivo ethylene glycol induced urolithiasis rat models. The results were analyzed by histopathological techniques. The expression of kidney stone related genes i.e. prothrombin fragment-1, osteopontin, Tamm Horsfall, and bikunin from kidney tissues and 24 h urine samples of experimental rats by RT and real time PCR was also measured. Results of these studies showed the preventive, as well as curative effects of B. pinnatum and caffeic acid.

Xanthine oxidase (XO) is a molybdo flavoenzyme that catalyzes the production of uric acid during purine catabolism. Hyperactivity of XO is associated with various diseases, such as gout, arthritis, kidney stones, and inflammatory disorders. Among them, hyperuricemia and gout are the common medical complications worldwide. Currently, allopurinol and feubxostat are the two mainstream drugs for the clinical management of hyperuricemia and gout. However, these drugs are associated with adverse side effects, such as skin rashes and GI tract disorders. Therefore, there is a need for the development of novel XO inhibitors in order to identify more effective and potent inhibitors with better pharmacodynamics profile than the allopurinol and feubxostat. We have screened more than 1,000 compounds of different classes through spectrophotometric xanthine oxidase inhibition assay. Around 160 compounds were found to be active in in vitro assay with IC₅₀ values range from 0.7-418 µM, in comparison to the standard inhibitor, allopurinol (IC₅₀= 2.0 ± 0.01 µM). Further the most active and non-cytotoxic compounds were evaluated in vivo, which indicated 20 to 44% inhibition of XO.

Multidrug resistance is a challenging problem for the health care sector and is very common in familiar pathogens, such as vancomycin-resistant enterococci and Staphylococcus aureus. Exposure and inappropriate use of the antibiotics is the measure cause of MDR, both in developed and developing regions. Our study, focusing on the discovery of natural and synthetic compounds, active against multidrug resistant bacteria Staphylococcus aureus and Pseudomonas aeruginosa have resulted in the identification of several novel and potent inhibitors of MDR Staphylococcus aureus, (EMRSA-17, EMRSA-16, MRSA-252, and Pak clinical isolates) from natural sources. Resistance-reversal studies at molecular level were carried out by employing flow cytometric and microscopic techniques. Synergistic and partial synergistic effects of these compounds, in combination with antibiotics, were investigated. This work has so far resulted in the identification of several novel “helper molecules”, which can increase the efficacy of existing antibiotics to over 1000-fold in some cases.

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**KNI-9**

*Track: Cancer Targeted Drug Delivery*

**HUMAN MONOCLONAL ANTIBODIES AGAINST CANCER AND VIRUSES**

**Dimiter Dimitrov**

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I will give an overview of the current state of the field. Then will discuss our group work on the identification, characterization and engineering of human monoclonal antibodies (mAbs) in IgG1, Fab, scFv, VH and CH2 formats, and as antibody drug conjugates, chimeric antigen receptors (CARs) and bispacific antibodies. First, candidate therapeutic mAbs against cancer two of which are now in clinical trials as CARs; second, engineered antibody domains and fragments with an emphasis on HIV-1 inhibitors for HIV-1 eradication; third, full-size mAbs against emerging and biodefense-related viruses with an emphasis on henipaviruses and coronaviruses mostly MERS-CoV especially for prophylaxis and therapy of humans.
**KNL-135**

*Track: Regenerative Medicine*

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**NANO- AND MICROFABRICATED HYDROGELS FOR REGENERATIVE ENGINEERING**

**Ali Khademhosseini**

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Engineered materials that integrate advances in polymer chemistry, nanotechnology, and biological sciences have the potential to create powerful medical therapies. Our group aims to engineer tissue regenerative therapies using water-containing polymer networks called hydrogels that can regulate cell behavior. Specifically, we have developed photocrosslinkable hybrid hydrogels that combine natural biomolecules with nanoparticles to regulate the chemical, biological, mechanical and electrical properties of gels. These functional scaffolds induce the differentiation of stem cells to desired cell types and direct the formation of vascularized heart or bone tissues. Since tissue function is highly dependent on architecture, we have also used microfabrication methods, such as microfluidics, photolithography, bioprinting, and molding, to regulate the architecture of these materials. We have employed these strategies to generate miniaturized tissues. To create tissue complexity, we have also developed directed assembly techniques to compile small tissue modules into larger constructs. It is anticipated that such approaches will lead to the development of next-generation regenerative therapeutics and biomedical devices.

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**KNL-5**

*Track: Cancer Targeted Drug Delivery*

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**BIOLOGY AND THERAPEUTIC TARGETING OF PAKS IN HUMAN CANCER**

**Rakesh Kumar**

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Reorganization of cytoskeleton and formation of motile structures are fundamental to the ability of cancer cells to invade. At the cellular level, these changes are regulated by the p21-activated kinases (PAKs) and its downstream effectors and targets. Biochemically, PAKs are enzymes with kinase and scaffolding activities. In addition, PAKs also function as signaling nodules due to their ability to cross-talk with signaling cascades and phosphorylate downstream effector molecules. The spectrum of PAK’s activities in cancer cells ranges from cell growth, invasion, gene expression and chromatin remodeling to DNA damage response and modifying therapeutic responsiveness of cancer cells. PAK family members are widely overexpressed in human cancers and the expression of PAK1 (as well as other family members) closely associates with an invasive phenotype. In addition, PAK’s dysregulation also contributes to the development of therapeutic resistance to anti-cancer therapies. The last decade has witnessed a substantial progress in developing approaches to target PAKs by a wide-variety of promising therapeutic agents with alone or in-combination with pathway-centered inhibitors. The lecture will discuss how our broader understanding of the PAK biology in cancer cells has helped to target the PAK family in cancer, the progress made during the last decade, the nature of limitations faced by the field to develop PAK-inhibitors, and the next step to develop effective PAK-directed molecules for cancer.
KNL-79

Track: Inflammation & Immunology

CONDITIONING OF IMMUNE RESPONSES BY CD39 AND PURINERGIC SIGNALING

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Extracellular signaling mediated by nucleotides and nucleosides has been implicated in the pathophysiology of several important diseases: these include vascular thrombosis, atherosclerosis, inflammatory autoimmune diseases, transplant rejection, sepsis and cancer. The activation of purinergic receptors has been shown to modulate vascular and immune responses during those adverse conditions, as seen in such human illnesses. The CD39/CD73-mediated ectoenzymatic cascades in the endothelium, on dendritic cells, myeloid cells, T and B cells subserve anti-inflammatory and immunosuppressive mechanisms, chiefly by generating adenosine. Importantly, CD39 and CD73 expression identifies different subtypes of T cells, being highly expressed in T regulatory cells and in suppressive T helper type 17 cells, when compared to resting or activated T cells.

Expression of vascular or immune cell ectonucleotidases regulates nucleotide/nucleoside-mediated responses within the vasculature and at local sites of injury. For instance, dynamic changes in the expression profile of ectonucleotidases within the vasculature regulate platelet activation, thrombus size and stability by modulating availability of purinoceptor ligands. Many tumors are proficient at converting ATP into the product adenosine, which serves as a checkpoint inhibitor, through the expression of the ecto-enzyme CD39 on cancer cells, regulatory immune cells and the vasculature. This derivative adenosine interferes markedly with immune responses to the cancer and promotes blood supply.

As a central component of the complex phenomenon of inflammation, regulating purinergic signaling by augmenting ectonucleotidase activity might improve outcomes in the management of inflammatory vascular and immunological disorders. In contrast, boosting immune responses can be achieved by blocking CD39, which will impede ATP scavenging and prevent adenosine production. This latter adjunctive approach has the potential of bolstering immunostimulatory effects of radiotherapy and/or chemotherapy in cancer.

KNL-4

Track: Cardiovascular Drug Discovery & Therapy

LYSOSOMOTROPIC AND ANTI-OXIDANT CARDIOPROTECTIVE PROPERTIES OF D-PROPRANOLOL AND 4-HYDROXY-PROPRANOLOL


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Abnormal iron deposition in patients with hemochromatosis and multiple blood transfusions can cause cardiac failure. We found that the non-beta-blocker enantiomer, D-propranolol (D-Pro) of racemic DL-propranolol, can accumulate in cultured endothelial cells in lysosomes and can provide major cytoprotection against oxidant-mediated endothelial cell injury caused by iron overload [1]. Hearts from moderate iron overloaded rodents contain releasable iron that induces in vivo oxidative stress to enhance myocardial susceptibility to subsequent ischemia/reperfusion (I/R) injury [2]; acute D-Pro pretreatment of isolated, perfused hearts from these animals prior to I/R stress was significantly protective. Moreover, chronic D-Pro treatment of rats during 5 weeks of an iron overload regimen substantially protected against in vivo oxidative stress injury and cardiac dysfunction (echocardiography) [3]. D-Pro, and its major metabolite, 4-hydroxy-propranolol (4-OH-Pro), have lysosomotropic/antioxidant properties; 4-OH-Pro is 8-fold more potent as an antioxidant than vitamin E and >100-fold more potent than racemic propranolol. High clinical plasma levels of 4-OH-Pro are attained during DL propranolol
therapy, and may contribute significant therapeutic efficacy against systemic oxidative stress. Thus, the lysosomotropic/antioxidant properties of D-Pro or its metabolite, 4-OH-Pro, may provide effective adjunct therapy for clinical studies in patients at risk for iron overload cardiomyopathy.

REFERENCES


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KNL-183

Track: Chemistry

CHEMISTRY EFFORT ON THE DEVELOPMENT OF SMALL MOLECULE INHIBITORS FOR NEW DRUG TARGETS

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Bromodomains proteins are epigenetic reader and have been identified as druggable targets for cancer and other diseases. Over a dozen small molecules such as JQ-1, BET151, and OTX-015 have been developed as potent bromodomain and extra terminal (BET) inhibitors and some of them are under early stage clinical trials. BET inhibitors usually have diazepine, isoxazole, pyrrole, quinolone, benzopiperazine, or other heterocyclic moieties as warheads. Through the collaboration with James Bradner’s lab in Dana-Farber Cancer Institute, we recently developed a new kind of isoxazole-type BET inhibitors bearing an imidazo[1,2-a]pyrazine scaffold. These compounds were prepared by three-component Groebke–Blackburn–Bienayme reaction (GBBR) for imidazo[1,2-a]pyrazine scaffold followed by the Suzuki-coupling for attaching 1,3-dimethylisoxazole warhead. Highly efficient 2-step synthesis allowed easy access of a compound library for rapid optimization. Lead compound UMB-32 shows 637 nM biochemical potency and 724 nM cellular potency in BRD4-dependent lines.

![Chemical structure of UMB-32](image)

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IL-99

Track: Pharmaceutical Research & Development

ENABLING FUTURE PHARMA: DRUG REPURPOSING EFFORTS GO MAINSTREAM

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Finding new uses or indications for existing medications has gained unprecedented momentum in recent years. NIH’s new venture in setting up Drug Discovery Institute is primarily to accelerate the drug repositioning efforts. There are over 50 companies with unique capabilities to support drug repositioning efforts. The approach is now systematic, and has become the chosen route for a number of biotechs and small pharmas. These ‘drugs’ include not only the FDA approved drugs, but also the drugs that have been withdrawn, and those that have gone through clinical trials but not marketed. Since these drugs have a significant ‘safety’ profile and possibly conquered the ‘valley of death’, the cost of taking these drugs in to the market is low, and faster. The questions remain as to who owns the intellectual property, and what prevents a physician prescribing the drug for off-label uses. The talk will analyze the drug repositioning strategies, assess opportunities and business models, highlight major challenges, explore intellectual property barriers, etc.

IL-27

Track: Cancer Targeted Drug Delivery

TARGETING EPIGENETIC ABERRATIONS IN CHEMORESISTANT OVARIAN CANCER

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Recent advances in cancer research reveal that distinct aberrant epigenetic events, including abnormal histone modification and DNA methylation, are important cancer hallmarks. The importance of systemic DNA hypomethylation for predicting clinical prognosis and response to chemotherapy is rarely explored. The recent discovery of the TET family of 5-methylcytosine (5-mC) hydroxylases, which convert 5-mC to hydroxymethylcytosine (5-hmC), has added an additional layer of complexity to the epigenetic regulation of DNA methylation.

A great challenge in platinum cancer therapy is the management of chemoresistant tumor cells, including cancer stem cells, which have a largely unknown molecular pathogenesis at the level of epigenetic regulation. Our work focuses on the development and validation of sensitive and reliable methods to detect global patterns of epigenetic 5-hmC loss in newly diagnosed aggressive cancers and/or chemoresistant relapsed tumors. These assays can be easily translated and implemented into routine clinical practice. We are currently conducting a whole genome-wide DNA methylation mapping of 5-hmC levels in ovarian tumors and compare key differences within the 5-hmC landscape between platinum sensitive and resistant tumors. In addition, our comprehensive study investigates the DNA methylation patterns and 5-hmC landscape of chemoresistant ovarian cancer stem cells and the findings will allow us to develop novel epigenetic strategies targeting these cells. This will be especially important for relapsed ovarian cancer patients for which current therapeutic options are extremely limited. The findings will help us learn how best to translate novel epigenetic discoveries into routine clinical care with the aim of improving current therapies for chemoresistant patients and develop reliable chemosensitivity markers and assays, which could accurately predict clinical outcome and response to platinum therapy. Our long-term goal is to develop combinatorial therapies that merge platinum compounds with epigenetic adjuvants for effective therapeutic intervention.

Keywords: Cancer epigenetics, platinum chemotherapy, systemic 5-hmC levels, epigenetic adjuvants, women’s health, ovarian cancer.
**A NEW AMINOTHIOL RADIOPROTECTOR TO SUPPRESS RADIATION-INDUCED DNA DAMAGE AND CANCER**

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A new aminothiol radioprotector, PrC-210, was designed and synthesized by our group, and was found to be highly radioprotective. The new aminothiol design includes positively-charged amines in the alkyl backbone for ionic interaction with the negatively-charged DNA backbone, and a branched alkyl side-chain with a terminal thiol that is projected away from the DNA backbone to provide scavenging of reactive oxygen species (ROS) before they attack DNA. This is in contrast to the linear amifostine molecule that lies within the DNA major groove. The branched PrC-210 geometry also likely explains the complete absence in PrC-210 of the amifostine nausea/emesis and hypotension side effects that may be related to an adrenergic pharmacophore within the linear amifostine/WR-1076 molecule. In rodents, PrC-210 conferred 100% survival to mice or rats from an otherwise 100% lethal dose of whole-body radiation (8.7 Gy) when administered ORALLY or by IP injection prior to irradiation. In a collaborative study (Uder et al., Erlangen, Germany), addition of PrC-210 to human blood at a concentration that we calculate will be safely achievable in patients by oral delivery, suppressed γ-H2AX-foci induced by 100 mGy irradiation to background. Numerous applications exist for the PrC-210 technology in diagnostic radiology, military, industry, space-travel, and cardiac protection during MI s. A PrC-210 pill, given 30-90 minutes before a CT scan, or an intravenous dose given minutes before a CT, could suppress risks associated with CT and other diagnostic radiation-induced DNA damage to background and make diagnostic radiology more broadly available, including routine management of patients who are genetically predisposed to cancer. WARF (www.warf.org) estimates a $2.9 Billion market for the CT scan indication alone, and there are no competing products in this market space. In a WARF survey, 93% of CT radiologists indicated “they would prescribe this radioprotector tomorrow if it was available as an FDA-approved drug”. The ability of PrC-210 to suppress x-ray-induced DNA damage to the background level seen in non-irradiated cells supports further development of PrC-210 for clinical use.

**THE MECHANISMS OF ASPARAGINASE-INDUCED PANCREATITIS**

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Asparaginase is an essential element in the successful treatment of Acute Lymphoblastic Leukemia, the most common type of cancer affecting children. However, in about 5 - 10% of cases this treatment causes Acute Pancreatitis (AP) as a side-effect. In AP, a potentially fatal human disease, the inactive pancreatic pro-enzymes become active enzymes inside the pancreatic acinar cells, digesting the pancreas and its surroundings.

Under physiological conditions intracellular calcium signalling and Mg-ATP level are the key elements needed for stimulant-evoked exocytotic enzyme secretion from pancreatic acinar cells. Physiological Ca^{2+} signals stimulate ATP production, whereas sustained global cytosolic Ca^{2+} elevations decrease ATP levels and cause necrosis leading to AP. Alcohol and gallstones are the major causes of the disease.

We have investigated the mechanism by which L-Asparaginase evokes AP. For the first time we have shown that like other pancreatitis-inducing agents, Asparaginase evoked excessive intracellular Ca^{2+} release followed by Ca^{2+} entry, decreased the intracellular ATP levels and reduced Ca^{2+} extrusion. The toxic Ca^{2+} signals induced by Asparaginase caused extensive cell necrosis. Our data indicate that the Asparaginase-induced pathology depends on protease activated receptor 2 and its inhibition prevented the toxic Ca^{2+} signals and necrosis. Inhibition of Ca^{2+} entry with GSK-7975A markedly reduced Asparaginase-induced cellular pathology.

We have demonstrated a reduction in the intensity of Ca^{2+} extrusion due to the reduction in the intracellular ATP level limiting the energy supply to the Ca^{2+} ATPase in the plasma membrane. Supplementation of the medium
with sodium pyruvate provided a similar degree of protection against pancreatic necrosis as PAR2 inhibition or GSK-7579A.

Ca$^{2+}$ and ATP play key roles in Asparaginase-pancreatic pathology and therapeutic strategies must take both into account. We suggest that combined pharmacological control of intracellular calcium and ATP levels will prevent or alleviate AP and improve childhood cancer treatments.

**Keywords:** Calcium, ATP, asparaginase, pancreatitis, leukaemia, calcium channels.

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**IL-120**

**Track:** CNS Drug Discovery & Therapy

**EVALUATION OF A SUSTAINED RELEASE FORM OF THE GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST EXENDIN-4 (PT302) IN A MOUSE MODEL OF MILD TRAUMATIC BRAIN INJURY**

_Nigel H. Greig, David Tweedie, Miaad Bader, Lital Rachmany, Yazhou Li, Ian A. Tamargo, Deboroy K. Lahiri, Chaim G. Pick and Dong-Seok Kim_

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Traumatic brain injury (TBI) is a common event occurring in civilian and military environments consequent to falls, full contact sports, automobile accidents, acts of violence and shockwaves generated by the detonation of explosives. Primary brain injury includes brain tissue deformation and/or damage. Secondary brain injury involves neuronal excitotoxicity, oxidative stress and inflammatory processes that can lead to focal and/or diffuse neuronal loss and both short- and long-term cognitive deficits and associated neurological impairments. Epidemiological evidence suggests that TBI may cause neurodegenerative disease later in life, providing a conduit to Alzheimer’s and Parkinson’s disease (AD, PD). Currently, there is no FDA approved drug for the management of secondary injury events following TBI. Our prior work described cellular and behavioral benefits and reversals of numerous TBI-induced hippocampal gene expressions leading to later neurodegenerative disorders, including AD and PD, by the glucagon-like peptide-1 (GLP-1) receptor (R) agonist exendin-4 in preclinical models of both concussive and blast TBI (Tweedie et al., Neurobiol Dis. 54:1-11, 2013; Tweedie et al., Exp Neurol. 239:170-82, 2013; Rachmany et al., Age 35:1621-36, 2013; Greig et al., Alzheimers Dement 10:562-575, 2014; Tweedie et al., Alzheimers Dement. 12:34-48, 2016). Here, we review these studies, describe recent research undertaken to cross-validate them across TBI preclinical models, and describe the actions of a sustained release form of exendin-4 (PT302) on TBI-induced behavioral deficits in a closed head weight drop model of TBI. Our focus is to develop an optimized exendin-4 form for evaluation in human clinical trials of TBI.

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**IL-12**

**Track:** Translational Medicine

**CALCIUM-SENSING RECEPTOR AGONISTS ON HYPERFUNCTIONING PARATHYROID DISEASES -FROM BENCH TO BEDSIDE, AND BEYOND**

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Hyperfunctioning parathyroid diseases such as primary hyperparathyroidism (PHPT) and secondary hyperparathyroidism of uremia (SHPT) are characterized by the abnormal secretion of parathyroid hormone (PTH). These hyperparathyroidisms are at high risk for fracture, urinary lithiasis, kidney failure in PHPT patients, and for fracture, cardiovascular mortality in SHPT on maintenance hemodialysis patients. Calcium-sensing receptor (CaSR) on parathyroid cells has a crucial role in PTH secretion by sensing extracellular calcium, and reduced CaSR expression was observed in PHPT and SHPT.
Cinacalcet HCl (cinacalcet) was developed as an allosteric modulator of the calcium-sensing receptor (CaSR), which suppress PTH secretion from parathyroid cells. *In vitro* analyses using human parathyroid primary cultured cells revealed that cinacalcet directly and dose-dependently suppressed PTH secretion [1]. Cinacalcet suppressed PTH secretion correlating with CaSR hypo-expression in the parathyroid glands *in vivo* in PHPT model mice, confirming that molecular target of cinacalcet is CaSR [2]. Cinacalcet also suppressed parathyroid cells growth *in vivo* [3], suggesting that this compound is able to prevent the advancement of hyperparathyroidism. Cinacalcet has marketing approval in many countries for the treatment of SHPT on maintenance hemodialysis patients. Many randomized clinical trials in dialysis patients led to significant reductions in the risk of parathyroidectomy, fracture, cardiovascular hospitalization, and mortality. Continuous hypophosphatemia markedly decreases bone mineralization resulting in rickets or osteomalacia. Cinacalcet elevates serum phosphate concentration by suppressing PTH-induced renal phosphate wasting, and this compound was beneficial in the treatment of hypophosphatemic rickets/osteomalacia. Cinacalcet is still expanding its clinical usefulness.

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**II-104**

**Track:** Drug Metabolism

**LOCALIZED AND TIMED DELIVERY OF MULTIPLE MORPHOGENS COUPLES VASCULARIZATION AND OSTEOGENESIS IN SKELETAL TISSUE REGENERATION**

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Osteogenesis and vascularization during development are coupled by spatiotemporal regulation of paracrine signaling in which the invading vascular endothelial cells secrete osteogenic morphogens to stimulate cell differentiation and bone formation. Conversely, the differentiating mesenchymal stem cells (MSCs) in the vicinity of the vascular endothelial cells release vasculogenic morphogens to further stimulate vasculogenesis for the metabolically highly active osteoblasts. The objective of this work was to investigate the effect of timed and localized release of an osteogenic morphogen, bone morphogenetic protein-2 (BMP2) and a vasculogenic morphogen, vascular endothelial growth factor-165 (VEGF), in a micro-patterned co-culture system on synergistic expression of paracrine signaling factors and coupling of osteogenesis and vasculogenesis. Nanogels (NGs) based on polyethylene glycol (PEG) macromers chain-extended with short lactide (L) and glycolide (G) segments were used for grafting and timed-release of BMP2 and VEGF. NGs with 12 kDa PEG molecular weight (MW), 24 LG segment length, and 60/40 L/G ratio released the grafted VEGF in 10 days (NG10-VEGF), NGs with 8 kDa PEG MW, 26 LG segment length, and 60/40 L/G ratio released the grafted BMP2 in 21 days (NG21-BMP2). Human MSCs and NG21-BMP2 were encapsulated in a high stiffness slow-resorbing matrix based on acrylate-functionalized lactide-chain-extended star polyethylene glycol (SPELA) hydrogel whereas the combination of human MSCs and endothelial progenitor cells (MSCs/EPCs) and NG10-VEGF were encapsulated in a compliant fast-resorbing matrix based on gelatin hydrogel. The effect of spatiotemporal release of VEGF and BMP2 on vascularized osteogenesis and paracrine signaling was assessed by biochemical, mRNA, protein analysis, and immunofluorescent staining. 10 and 21 days timed-release of timed-release of VEGF and BMP2 from the NGs resulted in the highest extent of vascularized osteogenesis by the encapsulated human MSCs and EPCs in the micro-patterned matrix. Further, localized and timed-release of VEGF and BMP2 in 10 and 21 days in the patterned matrix, respectively, led to a sharp increase in the expression of paracrine signaling factors basic fibroblast growth factor (bFGF, vasculogenic), platelet-derived growth factor (PDGF, vasculogenic), and transforming growth factor-beta (TGF-β, osteogenic) by the encapsulated human MSCs and EPCs. These results suggest that mineralization and vascularization are coupled by the encapsulated secretion of paracrine signaling factors by the differentiating MSCs and EPCs.

**ACKNOWLEDGEMENTS**

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**Keywords:** Nanogel, spatiotemporal protein delivery, vascularized osteogenesis, skeletal tissue regeneration.
**II-119**

**Track:** Women’s Health Drug Discovery & Therapy

**PLACENTAL GROWTH FACTOR RESTORES THE ANGIOGENIC BALANCE AND IMPROVES THE ENDOTHELIAL NO-CGMP RELAXATION PATHWAY IN HYPERTENSION-IN-PREGNANCY**

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Preeclampsia (PE) is a pregnancy-related hypertensive disorder (HTN-Preg) with unclear mechanism. An imbalance between anti-angiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) and angiogenic placental growth factor (PIGF) has been observed in PE, but the vascular targets and signaling pathways involved are unclear. We tested if inducing sFlt-1/PIGF imbalance by infusing sFlt-1 (10 µg/kg/day) in day-14 pregnant (Preg) rats increases blood pressure (BP) and vascular reactivity; and vice versa, if restoring sFlt-1/PIGF balance by infusing PIGF (20 µg/kg/day) in a rat model of HTN-Preg produced by reduction of uteroplacental perfusion pressure (RUPP) would improve BP and vascular function. On gestation day 19, BP was in Preg+sFlt-1 and RUPP > Preg and in RUPP+PIGF < RUPP. Plasma sFlt-1/PIGF ratio was increased in Preg+sFlt-1 and RUPP, and was reduced in RUPP+PIGF rats. In isolated endothelium-intact aorta, carotid, mesenteric and renal artery, phenylephrine (Phe) and high KCl-induced contraction was in Preg+sFlt-1 and RUPP > Preg and in RUPP+PIGF < RUPP. The differences in vascular reactivity to Phe and KCl between groups were less apparent in vessels treated with the NOS inhibitor L-NAME or guanylate cyclase inhibitor ODQ or endothelium-removed, suggesting changes in endothelial NO-cGMP pathway. In Phe precontracted vessels, acetylcholine (ACh)-induced relaxation was in Preg+sFlt-1 and RUPP < Preg and in RUPP+PIGF > RUPP, and was blocked by L-NAME or ODQ treatment or endothelium-removal. Western blots revealed that aortic total eNOS and activated phospho-eNOS were in Preg+sFlt-1 and RUPP < Preg and in RUPP+PIGF > RUPP. ACh-induced vascular nitrate/nitrite production was in Preg+sFlt-1 and RUPP < Preg and in RUPP+PIGF > RUPP. Vascular relaxation to the exogenous NO donor sodium nitroprusside was not different among groups. Thus, a tilt in the angiogenic/anti-angiogenic balance towards anti-angiogenic sFlt-1 is associated with decreased vascular relaxation via NO-cGMP and increased vasoconstriction and BP. Restoring the angiogenic/anti-angiogenic balance using PIGF enhances endothelial NO-cGMP vascular relaxation and decreases vasoconstriction and BP in HTN-Preg rats, and could be a new approach in the management of PE.

**SL-166**

**Track:** Innovative Drug Discovery and Nanotechnology

**MICROSCALE CALORIMETRIC DEVICE FOR DETERMINING REACTION PARAMETERS**

Gregory J. Kowalski

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A microscale calorimeter design that reduces the compound use by a factor of 200 and the time to perform experiments by an order of magnitude is described. This unique device measures the thermodynamic properties of reaction, Enthalpy of reaction, Equilibrium constant and Gibbs free energy change using the observed change in the extraordinary optical transmission through a nanohole array sensor. Different configurations of the calorimeter will be discussed with an emphasis on the co-flow microfluidic device. The features of this calorimeter make it attractive to the drug discovery process as well as having a potential for high throughput screening which would provide key information earlier in the testing process and for multiplexing experiments.

Preliminary results indicate that the device can determine the concentration changes related to a reaction to within 5%. A relative comparison of the enthalpy of reaction at different reactant concentrations are within 5% of those predicted using literature values. Experimental results for the EDTA – CaCl₂ as well as simulation confirming the developed algorithms for determining the thermodynamic properties are presented.
**invited lectures**

**track:** CNS Drug Discovery & Therapy

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**NOVEL microRNAs IN ALZHEIMER'S DISEASE: DIMMER SWITCHES FOR CELLULAR HOMEOSTASIS**

**D.K. Lahiri, N. Chopra, J.T. Rogers, N.H. Greig, K. Sambamurti and S. Chakrabarti**

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Alzheimer’s disease (AD) results, in part, from over-production of amyloid-β peptide (Aβ), a product of Aβ precursor protein (APP). Expression studies suggest that dysregulation of proteins involved in Aβ production, such as APP and β-secretase, or BACE1, contribute to excess Aβ deposition. Elucidating the regulation of these proteins’ expression will ultimately reveal new drug targets. In addition, vascular deterioration routinely co-occurs with AD, and impaired neural tissue perfusion contributes to neurodegeneration. Deficiencies in vascular endothelial growth factor (VEGF) significantly contribute to impaired neural tissue perfusion. Diabetes also associates with cognitive decline and accelerated aging in all tissues. We study the regulation of these gene products by microRNA (miRNA), an abundant class of small RNAs with inhibitory effects on gene expression. Our results reveal a novel regulatory interaction between two important AD-related genes (APP and BACE1) and specific endogenously-expressed miRNA species. We also observed specific miRNAs regulating APP levels via interactions with the APP-3’UTR or APP-5’UTR in human primary neuronal cultures. These regulatory interactions may serve as novel therapeutic targets and enable the development of treatment strategies beneficial for AD. In separate experiments, we observed that diabetes induction in wild-type mice resulted in a brain-region specific decrease of APP levels in hippocampus, a decrease of VEGF levels in cortex, and an increase of synaptosome associated protein-25 kDa (SNAP25) levels in cortex (but a slight decrease in hippocampus). Hippocampal atrophy may be an early sign or precursor of AD. Prior endothelial overexpression of miR200b in transgenic mice prevented diabetes-induced changes for APP, VEGF and SNAP25. We also show reduced expression of specific miRNAs, particularly miR200b, in mice after induction of diabetes. Our results suggest a potential prophylactic role for miR200b, and support the hypothesis that peripheral administration of miRNA mimics may be an effective early treatment for AD or pre-AD conditions. We sincerely thank grant supports from the National Institute on Aging (US NIH) R01-AG051086, and Indiana Clinical & Translational Sciences Institute (ICTSI) and ISDH Spinal Cord and Brain Injury Board Fund.

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**track:** Protein and Peptide Sciences

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**TOWARD MECHANISM-BASED ANTI-CANCER DRUG DEVELOPMENT**

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The epidermal growth factor receptor (EGFR) family plays essential roles in cellular processes, including cell-cycle control, survival, proliferation, motility and differentiation. The family members are all synthesized as single-pass transmembrane proteins and bind polypeptide growth factors. It has long been thought that all the family members are activated by ligand-induced dimerization of the receptors. An increasing number of diverse studies, however, indicate that the family members, previously thought to exist as monomers, are present as pre-formed, yet inactive, dimers prior to ligand binding. The non-covalently associated dimeric structures are reminiscent of those of the insulin receptor family, which has a disulfide-linked dimeric structure. Furthermore, recent progress in structural studies has provided insight into the underpinnings of conformational changes during the activation of the family dimers. The conformational changes include ligand-induced rotation of the receptors’ transmembrane domains in their preformed dimeric structure, and the rotation in turn dissociates and rearranges intracellular kinase domain dimers for activation (“The rotation model”). Based on the model, we will discuss how anticancer antibody and peptides regulate the activity of the family receptors, and how novel anti-cancer drugs can be developed.
**IL-156**

Track: In-silico Drug Design and in-silico screening

**TARGETING CHALLENGING PROTEIN-PROTEIN AND PROTEIN-DNA INTERACTIONS: DISCOVERY OF MCL-1 AND PAX2 INHIBITORS USING STRUCTURE-BASED VIRTUAL SCREENING**

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Virtual screening is a computational technique used in early-stage drug discovery for identifying novel lead compounds. The compound library used for screening, the experimentally solved or computationally modeled target structure, and understanding the ligand-target binding interactions are essential components for successful discovery of innovative lead compounds. We will present our successful efforts in identification and validation of lead compounds targeting challenging protein-protein and protein-DNA interactions.

Myeloid cell leukemia-1 (Mcl-1) is a critical survival factor in a broad range of human cancers and mediates its effects primarily through protein-protein interactions. Applying an integrated screening strategy through combining high throughput and virtual screenings, several lead compounds with structural diversity were identified as Mcl-1 inhibitors. Followed by structure-based drug-design supported by HSQC NMR and crystallographic studies, we have optimized and developed potent small-molecule Mcl-1 inhibitors and characterized their activity on a biochemical, functional and cellular level.

The paired-domain transcription factor Pax2 is essential for proper development of the kidney and the reproductive system and has been implicated in a multitude of urogenital disorders. Pax2 has not been investigated as a therapeutic target and in general, DNA-binding transcription factors represent challenging drug targets. To discover small molecules capable of targeting the Pax2 and disrupting DNA-binding, we utilized homology modeling in determining Pax2 3D structure followed by structure-based virtual screening and in-vitro techniques to identify, validate, and characterize small-molecules that target the Pax2 paired domain.

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**IL-82**

Track: Inflammation and Immunology

**INVESTIGATION OF ANTIBODY-DRUG CONJUGATES TO TARGET GLUCOCORTICOIDS TO IMMUNE CELLS**

Anthony Palmieri and Philip E. Brandish

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The magic bullet idea of using antibodies to target cytotoxic agents to tumor cells has proven feasible and we sought to build on those successes to enable dose-limited therapeutics beyond oncology. Using glucocorticoids as an example, we have used site-specific incorporation at a genetically encoded non-natural amino acid, novel linker chemistry, and a potent glucocorticoid receptor agonist to assess the feasibility of the general approach.
**NEW DEVELOPMENTS IN CHOLINESTERASE STRUCTURE-BASED THERAPIES OF ORGANOPHOSPHATE INTOXICATION**

Andrey Kovalevsky, Oksana Gerlits, Donald Blumenthal, Xiaolin Cheng, Mikolai Fajer, Valery V. Fokin, Zrinka Kovarik, Palmer Taylor and Zoran Radić

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Acetylcholinesterase (AChE; EC 3.1.1.7), an alpha/beta fold serine hydrolase, is a key enzyme in vertebrate cholinergic neurotransmission and a primary target in acute intoxication by nerve agents and organophosphate (OP) pesticides that covalently inhibit its remarkably high catalytic activity. The worldwide incidence of poisoning by OPs remains high, causing more than 200,000 fatalities annually. The only well-established approach to recovering catalytic activity of OP-AChE conjugates is through nucleophilic oxime reactivation. Our two orthogonal approaches to develop improved oxime-based pharmacotherapeutics for treatment of OP intoxication are: 1) Design of novel, accelerated oxime reactivators of OP-conjugated tissue AChE where reactivation acceleration is achieved by improved understanding of human AChE (hAChE) structure at the room temperature and in aqueous solution guided by advanced biophysical studies. Here, we demonstrate previously undetected changes in hAChE solution structure upon OP inhibition and oxime reactivation by using solution small-angle X-ray scattering profiles of hAChE. We have also resolved, for the first time, room temperature (22 °C) X-ray crystal structures of hAChE in complex with oximes and other ligands, that reflect their physiological interactions much more accurately than X-ray structures conventionally determined at -173 °C (100 K). 2) Catalytic OP bioscavenging assisted by oximes to efficiently remove offending OPs from exposed tissue before these inhibit tissue AChE. Our advanced hAChE mutant-based and butyrylcholinesterase (EC 3.1.1.8)-based bioscavenging, have demonstrated fast *in vitro* and *ex vivo* OP detoxification and improvement in survival of nerve agent OP-exposed mice upon treatment with bioscavengers, even in exposure to the fastest-aging nerve agent soman.

**TOWARD A JOINT ACTION: LINKING COMPUTERIZED BIOMARKERS OF REAL HUMAN FUNCTION TO DRUG INFLUENCE DETECTION – WHY AND HOW?**

Sara Rosenblum

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Handwriting is an ancient medium of human communication representing a complex activity that entails an intricate blend of cognitive, kinesthetic, and perceptual motor components. As person’s handwriting is unique and as distinctive as a fingerprint, detecting handwriting production may serve for disease diagnosis, and for detection of drug or other therapeutic intervention methods influence on the individual's daily function abilities.

The aim of the lecture is to present the Computerized Penmanship Evaluation Toll (ComPET) developed by Rosenblum which supplies objective temporal, spatial and pressure measures of the handwriting production. Handwriting data gathered from about 2000 participants of different age groups, languages and pathologies enables creation of unique sophisticated handwriting analysis techniques.

This system's benefits for the medical field will be presented while emphasizing study results related to diagnosis and evaluation of drug contribution to human's function and health. Following, presentation of the ComPET’s data collection and analysis methods, results of detection drug influence on children with Attention Deficit Hyperactive Disorders (ADHD) and adults with Multiple Sclerosis (MS) will be presented.
Furthermore, future use of the system for evaluation of drugs and other therapeutic methods influence among people with depression, and Alzheimer's disease will be discussed based on previous study results among these populations.

**IL-125**

*Track: Enabling Technologies*

**PWS NANOCYTOLOGY TO STUDY NUCLEAR NANOARCHITECTURE**

Hariharan Subramanian, Yolanda Stypula-Cyrus, Lusik Cherkezyan, Parvathi Vishwanathan, Radha Iyengar, Dhwanil Damania, Scott Gladstein, Di Zhang, Hemant K. Roy and Vadim Backman

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Alterations in nuclear structure is a common marker in carcinogenesis. While the changes to the nuclear structure in the late stages of cancer are clearly detectable using conventional wide field microscopy, similar changes to the nuclear structure at the early and treatable stages of cancer are often unknown. It is important to understand these early changes to better control aberrant genetic/epigenetic changes in the nucleus and target therapies that provides an improved chance of patient survival. The principal limitation to detect these nuclear changes at early stages of cancer is that these changes are often at the nanoscale and are below the diffraction limited resolution of conventional microscopy (~ 200 nm). Our group has developed a novel spectroscopic microscopy technique, Partial Wave Spectroscopic (PWS) microscopy (simply, nanocytology), to detect nanoscale changes in the nuclear architecture. The PWS nanocytology measures disorder strength (Ld) which quantifies the statistical properties of nanoscale chromatin and has been found to be increased in multiple cancer types. These nuclear changes have been found to be related to the chromatin structure, changes to gene expression and epigenetic modifications in cancer. Our data from lung, colon, prostate, esophageal, pancreas, thyroid and ovarian cancers show that nuclear Ld is significantly increased confirming its utility as a promising new approach to screen early cancer and develop novel therapeutics.

**IL-65**

*Track: Biologics*

**MAKING HIGH-CONCENTRATION SOLUTIONS OF PROTEIN DRUGS MUCH LESS VISCOSUS**

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Many biologics, particularly monoclonal antibodies, are dosed at several mg/kg of body weight, resulting in doses of 500 mg or more. Consequently, high-concentrations are required for subcutaneous administration, which is limited to less than 2 mL of dose volume. At concentrations exceeding 100 mg/mL, many biologics are highly viscous, and can suffer stability and opalescence problems. Formulation designs targeting the protein-protein interactions mediating these problems can produce highly-concentrated drug products with good stability, syringeability, and injectability characteristics. These advanced high-concentration formulations allow biologics that would otherwise be dosed by i.v. infusion to be administered by s.c. injection, or delivered by low-volume devices.
A SENSITIVE IMMUNOASSAY FOR THE DETECTION OF LOW MOLECULAR WEIGHT PROTEINS AND PEPTIDES

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Low molecular weight proteins and peptides perform numerous regulatory roles in biological systems and could be useful as biomarkers. Hence qualitative and quantitative measurements of peptide levels have become increasingly important. This study aims to develop a sensitive dot immunoblot assay (DIA) by modifying existing protocols. Aliquots of 0.2µl, 0.5µl and 1µl synthetic FMRFamide neuropeptide were spotted on 0.2µm nitrocellulose membrane. The membrane was air-dried at room temperature for 30 minutes and baked at 100°C for 30 min to fix the peptides to the membrane. After cooling to room temperature, the membrane was washed for 10 min in a small volume of 0.1M Tris buffer (pH 7.4) with 0.05% Tween 20 (v/v; buffer 1), then incubated for 60 min in a blocking solution containing 3% BSA in 0.1M Tris buffer (pH 7.4). The membrane was then incubated overnight in anti-FMRFamide polyclonal antibody (1:10,000 in buffer 1) and washed 3 times for 5 min each in buffer 1 before incubation in Alkaline Phosphatase-conjugated goat anti-rabbit secondary antibody (1:500 in buffer 1) for 1 hour. Membrane was washed again 3 times for 5 min each in buffer 1 and developed with NBT/BCIP (1:100 in development buffer). After about 15 minutes, membrane was washed in distilled water, air-dried and photographed. Results indicates that the technique could measure up to 33.4fmole (33.4 x 10^-15) of FMRFamide peptide with a sample volume of 0.2µl. The sensitivity of this protocol is thus comparable with that of ELISA or radioimmunoassay techniques, with the additional advantage of simplicity, speed, small sample volume, low cost and production of non-hazardous waste. This DIA protocol might be useful in resource-poor settings and laboratories with low budgets.

Keywords: Peptides, dot immunoblot assay, FMRFamide.

OCULAR HAEMODYNAMIC PARAMETERS OF ASYMPTOMATIC HAART-EXPERIENCED HIV-INFECTED UNDER-FIVE CHILDREN


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Background: Africa has the highest number of HIV/AIDS infected persons and increasing access to HAART. HAART’s impacts on eyes are yet to be documented.

Objectives: Study aimed at evaluating HAART’s impacts on retinal blood flow (RBF).

Method: Thirty asymptomatic HAART-experienced HIV-infected children (aHHC) and three seronegative children (SC) among 60 convenience-sampled under-fives fulfilled conditions for ocular ultrasonography. Ocular ultrasonography was done on participants in supine position with closed-eyes. Maximum velocity (Vmax), pulsatility index (PI), resistive index (RI), optic nerve diameter, lens thickness and axial diameter were measured. Results of aHHC were not compared with SC because of unequal size. Data were analysed by using ANOVA and level of significance was considered at p<0.05.

Results: Vmax of RBF in central retinal artery (CRA) of aHHC was 12.2cm/s while that of SC was 13.4 cm/s. The PI and RI of RBF in CRA of aHHC were 0.8 and 0.5 respectively while SC had 0.6 and 0.4 respectively. Vmax of RBF of CRA was significantly associated with increased PI and RI.

Discussion: Vmax of CRA of aHHC was reduced because of increased PI and RI suggesting an increased resistance to RBF in aHHC.
**Conclusion:** Reduced Vmax of RBF of CRA was significantly associated with increased PI and RI of aHHC.

**Keywords:** Ophthalmic artery, Central retina artery, Maximum velocity, Seropositive children, HAART.

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**SL-133**

**Track:** Enabling Technologies

**LIVE CELL PARTIAL WAVE SPECTROSCOPIC MICROSCOPY: REAL-TIME IMAGING OF THE CELLULAR NANO-ARCHITECTURE**


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In biological systems, structure is tightly bound to molecular function. In chromatin, which houses most genes, *ex vivo* evidence is increasingly showing that regulation of critical processes including gene transcription, DNA replication, and DNA repair depend on the local nanoscopic topology. Further, recent data has shown that the organization of chromatin ranging from the nucleosomal (10nm) to the chromosomal (>200nm) is a critical regulator of these functions and are frequently transformed during tumor formation. To date, only super-resolution fluorescent techniques such as STORM or STED can study these molecules in live cells below 200nm. However, due to the high laser intensities needed and the toxicity inherent to fluorescent dyes these techniques may alter the native structure under study. Here we present an extension of Partial Wave Spectroscopic (PWS) Microscopy, a label-free imaging technique previously demonstrated to detect nanoscopic changes in cells during carcinogenesis, to study live cells. Using live cell PWS, we investigate the real-time behavior of chromatin due to UV-induced DNA damage, in relation to cellular ionic conditions, and mitochondrial function. Given its capability to directly measure the nanoscopic organization of cellular structures, live cell PWS allows real-time study of the structure-function relationship in cells without perturbation.

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**SL-7**

**Track:** Nutraceutical Drug Discovery & Therapy

**CASES OF NON-ANTIBODY-MEDIATED SKIN DISORDERS ASSOCIATED WITH HYPERHOMOCYSTEINEMIA TREATED WITH HIGH DOSE FOLIC ACID, VITAMINS B6 AND B12**

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Published reports show daily folic acid (FA) (5-7 mg) with vitamins B6 (100 mg) and B12 (1000 mcg) improves psoriasiform contact dermatitis [1] and palmar plantar pustulosis [2]. Psoriasis cases have been published [3] and presented [4] some also shown that flared on 1-2 mg daily FA, B6 and B12 yet improved when the folic acid dose was increased to 4-7 mg [4]. Five mg FA, B6 and B12 were added to patients on 16 weeks of adalimumab, 2 of 7 patients’ psoriasis worsened. Both had body mass indices under 24 and baseline vascular endothelial growth factor levels at or above 140 pg/ml [5, 6]. Lower doses of FA can be pro-inflammatory through creation of monomeric endothelial NOS. High doses can be anti-inflammatory through anti-inflammatory conjugated eNOS, BH4 recycling and deactivation of peroxynitrite derived radicals.
Homeocysteine (Hcy) reduces expression of VEGF-A and VEGFR-2. Reducing Hcy with 1-2 mg daily FA may promote psoriasis by allowing VEGF effect to act unopposed [5,6].

Reducing or stopping these high FA doses may place a patient at risk for comorbid events due to the passage through pro-inflammatory FA levels. The safety of stopping this therapy requires study.

FINANCIAL CONFLICTS OF INTEREST

Aronson Peter J: Investigator initiated Study: A single center open-label study to Assess the effects of the addition of modulators of homocysteine to adalimumab in the treatment of moderate to severe plaque psoriasis. Abbott Pharmaceuticals(ABBVIE), HUM 07-035, clinicaltrials.gov NCT10704599. OBSERVE 5: 5 year safety study of etanercept for moderate to severe plaque Psoriasis. Amgen. Clinicaltrials.gov. NCT00322439. Note: permission from Amgen was obtained to use the etanercept case for this manuscript.

REFERENCES


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**SL-137**

**Track: Enabling Technologies**

**CHROMATIN PROTECTIVE THERAPIES: SYSTEMS THERAPEUTICS FOR INCREASED CHEMOTHERAPEUTIC EFFICACY**


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Ovarian cancer remains one of deadliest cancers among women. Despite successive rounds of treatment, cells can evade chemotherapies thus limiting chemotherapeutic efficacy. We present a class of adjuvants, Chromatin Protection Therapies (CPTs), which modify the physical nano-architecture of chromatin to prevent the ability of malignant cells to transform their transcriptome during treatment with existing chemotherapeutic compounds. We utilized state-of-the-art live cell Partial Wave Spectroscopic (PWS) microscopy to monitor changes in the physical structure of chromatin in wild type and mutant ovarian carcinoma cell (OCC) lines upon treatment with potential CPTs. These measurements of nanoscale chromatin topology reflect chemotherapeutic efficacy and drug resistance. Critically, compounds that reduced chromatin heterogeneity made cells more susceptible to traditional chemotherapies. For instance, our results show that Celecoxib and Digoxin, compounds with vastly different mechanisms of action, can regulate chromatin structure within minutes of treatment. While mono-treatment with these CPTs did not increase cell death, the combination therapy with traditional agents greatly expanded their therapeutic efficacy. For example, we observed 100% clearance in both OCC lines that were co-treated with Digoxin and Paclitaxel. This work demonstrates a new paradigm in tumor intervention and a high-throughput, low cost method for identification and development of adjuvant onco-preventative agents.
SL-20

Track: Systems Biology in Drug Design

ON P53 REVIVAL USING SYSTEM-ORIENTED DRUG DOSAGE DESIGN AND PULSATION

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We propose a new paradigm in the drug design for the revival of p53 pathway in cancer cells. It is shown that the current strategy of using small molecule based Mdm2 inhibitors is not enough to adequately revive p53 in cancerous cells, especially when it comes to extracting pulsating behavior of p53. This fact has come into notice when a novel method for the drug dosage design is introduced using system oriented concepts. As a test case small molecule drug Mdm2 inhibitor Nutlin 3a is considered. The proposed method determines the dose of Nutlin to revive p53 pathway functionality. For this purpose PBK dynamics of Nutlin have also been integrated with p53 pathway model.

p53 pathway is the focus of researchers for the last thirty years for its pivotal role as a frontline cancer suppressant protein due to its effect on cell cycle checkpoints and cell apoptosis in response to a DNA strand break. This is the reason for finding p53 being absent in more than 50% of tumor cancers. Various drugs have been proposed to revive p53 in cancer cells. Small molecule based drugs are at the forefront and are the subject of advanced clinical trials. The dosage design of these drugs is an important issue. We use control systems concepts to design the drug dosage so that the cancer cells can be treated in appropriate time. We investigate by means of a computational model how p53 protein responds to drug Nutlin 3a, an agent that interferes with the MDM2-mediated p53 regulation. The proposed integrated model describes in some detail the regulation network of p53 including the negative feedback loop mediated by MDM2 and the positive feedback loop mediated by Mdm2 mRNA as well as the reversible inhibition of MDM2 caused by Nutlin. The reported PBK dynamics of Nutlin 3a are also incorporated to see the full effect. It has been reported that p53 responds to stresses in two ways. Either it has a sustained (constant) p53 response or there are oscillations in p53 concentration. The claimed dosage strategy achieves the p53 response in the first case. However, for the induction of oscillations, it is shown through bifurcation analysis that in order to achieve oscillating behavior of p53 inhibition of Mdm2 is not enough, rather antirepression of the p53-Mdm2 complex is also needed which leads to the need of a new drug design paradigm.

Keywords: p53, Mdm2, Cancer, Nutlin, PBK, Drug dosage.

SL-131

Track: Genomics

THREE-DIMENSIONAL INTERACTIONS OF GENETIC VARIANT RS1165505 AT THE BRCA1/NBR2 BI-DIRECTIONAL PROMOTER IN NORMAL AND CANCER HUMAN CELLS

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Expression of the BRCA gene 1 is involved in aetiology of familial and non-familial (sporadic) breast cancers and is critical for the majority of chemotherapy. The higher cancer risk among BRCA1 mutation carriers with a strong family history, suggests that genetic variants-modifiers of BRCA1 also have an impact on breast cancer risk. As has been reported, complex genetic relationships, including parent of origin effects may significantly influence the contribution of a particular genetic variant to the risk of disease and produce asymmetry in family history (e.g., skewing it toward maternal versus paternal lineage). We previously obtained suggestive evidence, that minor (T) allele and minor genotype (TT) of polymorphic variant rs1165550565 are associated with breast cancer risk in women with a reported maternal history. The variant falls into the regulatory region, (bi-directional promoter and enhancer) for the BRCA1 gene and the LcnRNA NBR2. Recent studies found multigene complexes of interacting promoters with correlated expression levels in the 3D space of the nucleus, which may suggest
the existence of a so-called “matrix of expression regulation”. Here we present the results of the analysis of available Hi-C and ChIA-PET data supplemented with DHS-linkage in order to characterize functional significance and genetic interacting partners of variant rs11655506 at the BRCA1/NBR2 promoter. Given the crucial role of BRCA1 in genomic integrity and the involvement of LncRNA NBR2 in kinase signaling and metabolic stress response, multigene complexes of the BRCA1 / NBR2 promoter are a potential targets for therapy.

**SL-49**  
*Track: Biologics*

**BIOSTRUCTURE-GUIDED DESIGN OF NOVEL AND CNS-BIOAVAILABLE OXIME REACTIVATORS OF GF-INHIBITED AChE**

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Crystal structures of GF-inhibited murine AChE and molecular docking simulations of novel oxime compounds using our Rhodium platform will be compared. Docking experiments and crystal structures demonstrate that, unexpectedly, some of our intended reactivators docked and also crystallized in unproductive poses, wherein the functional oxime group was oriented away from the target active site and toward the opening of the mAChE enzyme pocket. In the case of functional reactivators, the poses are in generally in agreement with crystal structures. Templates derived from initial docking experiments on HI-6 were used to guide the re-direction of polar contacts, leading to new structural series that were subsequently developed by incorporating features of Tacrine and 1 Donepezil. Ternary crystal structures of mAChE, GF, and our novel reactivators will be presented.

**SL-110**  
*Track: Drug Metabolism*

**BUILDING METABOLISM IN THE DRUG STRUCTURE: RECENT DEVELOPMENTS IN THE SOFT DRUG APPROACH**

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Incorporating a designed metabolic pathway into the structure of new drugs is an important, but often overlooked aspect of drug design. Because both soft drug (SD) and prodrug approaches rely on predesigned metabolic pathways (most often involving hydrolytic degradation), they tend to be confused even though they are conceptual opposites. Prodrugs are pharmacologically inactive and are converted into the active drugs by a predesigned mechanism, whereas soft drugs are active therapeutic agents and are converted into inactive metabolites in a predictable and controllable manner after exerting their desired therapeutic effect. SDs can be designed for almost any therapeutic application, but they are particularly well suited for cases where the desired activity is localized, relatively short-lived, or susceptible to easy titration. Here, the major aspects of rationally designed SDs that are already approved for clinical use (e.g., clevidipine, esmolol, laniodiol, loteprednol etabonate, and remifentanil) will be reviewed together with others that are still in clinical development (e.g., remimazolam and AZD3043) or can be considered as ‘accidental’ SDs (e.g., articaine and methylphenidate).
E-PODOFAVALIN-15999: BIOLOGICAL PROPERTIES AND PHARMACOGENETICS IN PARKINSON’S DISEASE

Ramón Cacabelos

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E-PodoFavalin-15999 (Atremorine®) is a novel biopharmaceutical compound, obtained by means of non-denaturing biotechnological processes from structural components of Vicia faba L., for the prevention and treatment of Parkinson’s disease (PD).

Preclinical studies (in vitro) revealed that Atremorine is a powerful neuroprotectant in (i) cell cultures of human neuroblastoma SH-SY5Y cells; (ii) hippocampal slices in conditions of oxygen and glucose deprivation; and (iii) striatal slices under conditions of neurotoxicity induced by 6-OHDA. *In vivo* studies showed that Atremorine (i) protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurodegeneration; (ii) inhibits MPTP-induced microglia activation and neurotoxicity in substantia nigra; and (iii) improves motor function in mice with MPTP-induced neurodegeneration.

Clinical studies have been performed in 3 groups of patients: (i) NP: naïve drug-free patients with PD (never treated with anti-parkinsonian drugs); (iii) AP: Parkinsonian patients chronically treated with L-Dopa; and (iii) MX: a heterogeneous sample of patients with Parkinsonian disorders. 30-60 min. after a single dose (5 g) of Atremorine, plasma levels of dopamine increased from 16.71 ± 14.38 pg/mL to 2286 ± 4218 pg/mL (p<0.001) in NP, from 4149 ± 7062 pg/mL to 13539 ± 12408 pg/mL (p<0.001) in AP, and from 860 ± 3445 pg/mL to 4583 ± 8084 pg/mL (p<0.001) in MX patients, with a parallel clinical improvement lasting for 3-6 hrs. Atremorine administration also increased the plasma levels of noradrenaline in NP (p<0.008) and MX (p<0.04), with no changes in AP. Adrenaline and serotonin levels were unchanged. Atremorine induced significant decreases in prolactin levels in NP (p<0.001) and MX (p<0.001), and in growth hormone levels in NP (p<0.003) and MX (p<0.002), with no changes in ACTH, cortisol, LH, FSH, estrogens or testosterone. Some changes in the levels of monoamines and hormones were genotype-specific.

Pharmacogenetic studies indicate that the therapeutic response induced by Atremorine in PD is associated with the pharmacogenetic profile of each patient.

This is the first study on the biopharmaceutical properties and pharmacogenetics of Atremorine in PD after patent application.

THE POTENTIAL TARGETS OF CHINESE MEDICINES IN THE TREATMENT OF PARKINSON’S DISEASE

Zenglin Cai, Xinzhi Zhang, Xiuming Li, Jing Xu, Jingfeng Ming, Yongjin Zhang and Xiaomin L

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This article system reviews the present research situation of the pathogenesis of Parkinson's disease and our recent research over the past decade, to discuss the potential targets of many traditional Chinese medicines in prevention and treatment of Parkinson's disease. Such as, to inhibit aggregate-prone protein aggregation and to promote its degradation, including by autophagy pathway (resveratrol, herbaceous peony and Paeoniflorin) and proteasome pathway (Paeoniflorin? Bilobalide);
inhibition of oxidative stress (Chroogomphus rutilus, Radix Puerariae and Puerarin, Gastrodin); improve mitochondrial energy metabolism (Tripterygium wilfordii and Triptolide); inhibit neuronal immune and inflammatory responses (Polygonatum and Polysaccharides); Reducing neurotoxicity (Tetrandrine); anti-apoptotic (Baicalein) and so on.

With the research and development in PD pathogenesis and clarifying the targets of a variety of traditional Chinese medicine, especially its monomeric components, the development of traditional Chinese medicine in prevention and treatment of PD will have very broad application value and prospect.

Fig. (1). Rapamycin and PF impact on α-synuclein and its degradation pathway Western blots (upper panel) and statistical analysis of optical density measurements (lower panel) in PC12 cells after treatment with MPP+, PF and RAPA for (A) E1; (B) LC3-Ⅱ; (C) P53; (D) α-synuclein. In MPP + group, RAPA increased LC3-Ⅱ, inhibited E1. PF upregulated both LC3-Ⅱ and E1 significantly. Values represent mean ± SEM (n = 5). #p < 0.05, ##p < 0.01 versus control group. *p < 0.05, **p < 0.01 versus corresponding control group.

SL-178
Track: Academic CRO/Industrial Collaborations in Drug Discovery

DIASTEREOSELECTIVE SYNTHESIS OF NOVEL NK₁ RECEPTOR ANTAGONISTS

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NK₁ receptor [1] (G-protein-coupled-receptor) research has been pursued aggressively over the last two decades by several pharmaceutical companies, in an effort to develop drugs that might be useful in a wide range of pathological affections: inflammatory conditions, migraine, emesis, schizophrenia, depression, anxiety, tinnitus, hearing loss, bronchoconstriction and regulation of gastrointestinal effects. Chemical diverse non-peptide NK₁ receptor antagonists have been identified since the discovery of CP-96,345 by Pfizer in 1991 [2]. In 2003 an NK₁ receptor antagonist (Aprepitant) [3] was approved and launched onto the market for the prevention of chemotherapy – induced nausea and vomiting (CINV).

Herein we report part of the work that has been carried out in partnership with Leo Pharma, [4] focused on the identification and synthesis of new NK₁ inhibitors, with potential activity in the treatment of inflammatory skin diseases.

Fig. (1).
A bicyclic core, containing the piperazine ring (Fig. 1), has been designed and synthesized through a diastereoselective approach. The synthesis involved two crucial cyclization steps: a first step mediated by [bis (trifluoroacetoxy)iodo]benzene (PIFA) [5] and a second condensation step that gave as product only the ANTI-derivative.

REFERENCES


SL-115

Track: Cancer Targeted Drug Delivery

ACTIVATED SALIVARY MMP-2: A POTENTIAL BREAST CANCER MARKER

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MMP-2 is strongly associated with the progression of malignancy of several types of carcinoma. It has been reported that MMP-2 is involved in the pathogenesis of breast cancer. Human saliva is a biological fluid of varying diagnostic potential with several advantages. The main objective was to detect and compare MMP-2 expression and activity in biological fluids in pre and post surgical conditions using non-invasive method. Here we report that saliva of breast cancer patients before surgery show highly active MMP-2 compare to postsurgical (same patients) and normal (non cancerous) individuals. Expression of activated salivary MMP-2 may be a potential marker for breast cancer. Interestingly the urine of the same breast cancer patients showed no MMP activity. The TIMP-2 conc in saliva is much higher in post surgical condition than pre surgical condition. The VEGF conc in saliva is much higher in pre than post surgical condition. Aims-Detection and comparison of MMP-2 expression and activity in saliva of breast cancer patients in pre and post surgical conditions of the same patients. Methods-Zymography, Immunoblot, ELISA. Results-Highly active MMP-2 detected in saliva of breast cancer patients before surgery compare to post surgical condition in the same patients. Conclusion-Activated salivary MMP-2 of breast cancer patients could be a potential breast cancer marker using non invasive method.

SL-180

Track: Green Techniques for Medicinal Chemistry

RAPID DETECTION OF IN-VIVO SENSITIVITY OF A MICROORGANISM TO AN ANTIMICROBIAL AGENT

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Conditions like septicaemia become fatal due to delay in antibiotic sensitivity detection. Conventionally, antibiotic sensitivity detection is taken around 48 to 72 hours. In the meantime people suffering from septicaemia develop toxicity in blood which affects major organs resulting in organ failure and finally mortality. Moreover the antibiotic sensitivity result as obtained from the conventional laboratory testing often does not match with the in vivo condition. One of the reasons of
this deviation in antibiotic sensitivity *in vivo* and *in vitro* is the fact that the clinical condition is due to pathogenic microbe in biofilm, which is many folds more resistant than the data obtained from the antibiotic testing done using planktonic/free floating cells. Hence the accurate prediction of antibiotic sensitivity is a major concern for treatment by the clinician. The purpose of this study was to rapidly detect whether a selected antibiotic was working in case of infection. This could be done following detection of bacterial contamination in blood. Mouse model was used in this study for detection of antibiotic sensitivity through monitoring of the reversal of WBC shrinkage as a result of administration of antibiotic. The WBC shrinks during blood infection (septicaemia) (Fig. 3). This shrinkage was observed to be reversible upon treatment with antibiotic to which the pathogen was sensitive. Moreover this approach was also used to detect antimicrobial effect of phytochemicals against multidrug resistant microbes. This study can be conducted in case of human subjects undergoing antibiotic therapy. Blood sample can be drawn hourly from the Intravenous channel post administration of the antibiotic. Within 3 hours the positive response to the antibiotic can be detected if administered at the right dose. In case the test fails to show any result, it is time for the clinician to understand that the antibiotic is not working in the present case. Similarly efficacy of phytochemical drugs was also tested in a bacterial infection model in mice.

Neutropenic mice infected with *P. aeruginosa* showed a mean decrease of ~20% in WBC size at 24 h PI (post infection), which corresponded with the increase in mean bacterial numbers (1.14 Log_{10} CFU/ml) during the same period. The decrease in WBC size upon infection was consistent with *in vitro* observations. In the efficacy experiment, Ciprofloxacin at 10 mg/kg showed significant efficacy relative to vehicle control, with a mean Log_{10} CFU/ml reduction of 2.2 at 10 h PI, compared to 2 h PI. This was also reflected in the prevention of WBC size decrease through the treatment with ciprofloxacin. The phytochemical showed significant dose dependent efficacy (*P*<0.001) at doses of 1000 and 2000 mg/kg at 10 h PI (8 h post treatment) compared to vehicle. The mean WBC size in the groups treated with the phytochemical was not significantly different from the uninfected control at 10 h and 26 h PI. In summary, the phytochemical showed a significant dose dependent increase of mean WBC size post treatment which corresponded with its bacteriostatic efficacy in neutropenic mice infected with *P. aeruginosa*. The reversal of shrinkage could be detected as early as 3 hours post administration of antibiotic. Hence this technique could minimize the mortality due to septicaemia by reducing the 48 to 72 hours delay in sensitivity detection to 3 hours as shown in the figure below. This novel approach for antibiotic sensitivity detection has been filed as an Indian patent (201631003917 dated 3rd Feb 2016) (Figs. 1 and 2).

![Fig. (1)](image1.png) Mean WBC size in neutropenic mice blood over time following infection with *P. aeruginosa*. Error bars indicate the SEM.

![Fig. (2)](image2.png) Mean Log_{10} CFU of *P. aeruginosa* in neutropenic mice blood over time following treatment with ciprofloxacin and phytochemical. Error bars indicate the SEM. The arrow on the X axis indicates the time of commencement of treatment (Rx).
Fig. (3). Photomicrographs of WBCs stained with Leishman’s stain. A) Uninfected mice; B) Mice infected with *P. aeruginosa*. Magnification 100 X.

Cell sizes were determined using Mshot® micrometry - diameter of each cell was measured in 3 axes indicated as red lines.

**SL-190**

*Track:* In-Silico Drug Design and In-Silico Screening

**VARIABLE SELECTION IN NEAR INFRARED SPECTROSCOPY FOR THE REAL-TIME QUANTITATIVE ANALYSIS IN PHARMACEUTICAL TECHNOLOGY**

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Near infrared spectroscopy is suitable for analyzing solid, liquid and biotechnological forms in pharmaceutical industry in a fast and non-destructive manner. Before building regression model for predicting property values, redundant information in input variables are normally removed either by using feature extraction or feature selection method. In this talk, a method based on physarum network will be introduced for the variable selection. This method can be used together with traditional feature extraction or feature selection method to further remove redundant information thus to simplify the prediction model and save the computational time.

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**SL-53**

*Track:* Biologics

**X-RAY CRYSTAL STRUCTURES OF A NOVEL HUMAN ACETYLCHOLINESTERASE CATALYTIC BIOSCAVENGING SYSTEM FOR TREATMENT OF ORGANOPHOSPHATE POISONING**

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Medical countermeasures against organophosphate poisoning are still in active development. A prophylactic strategy involving recombinant human acetylcholinesterase mutants paired with reactivators may circumvent practical limitations of traditional approaches. Functioning as a catalytic bioscavenger, this approach would not be limited to one-to-one reaction stoichiometry as is butyrylcholinesterase, would be less likely to trigger an adverse immune response expected with use of non-mammalian proteins, and would not need to cross the blood brain barrier to be effective. We have
determined high resolution crystal structures of the aging-resistant human acetylcholinesterase Y337A/F338A mutant in complex with the conventional oxime H16, and the novel pyridinium-imidazole aldoxime RS2-170B. This mutant exhibits enhanced rates of reactivation compared to the wild-type enzyme. Our structural studies reveal an enlarged active site gorge that allows reactivators to bind with better access to the organophosphate conjugate, elucidating an atomic basis for enhanced reactivation and providing a platform for structure based drug design.

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**SL-50**

*Track: Hot Topics in Natural Products*

**ETHNO-PHARMACOLOGICAL PROPERTIES OF FRUIT EXTRACTS OF WAN KHAN MAK (AGLAONEMA SIMPLEX BL.)**

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Wan Khan Mak (WKM; Aglaonema simplex Bl.) has been referred to possess anti-allergy and longevity properties. Nevertheless, there is still no studies of ethno-pharmacological properties of WKM. This study aimed to investigate the phytochemicals and explore anti-oxidant, anti-allergic and anti-inflammatory activities of 95% ethanol extract of dried fruits of WKM. The results suggested that the contents of total phenolics, flavonoids, and proanthocyanidins in the extract were 56.73 ± 0.37 mg GAE/g dry extract, 5.03 ± 0.03 mg CE/g dry extract, and 7.02 ± 0.12 mg CE/g dry extract, respectively. The extract possessed fairly anti-oxidant activity as evaluated by the DPPH radical scavenging activity and the reducing power in the FRAP assay. Importantly, WKM extract effectively attenuate tBuOOH-induced intracellular oxidative stress in RAW264.7 cells using the DCFH-DA fluorescent probe. *In vitro* anti-allergic activity of the extract was evidenced by a dose-dependent suppression of DNP-BSA-induced degranulation of RBL-2H3 cells. At non-toxic concentration, the extract also significantly and dose-dependently suppressed NO production in LPS plus IFN-γ-stimulated RAW264.7 cells. The anti-inflammatory property of the extract was further supported by a concomitant dose-dependent suppression of iNOS and COX-2 protein expression in the stimulated RAW264.7. Overall, the results suggest that WKM is a source of natural antioxidants with anti-allergic and anti-inflammatory properties.

**Keywords:** Aglaonema simplex Bl., NO, iNOS, COX-2, anti-oxidant, anti-allergy, anti-inflammatory.

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**SL-85**

*Track: Inflammation and Immunology*

**RESOLVIN D1: A BIOACTIVE LIPID DERIVATIVE AS AN ADJUNCT PERIOPERATIVE THERAPEUTIC APPROACH FOR THE TREATMENT OF BREAST CANCER METASTASES**

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**Introduction:** Breast cancer is the most common cancer affecting women worldwide. Surgery remains the appropriate treatment for most breast cancers however removal of the primary tumour increases the formation and growth of metastases. The perioperative period, a time of extensive paracrine, endocrine, and immunological distress, offers a therapeutic window to improve patient outcomes with adjuvant treatment. The omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), inhibit the growth of human breast cancer cells in animal models. Resolvin D1 (RvD1) is a stereospecific lipid derivative of DHA and a potent anti-inflammatory agent. We hypothesis that lipid mediators can alter immune tolerance and augment anti-tumour immune responses at the time of surgery.
Results: In vitro studies demonstrate that RvD1 suppresses breast cancer cells invasive and metastatic potential by modulating tumour cell adhesion receptor expression and MMP 9 production. RvD1 reversed L-selectin shedding from human neutrophils induced by breast tumour conditioned medium. L-selectin shedding is the first step in the extravasation process which initiates tethering to the endothelial surface of the blood vessel. Interestingly RvD1 had no effect on IL-1b stimulated L-selectin shedding from neutrophils suggesting that RvD1 mediated inflammatory resolution feedback loops respond differently to different stimulatory signals. This data suggests that RvD1 may reduce tumour cell mediated inflammatory responses yet preserve infection mediated responses. Epigenetic data suggests that RvD1 treatment may alter miRNA expression of 4T1 cells. In a pilot in vivo metastatic study using the murine tail vein injection model RvD1 treatment (200ng/day/IP/8 days) significantly reduced lung metastasis of 4T1 breast tumour cells.

Conclusion: During surgical excision mechanical manipulations disrupt the structural integrity of the tumour and the blood vessels feeding the tumour which increases shedding of malignant cells into the blood and lymphatic circulations. Surgery augments the invasion capacity of free malignant cells by inducing the release of MMPs, and by enhancing adhesion-molecule expression on tumour cells. Our results demonstrate that RvD1 can prevent tumour cell adhesion receptor expression and MMP-9 production. RvD1 may be working in a negative feedback loop involving miRNA expression. RvD1 treatment reduced lung metastasis in vivo. In clinical practice, breast cancer surgery is a component of an integrated system of practice, and in this context, adjunct immunomodulation with lipid mediators may be a useful therapy to augment host anti-cancer defence mechanisms essential in the perioperative period. The immune system regulates many tumorigenic processes, and a better understanding of the cellular relationships driving metastases could yield potential adjunct immunomodulatory therapies.

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SL-140

Track: CNS Drug Discovery & Therapy

EVIDENCE FOR A NEUROPROTECTIVE microRNA PATHWAY IN AMNESIC MILD COGNITIVE IMPAIRMENT

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The widespread influence of small, noncoding microRNA (miRNA) regulation on neuronal physiology suggests that perturbations in miRNA function might be involved in the pathogenesis of complex neurodegenerative disorders such as Alzheimer’s disease (AD). Indeed, AD brains display altered expression of several miRNAs that regulate the β-secretase BACE1, a key enzyme involved in the generation of β-amyloid plaque pathology. However, whether miRNA networks are dysregulated in the brains of people in the prodromal stages of AD such as amnestic mild cognitive impairment (aMCI) and the extent to which these changes have physiologic consequences for the onset of AD remain underexplored. To begin to address these knowledge gaps, we performed large-scale microarray and quantitative PCR (qPCR) studies to compare the levels of miRNAs in postmortem frontal cortex tissue from Rush Religious Orders Study participants who died with an antemortem clinical diagnosis of no cognitive impairment (NCI, n = 12), aMCI (n = 10) or early-stage AD (n = 10). Of note, two functional miRNA families, miR-212/132 and miR-23a/b, were significantly decreased ~40-50% in frontal cortex of aMCI and AD subjects compared to NCI (p < 0.01). Surprisingly, human miRNA databases revealed that down-regulation of either miR-212/132 or miR-23a/b was predicted to up-regulate the deacetylase sirtuin 1 (sirt1), which mediates neuroplasticity and neuroprotective cell stress responses. To this end, qPCR studies using the same frontal cortex samples revealed that sirt1 mRNA levels were ~50% higher in aMCI compared to NCI subjects (p < 0.01). Given the relatively delayed involvement of frontal cortex in AD pathogenesis and the ability of this region to respond to the onset of dementia by neuronal reorganization, these data suggest that miRNA-mediated up-regulation of sirt1 might represent a compensatory response to mounting disease processes. To explore this hypothesis mechanistically, in vitro studies using human hNT neuronal cells showed that the coordinated experimental down-regulation of miR-212 and miR-23a increased sirt1 protein expression by ~100% (p < 0.01). Moreover, down-regulation of miR-212 and miR-23a provided ~80% neuroprotection when the cultures were challenged with toxic β-amyloid (p < 0.01), and this effect was reversed in the presence of the sirt1 inhibitor EX527. Taken together, these data suggest that we have uncovered a novel miRNA-
mediated neuroprotective pathway activated during prodromal AD. These findings may reveal new mechanistic insights into gene regulation pathways in AD leading to innovative therapeutic avenues for modifying disease progression.

Support: NIH AG042146, AG014449, Brinson Foundation.

**SL-47**

*Track: Protein and Peptide Sciences*

**DEVELOPMENT OF AN EFFECTIVE PROTEIN VACCINE AGAINST GRAM NEGATIVE INFECTIOUS AGENTS**

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As a new approach to developing vaccines against Gram-negative bacteria, the extracellular proteins produced by *Salmonella enterica* serovar Typhimurium LT2 were collected during exponential growth in M9 medium. The cells were removed by centrifugation, the supernatant fluid filtered through a 0.45 µm PVDF filter and passed over a Polymyxin B affinity resin to remove lipopolysaccharide (LPS). The protein mixture was dialyzed against saline (PBS) and filter sterilized. Male CD-1 mice (35 – 50 g) were vaccinated with 200 µl of the protein mixture injected into the peritoneal cavity. Controls consisted of mice sham vaccinated with a sterile solution of bovine serum albumin (BSA) in PBS. The total protein administered per animal was ~ 2 – 3 µg. After boosting, the animals were challenged on day 36 with virulent *S. typhimurium* strain 14028s. The cells were harvested at mid-exponential phase, washed and suspended in sterile PBS, with 2 x 10^4 total cells administered in 200 µl into the peritoneal cavity. The controls became ill on day 2 and started dying on day 3. The vaccinated mice showed no signs of illness over a three week period, at which time the trial ended. Additional vaccines were prepared in an identical manner from other bacterial species, including Gram-positive organisms. The results showed that vaccinated mice were protected from lethal challenges ranging from complete to partial protection. In addition, cross protections were noted. For example, mice vaccinated with a *Staphylococcus aureus* (MRSA) prepared vaccine were completely protected from lethal *S. typhimurium* challenge. Western blot analysis showed a conserved protein common to all bacteria tested suggesting that a single common protein was responsible for these protective effects. Current research continues on the identification of this active component, along with a strategy to characterize the active protein component using molecular modeling.

**SL-159**

*Track: Drug Delivery & Targeting*

**COATING SILICA PARTICLES ON ELONGATED MICROPARTICLES TO ENHANCE SKIN DELIVERY**

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Nanoparticles have been increasingly used to improve the therapeutic value of various drugs and bioactive molecules. However, nanoparticle penetration into the skin is not feasible through topical application alone. Physical penetration enhancing techniques such as elongated microparticles have been proven to significantly enhance topical nano-and microsphere delivery in an in vivo porcine model. This study developed formulations to coat nanoparticles (50nm, 200nm and 500nm) on elongated microparticles to obtain a dry formulation. It was shown that coating nanoparticles on elongated microparticles enhanced the delivery of nanoparticles into the skin. These dry forms also offer advantages over the wet form in term of storage and usage. Crosslinking between alginate and calcium chloride formed a coating layer which dissolves slowly thus prolong the release if a therapeutic
drug is loaded into the silica particles or directly coating on the surface of elongated microparticles. Nanoparticles ranging from 50 to 200nm usually cover size of many vaccines so this coating technique can be developed for dry vaccination.

**SL-167**

Track: Inflammation and Immunology

ANTI-INFLAMMATORY AND IMMUNOMODULATORY PROPERTIES OF MP-012: A COMPOUND ISOLATED FROM RHODOPHALA BIFIDA

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**Background/Purpose:** MP-012 is a compound isolated from Rhodophalia bifida, a plant used in folk medicine but never before tested in inflammatory diseases. Based on this, the purpose of the work was to evaluate the effect of MP-012 as an in vivo anti-inflammatory therapy in Antigen-induced Arthritis (AIA) and Collagen-induced Arthritis (CIA) models, and to characterize its effects on immune and hematologic phenotypes in vivo and in vitro, including fibroblast-like synoviocytes (FLS) invasiveness.

**Methods:** AIA was induced in 24 Male BALB/c mice with methylated bovine serum albumin (mBSA) and mice were divided into 4 groups: vehicle (saline) or MP-012 at 0.3, 1 or 3 mg/kg given as a twice-daily intraperitoneal dose. Treatment started one day before the intra-articular injection of mBSA. Paw nociception at 0, 3, 5 and 24 hours and leukocytes migration into the knee joints at 24 hours were evaluated. DBA/1J mice were induced with CIA and divided into a preventive (n=24; 16 days at 0.05; 0.25 and 0.5 mg/kg) or therapeutic group (n=23; 10 days of treatment at doses 0.5 and 1.5 mg/kg starting after the onset of arthritis). BALB/c controls (n=36) were treated for 14 days at doses 0.05, 0.5 and 1.5 mg/kg and hematology, cytokine profile, leukocyte subpopulation and histopathology of lymphoid organs were evaluated. MP-012 1μM was used for lymphocyte proliferation assay with ConA (n=7). FLS invasion over 24 hours was assayed in a transwell Matrigel-coated chamber in the presence or absence of MP-012 1μM (n=5). Statistical analysis: ANOVA or t-test.

**Results:** In AIA MP-012 decreased leukocyte articular migration in a dose-dependent manner by as much as 90% (3mg/kg: 4.15±1.46x10⁴ leukocytes/cavity) compared with vehicle (43.5±9.73x10⁴ leukocytes/cavity) (p<0.001) and reduced nociception in all doses at 5 and 24h (p<0.01), compared with vehicle. In the CIA preventive treatment with MP-012 0.25 and 0.5 mg/kg also significantly reduced CIA joint severity score by as much as 39% compared to vehicle in the therapeutic arm (treatment after disease onset), an effect that was noticed as early as day 3 and persisted throughout the observation period (p<0.05). MP-012 0.5mg/kg also significantly reduced CIA joint severity score by as much as 39% compared to vehicle in the therapeutic arm (treatment after disease onset), an effect that was noticed as early as day 3 and persisted throughout the observation period (p<0.05), with reduced histology damage (p<0.03). Nociception was significantly reduced at days 2 and 10 (p<0.05) compared with vehicle. MP-012 inhibited lymphocyte proliferation stimulated with ConA by 54% (p<0.01). MP-012 1μM decreased FLS invasion by 54% (p<0.05). MP-012 did not have any significant effect on the hematologic and immunological parameters analyzed.

**Conclusion:** MP-012 significantly improved experimental arthritis reduced joint damage and nociception in both acute and chronic models. Moreover, MP-012 reduced lymphocyte proliferation and FLS invasion; two processes implicated in RA pathogenesis and did not have any obvious toxicity. These results suggest that MP-012 has the potential to become a new class of drugs to treat inflammatory and autoimmune diseases such as arthritis.

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MOLECULAR MODELING AIDED DESIGN TO MITIGATE hERG LIABILITY

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hERG (human ether-a-go-go related gene) encodes for a protein known as Kv11.1 and its inhibition can lead to QT syndrome which is a lethal phenomenon. Thus, hERG inhibition is an undesirable off-target effect that should be minimized or eliminated during lead optimization. In this presentation, two examples will be presented to show how to use molecular modeling to help mitigate hERG liabilities while maintaining on-target potency: 1) Structure-based design of potent soluble epoxide hydrolase inhibitors with improved hERG profile; 2) Use of molecular modeling aided design to dial out hERG liability in adenosine A2A receptor antagonists. The strategies present in the modeling work can be applied to other medicinal programs to help improve their safety profile.

MULTI TARGET TREATMENT OF HEPATIC ENCEPHALOPATHY, POSSIBLE MECHANISMS OF SYNERGISTIC ACTION OF THE SUBSTANCES INCORPORATED INTO COMPLEX FORMULATIONS

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Current State of the Problem: Hepatic encephalopathy (HE) affects millions people around the world and develops in more than 50% of patients with cirrhosis. I. Pavlov and M. Nenski were the first (1893-96), who developed portacaval shunt and discovered neurological alterations produced by ammonia. Modern therapeutic options of HE treatment are founded on S. Sherlock, W. McDermott and their colleagues works and directed towards the treatment of precipitating factors and reduction of circulating ammonia and glutamine. New «neuroprotective strategies» are mostly based on application of the inhibitors or antagonists of multiple proteins, attacked by ammonia or related toxins. Systemic application of inhibitors might have side effects.

The Aim and Results: Our aim is to develop a line of complex preparations (in dependence of etiology and stage of HE), comprising compounds, having multiple functions and combined synergistic action on different metabolic and signaling systems, deregulated by ammonia and related toxins. Based on the experiments with animals, brain and liver cells and modeling, we have developed 2 complex compositions. The results of preliminary trials on the patients with HE show that these compositions are effective and don’t have rebound effects after cessation of treatment. Therapeutic effect is preserved during one month of post treatment period.

Conclusion: The etiology of HE is multi factorial and very complex and to address this issue the multi target therapy should be developed.
**SL-61**

*Track:* Biologics

**BENEFITS OF INTEGRATING MEDICINAL CHEMISTRY WITH FUNDAMENTAL SCIENCE: A CASE STUDY OF ACETYLCHOLINESTERASE**

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Through a number of studies, we demonstrate the benefits of using specifically designed ligands as probes in basic studies of molecular recognition and protein function. We also illustrate how ambiguities in the data generated in applied, high-throughput drug discovery programs have the potential to inspire and initiate fundamental studies. Finally, we illustrate how a multidisciplinary and integrated research provides a solid foundation for the development of novel nerve agent antidotes and the discovery of inhibitors selectively targeting the mosquito vectors of malaria and dengue fever.

The essential cholinergic enzyme acetylcholinesterase (AChE) has an uncommon molecular architecture featuring an almost 20 Å deep, sterically restricted, and highly aromatic active site gorge. The molecular recognition between AChE and small molecules is intricate, typically involving multiple transient binding sites, aromatic interactions and non-classical hydrogen. Thus, AChE is interesting for both basic and applied research and an important target for medicinal chemistry and/or 3D-structure driven drug discovery programs.

**Keywords:** Acetylcholinesterase, DFT, Drug discovery, HTS, X-ray crystallography, kinetics.

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**SL-58**

*Track:* Hot Topics in Drug Targets

**MUTANT MITOCHONDRIAL DNA AS A TARGET FOR OLIGONUCLEOTIDE DRUGS**

Romuald Loutre, Ilya S. Dovydenko, Anne-Marie Heckel, Aliya G. Venyaminova, Ivan Tarassov and Nina Entelis

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Mutations in mitochondrial genome (mtDNA) often cause severe cellular respiration defects leading to the onset of many diseases, mostly muscular or neurodegenerative, for which no efficient therapy has been developed. Most of these pathogenic mutations are heteroplasmic, which means that mutant and wild-type genomes are present simultaneously in a same cell. Potential therapeutic strategy could consist in decreasing the proportion of mutant mitochondrial genomes below the pathogenic threshold.

Small RNA molecules are increasingly used in clinical applications. Our team focuses on small non-coding RNAs targeting into mitochondria, a pathway that appears to be the unique natural mechanism to address nucleic acids in these organelles. We have designed mitochondrial RNA vectors that can be used to target oligoribonucleotides with therapeutic potential into human mitochondria. Imported oligonucleotides designed to target pathogenic mutations in mtDNA were able to induce a decrease in the proportion of mutant mitochondrial genomes by stalling their replication (Comte *et al.*, NAR 2013; Tonin *et al.*, JBC 2014). More recently, we described an approach of carrier-free targeting of mitochondria-importable RNA molecules into living human cells by use of oligoribonucleotides conjugated with cholesterol residue through cleavable covalent bonds (Dovydenko *et al.*, Biomaterials 2015).

Alternative strategies aiming to decrease the heteroplasmy level of mtDNA pathogenic mutations in various cell models will be discussed.

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DEVELOPMENT OF HEAT-STABLE OXYTOCIN FORMULATIONS FOR ORAL INHALATION

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Drug delivery by oral inhalation has long been the standard of care for pulmonary diseases like asthma. Recently, however, an inhaled formulation of insulin (Afrezza® inhalation powder; MannKind Corporation) was approved by the FDA for the treatment of diabetes, opening drug delivery by oral inhalation for use in other systemic diseases. Herein, we present work toward developing an orally inhaled oxytocin dry powder formulation. Oxytocin, a peptide hormone, is the first choice among uterotonic agents to prevent post-partum hemorrhage (IV/IM 10 IU). However, access to oxytocin therapy in developing countries, is limited by the requirements for injected delivery and cold chain storage. These limitations result in a higher maternal death rate from post-partum hemorrhage in these countries. Therefore, prototype inhalable oxytocin dry powders were prepared, focusing on excipients that promote oxytocin stability and engineered particles suitable for patient self-delivery by oral inhalation. These powders were evaluated for chemical and physical stability at accelerated conditions, and for pulmonary delivery performance through an inexpensive and robust breath powered Dreamboat™ inhaler. Critical attributes required for powder performance were identified. In vivo systemic drug exposure following pulmonary insufflation was confirmed in rats.

MECHANISM OF EUPHORBIA FISCHERIANA STEUD'S INHIBITION EFFECT ON MALIGNANT MELANOMA

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Euphorbia fischeriana Steud, a traditional Chinese medicine, has been shown to inhibit the growth of various cancers by the induction of apoptosis and cell cycle arrest. The purpose of the present study was to investigate the association between the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway and the inhibitory effect of Euphorbia fischeriana Steud on the growth and metastasis of melanoma B16 cells in vitro, and the underlying mechanisms. MTT assay results indicated that Euphorbia fischeriana Steud inhibited the growth of B16 cells in a time- and dose-dependent manner. Flow cytometric analysis revealed that Euphorbia fischeriana Steud markedly induced apoptosis of the B16 cells, with arrest at the G0/G1 phase of the cell cycle. In addition, in a Transwell assay Euphorbia fischeriana Steud significantly suppressed the migration of B16 cells. Western blot analysis revealed that the expression levels of phosphatase and tensin homolog (PTEN) were upregulated, and the phosphorylation of Akt was downregulated, which resulted in inhibition of the PI3K/Akt signaling pathway and the eventual suppression of its downstream targets, such as matrix metalloproteinase-2 mRNA, in B16 cells. The results demonstrated that Euphorbia fischeriana Steud inhibited the growth and migration of B16 cells, possibly via modulation of the PI3K/Akt signaling pathway and upregulation of PTEN expression levels, in addition to downregulation of p Akt expression. The aforementioned findings suggest that Euphorbia fischeriana Steud may have broad therapeutic applications in the treatment of malignant melanoma.

Keywords: Euphorbia fischeriana Steud, malignant melanoma, PI3K/Akt signaling pathway, traditional Chinese medicine.
**SL-59**

*Track: Protein and Peptide Sciences*

**IMMUNE-MODULATING EFFECTS OF PRE-TREATED MILK-DERIVED BIOACTIVE PEPTIDE QEPV ON LPS-INDUCED INFLAMMATION**

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Milk-derived bioactive peptides are isolated from fermented dairy products. One of the milk-derived bioactive peptides, Gln-Glu-Pro-Val (QEPV) is evaluated on its function. Our results show that QEPV has significant immune-modulating effects both in vitro and in vivo. Pre-culturing with QEPV can promote the proliferation of mouse lymphocytes, of which, the expression of pro-inflammation cytokines such as IL6/IL/12 are significantly reduced, while expression of anti-inflammation cytokine IL-10 is enhanced. Transcription levels of iNOS and COX-2 genes also decrease. QEPV can also inhibit LPS-induced inflammation by regulating the release of NO and the producing of INF-γ, IL-12 and PGE2 in mice that are pre-injected with QEPV. Overall, QEPV has significant immune-modulating effects on lymphocytes and contributes to inflammation treatment as a functional food ingredient.

**Keywords:** Polypeptide, fermented milk, lymphocyte, LPS, inflammation.

**SL-67**

*Track: Protein and Peptide Sciences*

**THE ROLE OF PANCREATIC STELLATE CELLS IN PANCREATIC DISORDERS**

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Abstract Details Normally quiescent pancreatic stellate cells (PSC) become activated in chronic pancreatitis (CP) and pancreatic cancer (PC). PC is characterized by an excessive desmoplastic reaction and a hypoxic microenvironment within the solid tumour mass. The most common form of PC is pancreatic ductal adenocarcinoma. CP patients are at significant risk of developing PC. Activation of PSCs during pancreatic injury induces proliferation as well as secretion of extracellular matrix components, thereby playing an important role in the fibrosis that occurs in CP and PC.

Our new data show that PSCs cells in their normal microenvironment (isolated mouse pancreatic lobules) are far from quiescent and capable of generating substantial Ca^{2+} signals. We have found that bradykinin (BK), at slightly above physiological plasma levels, consistently elicited substantial Ca^{2+} signals in PSCs, but never in neighbouring PACs. The BK-induced Ca^{2+} signals were mediated by bradykinin type 2 (B2) receptors, while B2 receptor blockade protected against PAC necrosis evoked by agents causing acute pancreatitis. The initial BK-induced Ca^{2+} rise in PSCs was due to Ca^{2+} release from the internal stores, whereas the sustained phase was fully dependent on external Ca^{2+} entry through store-operated (CRAC) channels. CRAC channel blockers inhibited Ca^{2+} signal generation in PSCs and therefore should be particularly beneficial in acute pancreatitis development and treatment. Our work indicates that combined treatment with inhibitors of CRAC channel and B2 receptor could be potentially useful against progression to PC.

**Keywords:** Bradykinin, Ca^{2+} signals, B2 receptors/ pancreatic stellate cells, ATP.
PROBING THE INFLUENCE OF CHIRALITY ON ANTICANCER ACTIVITIES OF ENANTIOMERIC PAIRS OF PALLADIUM N-HETEROCYCLIC CARBENE COMPLEXES

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With the dual objectives of exploring the viability of palladium as alternative to platinum in cancer therapy and also of investigating the influence of chirality on its anticancer properties, several achiral and chiral palladium complexes of N-heterocyclic carbene (NHCs) ligands have been studied. The palladium complexes of the type (NHC)$_2$PdX$_2$ (X = Br) exhibited significant anticancer activities arresting the cell cycle at G2/M phase and subsequently triggering cell death by the desired apoptotic pathway. The potency of these palladium N-heterocyclic carbene complexes were further improved, as seen by the lowering of their IC$_{50}$ values to a sub-mM range, by the replacement of the Br anion in the (NHC)$_2$PdX$_2$ type complexes with a more polar CF$_3$CO$_2$ anion. Interestingly, no differential anticancer activities were observed for any of the enantiomeric pairs in case of the chiral palladium N-heterocyclic carbene complexes, and which pointed towards a possible steric mismatch between the sizes of the chiral moieties in the palladium N-heterocyclic carbene compound and that of the binding site of a chiral DNA molecule in the nucleus of the cancer cell.

MORPHOLOGY, ANTIOXIDANT AND ANTIHYPERTENSIVE ACTIVITY PROPERTIES OF α-CASEIN TREATED WITH UV-C AND FAR-IR RADIATIONS

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α-casein is the most important bioactive protein in bovine milk. After treated with UV-C at 11.8 W/m$^2$ and far-infrared radiation (FIR) at 500 W, the morphology, antioxidant and antihypertensive activity properties changed in different levels. The AFM results indicate the surface of untreated α-casein sample with a relatively consistent size in general and evenly distribution. Ra and Rmax value of untreated α-casein was 0.21nm and 3.10nm respectively. UV-C (15 min) showed the increase of Ra and Rmax value to 0.30nm and 5.24nm. FIR (15 min) increased the Ra and Rmax value to 0.31nm and 5.13nm. The antioxidant and antihypertensive activities of α-casein increased after UV-C and FIR treatments. The DPPH and ABTS value of untreated α-casein was 21.26% and 55.95%. UV-C (15min) and F-IR (15min) caused the most significant increase in antioxidant activity compared with control and 5min treatments. The ACE-inhibitory activity of both UV-C and FIR treatments increased from 40.07% (control). Ultra-performance liquid chromatography-tandem mass (UPLC-MS/MS) spectrometry analysis showed the different levels of increase and decrease of released peptides related to those bioactivities. The peptide related with antihypertensive activities increased significantly after UV-C and FIR treatments compared with control sample. UV-C (15min) treatments efficiently changed the morphology and increased the antioxidant and antihypertensive activities of milk.

Keywords: UV-C, far-IR, α-casein, antioxidant, antihypertensive, UPLC-MS/MS.
**A NOVEL MOLECULAR IMAGING PROBE WITH A DUAL NEAR-INFRARED FLUOROCHROME FOR ALZHEIMER’S DISEASE-RELATED ENZYMES-BACE1 AND CATHEPSIN D**

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Alzheimer’s disease (AD) has become a pandemic due to our nation’s burgeoning aging population. A membrane embedded aspartyl protease complex with presenilin as the catalytic component-γ-secretase and β-site aspartyl cleaving enzyme (BACE1) or β-secretase are responsible for synergistic proteolytic cleavages of amyloid precursor protein (APP) and ultimate generation of amyloid Aβ peptides in AD patients’ brain. Their inhibition and modulation have been proposed as therapeutic strategies for AD. Nevertheless, BACE1 knockout mice have phenotypes such as sensorimotor impairments, spatial memory deficits, and displayed seizures. On the other hand, lysosomal aspartyl protease-cathepsin D (CatD) is downregulated at both transcriptional and translational level and its processing is altered in AD fibroblasts. Thus, both BACE1 and CatD have been suggested as potential AD biomarkers. Hence, we intend to develop in vivo smart probes targeting BACE1 and CatD as they may be tools for the preclinical and even clinical development of AD therapy and diagnosis. To achieve this goal, we have created a multi-wavelength molecular imaging probe to report on the simultaneous activities of cathepsin D (CatD) and BACE1, and validated this probe with pure enzyme mixtures and cell lines.

Magnetofluorescent nanoparticles (cross-linked dextran iron oxide nanoparticles or CLIO) served as a starting material. Peptide substrates containing a terminal near-infrared (NIR) fluorochrome (a fluorophore emitting at 688 nm for CatD or a fluorophore emitting at 775 nm for BACE1) were conjugated to the CLIO nanoparticles. The CatD substrate contained a phenylalanine-phenylalanine cleavage site more specific to CatD than BACE1. The BACE1 substrate contained the sequence surrounding the leucine-asparagine cleavage site of BACE1 found in APP, which is more specific to BACE1 than CatD. The nanoparticles were purified by gel filtration and their fluorescence intensities were determined using a fluorescence plate reader.

The CatD nanoparticle demonstrated a 17-fold increase in fluorescence when incubated with CatD, approximately 3 times higher in fluorescence than BACE1. The BACE1 probe exhibited a 8-fold increase in fluorescence when incubated with BACE1, approximately 2 times higher in fluorescence than CatD. Probe specificity was also demonstrated in the human SH-SY5Y cells, in which the probe monitored enzymatic cleavage. In the SH-SY5Y cells, there was a 6-fold increase in CatD fluorescence as well as a 2-fold increase in BACE1 fluorescence.

We conclude that this novel molecular imaging probe with a dual NIR fluorochrome can detect both BACE1 and CatD enzymatic activities selectively in either pure enzyme mixtures or cell lines, demonstrating its potential utility as a tool for development of AD therapy and diagnosis.

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PHENAZINES AND QUINONES: A PROMISING SCAFFOLDS IN THE FIGHT AGAINST MALARIA

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The WHO illustrated in 2013 that malaria affected ca. 200 million people and caused 600,000 deaths and mostly young children. Moreover eradication of malaria has 4-5 major challenges and one of the major challenges is resistance to low cost drugs viz., chloroquine and Fansidar. Our aim was to synthesize phenazines and quinones [1-3] (Fig. 1) and to evaluated their antimalarial activity towards chloroquine resistant strains (Pf/NF-54 and Pf/K-1) of Plasmodium falciparum. It is noteworthy that phenazine and quinones illustrated significant antimalarial activity towards chloroquine-resistant strains of P. falciparum. Furthermore most of analogs of phenazine and quinones illustrated promising in vitro potentials with IC<sub>50</sub> less than 5 μM and some tested molecules have IC<sub>50</sub> < 1 μM. Moreover phenazine and quinone derivatives which showed promising in vitro activities also demonstrated significant in vivo activities.

Fig. (1). Antimalarial activities of phenazines and quinone derivatives.

REFERENCES

SL-174

Track: Hot Topics in Medicinal Chemistry

MERCAPTO-ACRYLOYL AND AZIDE-ALKyne CONJUGATIONS TO INCORPORATE LIPID ADJUVANTS INTO MULTITIGENIC ANTICANCER VACCINES

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N-termini conjugation of unprotected peptides is a promising technique to produce branched multiantigenic vaccines. In this study, a double conjugation strategy was established. This technique includes mercapto-acryloyl Michael addition and a copper-catalysed alkyne-azide 1,3-dipolar cycloaddition (CuAAC) reaction to synthesize self-adjuvanting branched multiantigenic vaccines.
vaccine candidates. These vaccine candidates aim to treat cervical cancer and include two HPV-16 derived epitopes and a novel self-adjuvanting moiety. This is the first study to apply mercapto-acryloyl reaction for the hetero conjugation of two unprotected peptides by their N-termini followed by incorporation of a novel synthetic lipoalkyne self-adjuvanting moiety via a CuAAC reaction. In vivo challenge experiment demonstrated that the most promising vaccine candidate completely eradicated tumors in 46% of the mice.

**SL-81**

*Track: Medical Imaging*

**INFECTION PATHWAY OF VIRUS IN LIVING CELL IN VIEW OF DIFFUSION THEORY**

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Infection pathway of virus in living cell is of extreme interest from the viewpoint of the physics of diffusion. It has experimentally been observed, by making use of the technique of real-time single-molecule imaging, that adenov-associated virus exhibits anomalous diffusion in cytoplasm of a living HeLa cell and the anomalous-diffusion exponent fluctuates depending on localized areas of the cytoplasm. Here, a kinetic theory for describing the infection pathway of the virus in the cytoplasm is discussed. After a brief introduction of fractional kinetic theory, this theory is applied to anomalous diffusion of the virus in the localized area. Then, a maximum-entropy-principle approach to a statistical distribution of exponent fluctuations proposed from the experimental data is examined. Finally, a generalized fractional kinetics based on the proposed distribution is found to imply that the motion of the virus over the cytoplasm obeys a scaling law.

**SL-23**

*Track: Bioactive Lipids*

**LIPID INDUCED DIMERIZATION OF VINCULIN AND META VINCULIN DIRECT THEIR DISTINCT FUNCTIONS AFFECTED IN CARDIOMYOPATHIES**

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Cadherin-mediated cell-cell adherens junctions and integrin-directed cell-matrix focal adhesions (FAs) are required for proper development, and here these receptors are linked to the actin cytoskeleton via vinculin, a highly conserved and structurally dynamic protein, which plays essential roles in intercalated discs that are necessary for muscle cell function and coordinated movement. This is especially evident in the development and function of the heart, where targeted deletion of vinculin leads to massive defects in cardiac development and embryonic death, and where vinculin+/− mice develop dilated cardiomyopathy (DCM). Humans bearing familial or sporadic mutations in vinculin suffer from chronic, progressively debilitating DCM that ultimately leads to cardiac failure and death. Further, autosomal dominant mutations in vinculin and in other components of myofilaments and Z-discs of the sarcomere can also provoke hypertrophic cardiomyopathy (HCM), a cause of acute cardiac failure. Cardiomyopathies are a major worldwide health problem, with patients often suffering cardiac arrest and premature death. Over the past decade several inherited and sporadic mutations in genes encoding components of adhesion complexes and of intercalated discs such as the muscle-specific, alternatively spliced isoform of vinculin termed metavinculin (MV), which are required for the coordinated movement of heart tissue, have been pinpointed as the cause of many cardiomyopathies. These mutations can trigger HCM, an acute cause of heart attack, as well as DCM, a chronic and progressively debilitating disease that leads to heart failure and death. The DCM-and HCM-associated mutants of vinculin behave as dominant alleles with altered functions. Here these mutations always occur in the specific 68-residue insert found in MV and they transform the function of MV to mimic vinculin. For example, MV provokes meshed networks of actin
filaments in cells, whereas vinculin triggers actin bundles, and here HCM-and DCM-associated metavinculin mutants behave like vinculin.

At physiological concentrations, vinculin homodimerizes in the presence of actin and oligomerizes in the presence of phosphatidylinositol 4,5-bisphosphate (PIP2) and we recently showed that the physiological oligomer is the dimer. We determined the long awaited vinculin/PIP2 crystal structure that defined the mechanism and function of this interaction. While MV readily heterodimerizes with PIP2-adsorbed vinculin, it was thought that only vinculin but not MV homodimerizes. However, here we demonstrate that contrary to dogma, MV forms lipid-induced homodimers by domain swap as seen for vinculin via quasiequivalent interactions. Significantly, the most severe mutation, R975W, is the only lipid binding residue residing on the α-helix that is distinct in the two isoforms and the only lipid binding residue that is not conserved between the two isoforms and thus likely the culprit for the distinct vinculin-vinculin versus MV-MV homodimers driven by equivalent and quasiequivalent interactions and domain swap. Collectively, our data suggest that MV homodimerization modulates microfilament attachment at muscular adhesion sites and furthers our understanding of MV mediated cardiac remodeling.

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**SL-132**  
**Track:** CNS Drug Discovery & Therapy

**NOSE-TO-BRAIN DELIVERY OF DRUG/siRNA WITH CELL-PENETRATING PEPTIDE MODIFIED POLYMER MICELLES**

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The potential for RNA-based agents to serve as effective therapeutics for central nervous system (CNS) disorders has been successfully demonstrated in vitro. However, the blood-brain barrier limits the distribution of systemically administered therapeutics to the CNS, posing a major challenge for drug development aimed at combatting CNS disorders. Therefore, the development of effective strategies to enhance siRNA delivery to the brain is of great interest in clinical and pharmaceutical fields.

In this study, to improve the efficiency of small interfering RNA (siRNA) delivery to the brain, we developed a nose-to-brain delivery system combined with cell-penetrating peptide (CPP) modified nano-micelles comprising polyethylene glycol–poly(caprolactone) (PEG-PCL) copolymers conjugated with the CPP, Tat(MPEG-PCL-Tat).

We first determined intranasal brain delivery of siRNA, by using MPEG-PCL-Tat. Intranasal delivery of dextran with MPEG-PCL-Tat improved brain delivery compared to intravenous delivery of dextran either with or without MPEG-PCL-Tat. We also studied the intranasal transfer of MPEG-PCL-Tat to the brain via the olfactory and trigeminal nerves, the putative pathways to the brain from the nasal cavity. We found that MPEG-PCL-Tat accelerated transport along the olfactory and trigeminal nerve pathway because of its high permeation across the nasal mucosa. Next, to develop a novel, efficient, and safe therapeutic strategy for managing brain disorders, we used MPEG-PCL-Tat micelles with a nose-to-brain delivery system to investigate its therapeutic effects on a rat model of malignant glioma using siRNA with a Raf-1 (siRaf-1)/camptothecin (CPT) codelivery system. MPEG-PCL-Tat/siRaf-1 and CPT-loaded MPEG-PCL-Tat/siRaf-1 have fostered cell death in rat glioma cells after the high cellular uptake of siRaf-1/drug by the MPEG-PCL-Tat carrier. Furthermore, compared to the unloaded MPEG-PCL-Tat/siRaf-1 complex, a CPT-loaded MPEG-PCL-Tat/siRaf-1 complex achieved the high therapeutic effect because of the additive effects of CPT and siRaf-1. These results indicate that drug/siRNA codelivery using MPEG-PCL-Tat nanomicelles with nose-to-brain delivery is an excellent therapeutic approach for brain and CNS diseases.
ANALYSIS OF MEDICAL IMAGING FEASIBILITY IN PRESENCE OF BODY FLUIDS USING MARKOV CHAINS

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A relatively wide field of view and high resolution imaging is necessary for navigating the scope within the body, inspecting tissue, diagnosing disease, and guiding surgical interventions. As the large number of modes available in the multimode fibers (MMF) provides higher resolution, MMFs could replace the millimeters-thick bundles of fibers and lenses currently used in endoscopes.

The MMFs have promising potential in transmitting images through multiple parallel optical modes. With multiple modes, it is possible to use smaller size bundles of fibers, replace lenses, and perform high quality images. In recent years, there has been made tremendous progress on the performance of MMFs for high-resolution images. Also, this research draws upon mostly primary sources including MMFs for high-resolution imaging, flexible MMFs, and fiber optic fluorescence imaging research work. Most prior goals were to research on comprehension of spatial distortion and flexibility of the fibers.

However, attributes of body fluids and obscurants such as blood impose perennial limitations on resolution and reliability of optical imaging inside human body. To design and evaluate optimum imaging techniques that operate under realistic body fluids conditions, a good understanding of the channel (medium) behavior is necessary.

In most prior works, Monte-Carlo Ray Tracing (MCRT) algorithm has been used to analyze the channel behavior. This task is quite numerically intensive. The focus of this paper is on investigating the possibility of simplifying this task by a direct extraction of state transition matrices associated with standard Markov modeling from the MCRT computer simulations programs. We show that by tracing a photon’s trajectory in the body fluids via a Markov chain model, the angular distribution can be calculated by simple matrix multiplications. We also demonstrate that the new approach produces results that are close to those obtained by MCRT and other known methods. Furthermore, considering the fact that angular, spatial, and temporal distributions of energy are inter-related, mixing time of Monte-Carlo Markov Chain (MCMC) for different types of liquid concentration is calculated based on Eigen-analysis of the state transition matrix and possibility of imaging in scattering media are investigated.

STEREOSELECTIVE PEPTIDE MODIFICATIONS – AN EFFICIENT TOOL FOR NATURAL PRODUCT AND DRUG SYNTHESIS

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Microorganisms are highly productive producers of natural products, and a wide range of their secondary metabolites became lead structures for the development of drugs. Peptides and cyclo(depsi)peptides formed by nonribosomal peptide synthetases (NRPS) are especially interesting from a pharmaceutical point of view. Many of these peptides contain not only (S)-and (R)-configured amino acids, but also rather unusual side chains. In classical peptide syntheses, these unusual amino acids are synthesized separately, and are subsequently coupled using suitable coupling reagents. In contrast, our group is taking advantage of peptide modifications to generate libraries of structurally related peptides by introducing (also highly functionalized) side chains onto a given peptide. The stereochemical outcome of the reaction can be controlled by the other amino acids of the peptide chain. Excellent
diastereoselectivities are obtained especially in transition metal catalyzed allylic alkylations. In general, an (S)-amino acid generates an adjacent new (R)-amino acid and \textit{vice versa}. The approach can be used in the straightforward synthesis of natural products. Latest results will be presented on the conference.

\textbf{SL-84}

\textit{Track: Medical Imaging}

SYNCHROTRON NANOSCOPY IMAGING STUDY OF SCALP HAIR IN BREAST CANCER PATIENTS AND HEALTHY INDIVIDUALS: DIFFERENCE IN MEDULLA LOSS AND CORTICAL MEMBRANE ENHANCEMENTS

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Nanoscopic synchrotron X-ray imaging was performed on scalp hair samples of patients with breast cancer and healthy individuals to investigate any structural differences as diagnostic tool. Hair strands were divided into 2-3 segments along the strands from root to tip, followed by imaging either in projection or in CT scanning with a monochromatic 6.78-keV X-ray using zone-plate optics with a resolving power of 60 nm. All the examined cancer hairs exhibited medulla loss with cancer stage-dependent pattern; complete loss, discontinuous or trace along the strands. In contrast, medullas were well retained without complete loss in the healthy hair. In the CT-scanned axial images, the cortical spindle compartments had no contrast in the healthy hair, but appeared hypointense in contrast to the surrounding hyperintense cortical membrane complex in the cancer hair. In conclusion, observation of medulla loss and cortical membrane enhancements in the hair strands of breast cancer patients demonstrated structural variations in the cancer hair, providing a new platform for further synchrotron X-ray imaging study of screening breast cancer patients.

\textbf{SL-63}

\textit{Track: Protein and Peptide Sciences}

SYNONYMOUS CODONS DIRECT CO-TRANSLATIONAL FOLDING TOWARDS DIFFERENT PROTEIN CONFORMATIONS

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In all genomes, most amino acids are encoded by more than one codon. Synonymous codons can modulate protein production and folding, but the mechanism connecting codon usage to protein homeostasis is not known. Here we show that synonymous codon variants in the gene encoding gamma-B crystallin, a mammalian eye lens protein, modulate the rates of translation and co-translational folding of protein domains monitored in real time by Förster resonance energy transfer and fluorescence intensity changes. Gamma-B crystallins produced from mRNAs with changed codon bias have the same amino acid sequence, but attain different conformations as indicated by altered \textit{in vivo} stability and \textit{in vitro} protease resistance. 2D NMR spectroscopic data suggest that structural differences are associated with different cysteine oxidation states of the purified proteins, providing a link between translation, folding, and the structures of isolated proteins. Thus, synonymous codons provide a secondary code for protein folding in the cell. This knowledge may facilitate production of recombinant proteins with structures closely similar to their native analogues.
REFERENCE


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**SL-177**

**Track:** Hot Topics in Medicinal Chemistry

**CHRONIC MYELOGENOUS LEUKEMIA-COMBATING T315I MUTATION**

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Imatinib is the first Bcr-Abl tyrosine kinase inhibitor used in the treatment of CML [1]. However, approximately 20-25% of patients initially treated with Imatinib need alternative therapy, due to drug resistance, which is often caused by the appearance of clones expressing mutant forms of BCR-ABL [2]. Alternative therapeutic drugs dasatinib, nilotinib and bosutinib demonstrate lack of efficacy and resistance in this patient population [3-6].

Based rational drug design we developed NRC-AN-019 [7, 8] and NRC-AN-024 [9, 10] high affinity phenyl amino pyrimidine based Bcr-Abl inhibitors. However, in preclinical studies, T315I mutated cell lines demonstrated decreased sensitivity to NRC-AN-019 and NRC-AN-024 compared with CML cell lines wild type for mutations.

Ponatinib [11] is approved for the treatment of CML and is intended to confer resistance especially due to the T315I mutation. However, during ponatinib treatment the risk of life-threatening blood clots and severe narrowing of blood vessels is noticed.

Thus, there is a need for newer selective tyrosine kinase inhibitors which are safer than existing therapies particularly with regard to decrease in risk of life-threatening blood clots and severe narrowing of blood vessels efficacious against the kinase mutations, including the T315I mutant. This led to the development of NRC-21T [12] which is potent inhibitor of Abl tyrosine kinase and their mutated forms, including the T315I mutant. This compound is devoid of some of the short comings of the existing drug products.

**Keywords:** CML, Resistance.

**REFERENCES**

DESIGN AND DEVELOPMENT OF TACRINE-BASED MULTIPOTENT COMPOUNDS IN ALZHEIMER'S DISEASE THERAPY

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Alzheimer's disease (AD) is a multifactorial malady and apparently involves several different etiopathogenetic mechanisms. Up-to-date, there is no curative treatment or effective disease-modifying therapy for AD. One of current directions in the field of development of novel drugs against AD is represented by the so-called Multi-Target-Directed Ligands (MTDLs), the therapeutic strategy followed also in other multifactorial diseases. MTDLs combine drug actions at different levels of the neurotoxic cascade. Within our contribution, novel trends in development of MTDLs proposed by our group as potential anti-AD drugs will be presented. Our newly designed and synthesized compounds usually combine tacrine scaffold as anticholinesterase agent with diverse moieties blocking other processes involved in AD pathogenesis. Further, these MTDLs are forwarded for in vitro assessment for their inhibitory potencies against cholinesterases, cytotoxicity, oxidative stress etc. depending on the type of combined moieties. Finally, the best candidate of each series is recommended for in vivo experiments.

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Keywords: Alzheimer's disease, Multi-target-directed ligands, Design and Development, Therapeutics, Tacrine

INNOVATIVE PHARMACOLOGICAL TREATMENT FOR ENHANCEMENT OF ANALGESIA AND PREVENTION OF MORPHINE SIDE EFFECTS BASED ON A NEW PHARMACEUTICAL COMPOSITION CONTAINING MORPHINE COMBINED WITH OMEGA-3 FATTY ACIDS

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The treatment of acute and chronic severe pain remains a major daily challenge for health professionals in clinical practice.

Morphine is a potent analgesic mostly used to control pain. However, long term treatment develops several problems, such as loss of analgesic efficacy (tolerance), increased sensitivity to pain (hyperalgesia) and adverse effects like constipation, nausea, vomiting, sedation, drowsiness, pruritus and weight loss. These effects, together with tolerance and hyperalgesia, may require the use of increasingly higher doses to get the same analgesic effect or discontinue its use, which constitutes a failure of the treatment against pain. This project describes a technological development with an innovative character, both in its pharmaceutical composition (morphine and omega-3 fatty acids) and in the pharmacological treatment associated with its use.

The main advantage of the new pharmaceutical composition and pharmacological treatment lies in the control of pain with a sub-therapeutic dose of morphine which would eliminate or potentially decrease its adverse effects. Other important clinical benefits of using it in terminally ill patients, (such as cancer sufferers) or patients with other types of chronic diseases are the decrease in tolerance to analgesic effect and the reduction in body weight loss and constipation.
SL-41
Track: Anti-Infectives

SCREENING STRATEGIES FOR DISCOVERING NOVEL TUBERCULOSIS DRUGS

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Tuberculosis is the world’s top infectious disease killer and there is a critical need for new drug treatment regimens to combat multidrug resistance as well as to shorten the long and complicated treatment options. Traditionally, antibiotics are discovered using phenotypic whole cell screens and so far target based screens have not yielded similar success rates. We approached our aim of finding novel hits through two unique approaches. In the first approach, we combined phenotypic screening with target specific assay. In the second approach we carried out a large-scale high throughput phenotypic screening directly without employing any secondary readouts. We have identified promising hits, which are currently undergoing target deconvolution and further development under the SPRINT-TB program.

SL-17
Track: Cancer Targeted Drug Delivery

A NOVEL APPROACH TO CANCER THERAPY: INTRATUMORAL TELOMERASE INHIBITION

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Our intratumoral insertion of a long term, slow release anticancer drug, shows potential for clinical oncology. Our polymeric drug delivery system (DDS) releases a telomerase-inhibiting drug, and during its 30-day degradation, significantly reduces tumor growth rate. It inhibits the activation of telomerase, present in >95% of all cancers types. Telomerase activation confers immortality to cancer cells by preventing the cells from shortening their telomeric ends of DNA. The inhibitor must be continuously available to all tumor cells, including newly dividing cells. If briefly absent from the tumor, telomerase rapidly reactivates and telomeres re-lengthen. We will present in vivo studies comprising 100 mice, with and without our DDS, showing the DDS reduces the tumor growth rate by a factor of 5 with a p-value of 0.0001. Importantly, measured blood serum levels of the drug, over time, were negligible. We are also investigating the use of our palladium (Pd)-tagged drug to increase the radiation dose of iodine-125 brachytherapy seeds while sparing normal tissues. The emission of Auger electrons in DNA, from photo-activated Pd, causes non-reparable damage to tumor cell DNA. Our approach has two clinical potentials: significant reduction in tumor growth and the negligible uptake in serum averting the adverse quality of life effects for the cancer patient.
**SL-78**

*Track: Medical Imaging*

**1H MRS LACTATE IMAGING OF NON-HODGKIN’S LYMPHOMA**

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Positron emission tomography (PET) and computed tomography (CT) are the current imaging standards for non-Hodgkin’s lymphoma patients, where CT provides anatomic details of a body while PET offers metabolic imaging by utilizing a high 18F-deoxyglucose (FDG) uptake by cancer cells. We have been developing a new magnetic resonance imaging (MRI)-based metabolic imaging that can supplement FDG-PET. Our method, 1H (proton) MRS (magnetic resonance spectroscopy) lactate imaging, exploits the ample production of lactate by cancer cells. Lactate is a central molecule in cancer metabolism that mirror and motor tumor malignancy. Lactate has been an early marker of therapeutic response in various preclinical tumor models, and a predictor of metastasis and tumor recurrence in head and neck cancers. We obtained 1H MRS lactate spectra from tumor of various subtypes and body locations of lymphoma patients using our novel Had-Sel-MQC-CSI pulse sequence at a 3 T MRI. We present two important potential applications of 1H MRS lactate imaging for non-Hodgkin’s lymphoma – detecting early response to novel signaling inhibitor therapies and distinguishing aggressive lymphoma from indolent lymphoma. For both applications, FDG-PET has substantial limitations. We present compelling data that support our reasoning and expectation that 1H MRS lactate imaging will play an important role for these cases.

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**SL-175**

*Track: Academic CRO/Industrial Collaborations in Drug Discovery*

**ABC TRANSPORTERS AS THERAPEUTIC TARGETS TO REVERSE MULTIDRUG RESISTANCE: PROMISE AND PITFALLS**

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Patients treated with the front-line drugs may initially show a response but most often drug resistance rapidly develops. One of the main mechanisms by which cancer cells become resistant, is up-regulation of various efflux pumps (ABC transporters, such as P-glycoprotein and Breast Cancer Resistant Protein (BCRP)) which efficiently remove the drug from the cell, thus causing the drug to lose its effect. Using flow cytometry, membrane vesicle transport assays, ATPase activity assays, small interference RNA and resistance reversal assays, we found that many of synthesized analogues of PCs inhibited the transport activity of the ABC transporters investigated. These compounds include heterocyclic cyclohexanone monocarbonyl analogues of curcumin, hop-derived prenylflavonoids, and analogues of falcarindiol. Our results also suggest some PCs may act as BCRP inhibitors and increase cellular mitoxantrone (MXR, a well-defined BCRP substrate) accumulation in isogenic cells while others can decrease its concentration in those cells. Our preliminary results suggest a quinidine-sensitive transporter may be involved into the active uptake of MXR. Since the balance between the uptake and efflux activities of transporter proteins determines cellular accumulation of a drug and consequently its anti-cancer efficacy, further investigation is warranted to elucidate the transport mechanisms of anticancer drugs.
DISCOVERY OF NOVEL DAPY-IAS HYBRID DERIVATIVES AS POTENTIAL HIV-1 INHIBITORS

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Diarylpyrimidine (DAPY) derivatives as HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) with prominent activity have attracted more and more attention in the last decades. Two most representative DAPYs, etravirine (TMC125) and rilpivirine (TMC278) (Fig. 1) have been approved by the US FDA for anti-HIV therapy in 2008 and 2011 respectively [1]. Indolylarylsulfones (IAS) represented by compound L-737126 (Fig. 1), are another class of NNRTIs endowed with distinct antiretroviral activity [2]. Molecular simulation study indicated that L-737126 occupied a similar binding mode and pharmacophoric features as rilpivirine. A novel series of DAPY-IAS hybrid derivatives through combining their privileged structural features using molecular hybridization strategy were designed and synthesized. The biological evaluation results revealed that some target compounds exhibited moderate activities against HIV-1 IIIB (wild type) strain, among which the most potent inhibitor possessed an EC50 value of less than 2 μM. Preliminary structure-activity relationships (SARs) are discussed in details, providing beneficial information for further modifications.

Fig.1. Structures of lead compounds rilpivirine and L-737126

REFERENCES


NANODRUG-DELIVERY SYSTEM: HELPING DRUGS TO REACH THEIR TARGETED DISEASE DESTINATION

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Nanomedicine has proven vast opportunities in therapeutic design, diagnosis, and prevention of disease. Among various applications of nanoparticles in medicine, most pronounced is the targeted drug delivery. To achieve these our goal is to focus on engineer nano-modules that result in fast, accurate, and cheaper diagnostics or therapeutics. In last decade studies in United States has shown an elevation in cancer specific mortality among HIV patients (CROI 2016). Center for Strategy and International Studies (CSIS) have reported that in case of women, cancer and HIV
Infection have a direct link resulting in deadly consequences. Those women having HIV infection are 4-5 times susceptible for cervical cancer then non-HIV infected women. Thus, here I will specifically focus on designing potential synthetic therapeutics mainly for cancer and HIV-1 infection.

For cancer therapeutics, our aim is developing target specific long acting treatment strategies. One strategy is to develop targeted nano-drug delivery systems. We have developed folate conjugated nanoparticles delivering simultaneously in the cancer cells siRNA against c-myc to overpower the uncontrolled proliferation capacity and wild type p53 leading to cancer cell apoptosis. Our second strategy is to boost the immune system by designing synthetic Immunotherapeutics that mimics functionality of dendritic cells attacking target specific cancer cells.

For HIV infection, we are designing combination Antiretroviral (cARV) loaded nano-delivery system to overcome the adherence burden in the HIV patient. We are the first to report to use PLGA encapsulated cARV drugs (i.e. TAF+EVG+FTC) NPs for treatment of HIV in a humanized mouse model.

Our perception is that in near future nano-drug delivery system will reduce the drug adherence burden, cost and lengthen with dignity the life of HIV/Cancer patient.

SL-46

Track: Hot Topics in Natural Products

DISCOVERY OF MEDICAL APPLICATION OF INNOVATIVE NATURAL PRODUCT WITH BROAD ADAPTOGENIC ACTIVITY

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From ancient times until now, people used a variety of natural medicinal substances to save their life. Currently, more than 60% of the drugs available on the market are of natural products origin. At earlier 50th Formal Soviet Union faced a serious urgency in new drug development with potential of human and animal defense from radiation. The unique product of organic nature named ACD was made by A.V. Dorogov, Ph.D 60 years ago from animal tissues by high thermal sublimation method and demonstrated a strong immune activity. It was officially registered and used in animal treatment and as prophylactic for people. Nevertheless, during many years of application ACD in veterinary and in human dermatology was observed by clinicians the unusual therapeutic activity of ACD in broad range of such somatic human diseases as non-specific chronic lung and bronchia diseases, gastrointestinal tract diseases, rheumatoid arthritis, chronic kidney and urinary tract infection. ACD also demonstrated activates of the central and autonomic nervous systems, increasing of the tissue and digestive enzymes activity, and increased resistance of the entire human body to stress and infection with normalization of the intracellular ion exchange.

After deep analysis of ACD applications cases, we hypothesized the adaptogenic mechanism of its biological activity. In order to explain the origin of such positive “side effect” of ACD we standardized the procedure of primary natural stock for ACD preparation and fractionation on ACD-fraction 2 and ACD-fraction 3. Our detail investigation of chemical composition of ACD-fraction 2 resulted in funding that ACD is an aqueous solution of various organic and inorganic compounds with pH 9.5 and in the range of density 1.009-1.135 g/ml. It contains up to 75% of water, 5% of 121 organic compounds and 20% of inorganic chemicals, which are mainly, composed of low fatty acid amides and ammonium salts. It consist of sulfur in the formulation in the form of ammonium sulfide, as well as organic compounds, small amounts of pyridine bases and phenols, and a large amount of nitrogenous compounds in the form of ammonia, and variety of ammonium salts. Based on chemical composition data we calculated the formula of this complex product as C0.14 H9.98 N1.65 O1.44 P0.01. Our resent in vivo study of geroprotective capacity of ACD on nematodes C. elegans model system revealed its efficacy in 2.3 times life span extension, compared with controls. In the presence of ACD, nematode’s resistance to heat-shock and oxidative stress was dramatically increased as well.

In this presentation, we provided new evidences on bioactivity of new natural product named ACD, which demonstrate new sources of innovation in the drug development. The possibility of its future therapeutic application in new areas of human health will be discussed.
**SL-95**

*Track: Drug Discovery in Pre-clinical Research*

**AMINOACETYLENIC ISOINDOLINE-1,3-DIONE DERIVATIVES MODULATE CYTOKINES IN FAVOR OF REGULATING INFLAMMATORY-BASED DISEASES**

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Increasing the production of inflammatory cytokines are highly associated with inflammatory-based autoimmune diseases and finding an inhibitor for such cytokines while increasing anti-inflammatory cytokines production would help in managing such diseases. We previously synthesized series of aminoacetylenic isoindoline-1,3-dione derivatives (ZM compounds) as inhibitors of cyclooxygenase 1 and 2. Such compounds were found to reduce carrageenan-induced inflammation as well as it has very few adverse events in comparison to non-steroidal drugs. In order to increase the clinical potential of these compounds, ZM compounds were tested on modulation of inflammatory and/or anti-inflammatory cytokines production following stimulation *in vivo* and *in vitro*. Six hours post oral (20 mg/kg) administration of ZM compounds and 5 h post i.p. administration of LPS, ZM compounds (ZM2, ZM3, ZM4 and ZM5 compounds) significantly reversed or prevented LPS effect on IL-12, IL-17, IFN-γ, TNF-α, IL-10 and TGF-β production from mice spleen. Furthermore, *in vitro* testing showed that all ZM compounds reversed LPS and LPS+PMA effect on TNF-α but no significant modulation was observed on IFN-γ or IL-10. As for TGF-β, ZM2, ZM4, and ZM5 significantly increased TGF-β production more than LPS or LPS+PMA-stimulated spleen cells. However, when ZM compounds were tested on stimulated CD4+CD25+ve cells, only ZM5 (N-(4-(2-Azepan-1-yl)-but-2-yn-1-yl)isoindoline-1,3-dione) significantly enhanced TGF-β1 production from CD4+CD25+ve T helper cells, whereas none of the ZM compounds modulated TNF-α from CD4+CD25-ve cells. In conclusion, these results indicate that all ZM compounds suppress TNF-α, IL-12 from monocytes/macrophage, reduce systemic stimulation of spleen IFN-γ and IL-17 levels, and only ZM5 enhances TGF-β production from T regulatory cells. Such results enhance the clinical potential of some of these basic aminoacetylenic isoindolines in managing inflammatory-based autoimmune diseases.

**Keywords:** Aminoacetylenic isoindolines, cytokine modulation, monocytes/macrophages, T regulatory cells.

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**SL-171**

*Track: Hot Topics in Medicinal Chemistry*

**NOVEL FUSED RING CHLORINS AS EFFICIENT THERANOSTIC AGENTS FOR CANCER**

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The research team has previously reported the synthesis of a new type of stable 4,5,6,7-tetraydropropyrazolo[1.5-a]pyridine-fused chlorins and bacteriochlorins *via* an [8π+2π] cycladdition of diazafulvenium methide with porphyrins and chlorins [1]. Absorption spectra of these chlorins and bacteriochlorins revealed intense absorption bands within the therapeutic spectral window, at 650 nm and 730 nm, respectively. Preliminary studies on phototoxicity of some of the compounds in melanoma cells proved this class of compounds to be very active as photodynamic agents against melanocytic melanoma (A375) and amelanotic melanoma (C32) cells [2]. Interestingly, di(hydroxymethyl)chlorin 1b was particularly active against human melanocytic melanoma cells (IC₅₀ = 31 nM) [2].

Near infrared (NIR) emitters are particularly important as their light output is in a region where organisms are highly transparent. In this context, NIR luminescent compounds based on platinum(II) derivatives of 4,5,6,7-tetraydropropyrazolo[1.5-a]pyridine-fused chlorins 2 have been prepared which proved to be very promising theranostic cancer agents [3]. Phosphorescence of these compounds is strongly quenched in the presence of oxygen whereas the fluorescence is relatively unaffected, opening the possibilities of their application as ratiometric oxygen sensors in...
chemical and biological media. Photocytotoxicity studied against human melanocytic melanoma cells (A375) indicate the potential of these compounds as photosensitizers to be used in photodynamic therapy. In this lecture, further details of this study will be presented and discussed.

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NUTRACEUTICALS AND DRUG DISCOVERY: A NETWORK BASED APPROACH TO HYPERTENSION CARE

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Many pathologies with a high incidence, such as metabolic syndrome and cardiovascular diseases, result from the alteration of different molecular networks influencing each others. The network based approach involves the shift from the “single chemical one target” strategy to the “network target multi components” and “network target single chemical” strategies. Several traditional systems, including Traditional Chinese Medicine (TCM) and Ayurveda, employ multicomponent mixtures which may exert synergistic effects and represent efficient approaches to the treatment of multifactorial diseases [1].

Studies aimed at identifying the chemical composition and the mechanisms of action of the vegetal extracts exhibit two main purposes:

- the development of efficient nutraceuticals
- the identification of new leads able to interact with several targets

In this study we focused on primary hypertension [2]. This multifactorial pathology still represents an outstanding risk factor for cardiovascular diseases, despite the progresses in knowledge pertaining molecular mechanisms involved in its pathogenesis and the availability of effective drugs [3].

Several vegetal extracts with antihypertensive effects hit different targets providing further cardiovascular benefits, resulting in a better patient outcome [2].
In particular, *Olea europea* L. leaves extracts rich in oleuropein and *Hibiscus sabdariffa* L. flowers extracts affect multiple pathways resulting in a hypotensive action.

In this work, cardiovascular effects of an *Olea europea* L. leaves extract (OEE), of a *Hibiscus sabdariffa* L. flowers extract (HSE), and of their 13:2 w/w mixture were tested [2]. The antioxidant and cytoprotective effects were assessed using primary vascular endothelial cells (HUVECs), while inotropic, chronotropic and vasorelaxant properties were evaluated using isolated guinea-pig left and right atria and aorta. In addition, the chemical composition of the two extracts was carried out by HPLC-MS/MS analysis.

OEE and HSE decreased the formation of intracellular reactive oxygen species, ameliorated cell viability and induced negative inotropic and vasorelaxant effects without affecting chronotropy. The mixture produced cytoprotective and antioxidant activities, exhibited an inotropic effect similar to the two vegetal extracts, it showed an intrinsic negative chronotropic activity diverse from those of the single extracts and a vasorelaxant effect with a potency similar to those of OEE and HSE. OEE was shown to contain, mainly, oleuropein and its isomers, luteolin-4-O and luteolin-7-O-glucoside, luteolin-4-O-rutinoside, ligstroside, elenolic acid, glucoside, verbascoside, and rutin, while hibiscus acid has been identified in HSE.

A deeper investigation demonstrated that a nutraceutical based on the previous mixture affects all the mentioned parameters, with a higher vasorelaxant potency, and exhibits a good toxicological profile [4].

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**THE FEASIBILITY OF REPLACING DIAZEPAM WITH PASSION FLOWER'S EXTRACT FOR REDUCING ANXIETY**

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Current study was carried out to compare the effects of passion flower hydroalcoholic extract and diazepam on reducing anxiety behaviors of laboratory mice. 60 mature mice from the weight range of 25-30 g were used. Treatment groups were Control, Stress, diazepam, and 50, 100 and 200 mg/kg of extract. To enforce the anxiety, mice were placed in a dark box for thirty minutes. After that, each mouse was located in a plus elevated maze and its behavior was recorded. Obtained data were analyzed using SPSS program. Hydroalcoholic extract decreased the presence time of animals in maze arm in 100 and 200 mg groups which indicates the anxiety reduction of these doses. According to results, the extract had anxiety reducing results similar to diazepam dose dependently.

**Keywords:** Passion flower, anxiety, diazepam, plus elevated maze, mice.
THE EFFECT OF MEAT MANGO ON THE LEVELS OF GONADOTROPINS, SEX HORMONES AND SPERMATOGENESIS IN RAT

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The meat of mango contains the chemical compound including saturated and unsaturated fatty acids, potassium, magnesium, zinc, cadmium and sucrose. Saturated fatty acids include stearic, palmitic, lauric, myristic and and unsaturated fatty acids include oleic and linoleic acid that this compounds causes to inhibit 5-alpha reductase enzyme and these compounds in meat have properties antioxidant, antitumor, hypercholesteremia. In the present research the effect of meat of mango on spermatogenesis, pituitary-gonad axis in adult male rats was studied for this propose 32 adults male rats with approximate weight of 220g were divided in to 4 groups of 8. Control group which did not take any meat of mango. Experimental groups which took minimum dose of mango meat about 1.25gr/kg. Medium group which took mango meat about 2.5gr/kg. Maximum group which took mango meat about 5gr/kg. After 21 days, preparing the blood serum of all gro up. LH, FSH and testosterone hormone levels were measured by γ-counter method. The sections of testis were prepared for histological studies. The results show that concentration of testosterone, the number sperm cells in seminiferous tubules experimental groups with control group have difference significantly. But the concentration of LH, FSH hormones, the number of spermatogonia, primary spermatocyte, spermatid, sertoli and leydig cells and the structure seminiferous tubules did not show difference significantly. Possibly, compounds in mango meaty texture, by inhibiting the 5-alpha reductase by increasing biosynthesis 17B-Hydroxy steroid dehydrogenase make the metabolism of steroids including testosterone to increase. Furthermore, Lauric acid, Myristic acid, Palmitic acid and sucrose can increase cholesterol and thereby increases testosterone levels. increased testosterone levels, in turn, can increase sperm density.

Keywords: Mango, gonadotropins, sex hormones, spermatogenesis, rat.

MODULATION OF PLASMA KALLIKREIN/KININ SYSTEM: THE ROLE OF HEPARAN SULFATE PROTEOGLYCANS

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Human plasma kallikrein/kinin system proteins are related to inflammation through bradykinin release from H-kininogen by plasma kallikrein in the proximity to its target cells. Heparan sulfate proteoglycans (HSGP) play a critical role in recruiting kinin precursors from plasma and in the assembly of kallikrein/kinin system components on cell surface. We have studied the endocytosis and activation of H-kininogen and prekallikrein mediated by HSGP using wild-type CHO-K1 and CHO-745 cells, its mutant deficient in glycosaminoglycans biosynthesis. In CHO-K1 the H-kininogen interaction is strongly inhibited by heparin and heparan sulfate. H-kininogen internalizes in CHO-K1 but not CHO-745 in endosomal acidic vesicles. The endocytosis process is lipid raft-mediated dependent on caveolae. Both CHO cells do not internalize bradykinin-free H-kininogen. At pH 7.35 bradykinin is released from Hkininogen on surface of CHO-745 only by serine proteases; nevertheless, in CHO-K1 are involved either serine or cysteine proteases. The CHO-K1 lysate shows different kininogenases. Prekallikrein endocytosis in CHO-K1 is independent of H-kininogen, and it is not internalized by CHO-745. The prekallikrein cleavage/activation is independent of glycosaminoglycans but kallikrein formation is
more specific on Hkininogen assembled on the cell surface through glycosaminoglycans. Our data show the importance of HSPG in the regulation of plasma kallikrein/kinin system proteins.

**Financial Support:** CAPES, CNPq and FAPESP.

**Keywords:** Kininogen, kallikrein, proteoglycans, endocytosis.

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**SL-98**

**Track:** Drug Discovery in Pre-clinical Research

**NOVEL MULTI-FUNCTIONAL DRUGS FOR THE TREATMENT OF INFLAMMATORY DISEASES**

**Abraham Nudelman, Shani Zeeli, Svetlana Furman, Tehilla Weill and Marta Weinstock**

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Chronic activation of the immune system and the release of pro-inflammatory cytokines TNF-α, IL-6 and interleukin 1β (IL-1β) occurs in a variety of disorders including ulcerative colitis, Crohn’s disease, rheumatoid arthritis, diabetes, atherosclerosis and multiple sclerosis. Drugs that inhibit the excessive release of these cytokines may be of therapeutic benefit in these disorders.

A new series of synthetic indoline derivatives were prepared and their activity for reducing TNF-α and IL-6, elevated by lipopolysaccharides (LPS) in a macrophage cell line was determined. The anti-inflammatory activity of indolines possessing various side-chain substituents found at positions 3 or 1 of the indolinic system, was compared. Additional SAR studies on this activity, examined the effect of substitution by electron donating or withdrawing groups on the benzo ring in compounds where the side-chain substituents were found in position 1. Some of the prepared compounds displayed highly potent anti-inflammatory activities in the nano- and pico-molar concentrations. The synthesis of the derivatives and their biological activity will be described.

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**SL-187**

**Track:** High throughput Screening & Laboratory Automation

**AUTOMATED HIGH-THROUGHPUT AND HIGH-CONTENT SCREENING PLATFORMS FOR DRUG DISCOVERY AND TESTING USING ZEBRAFISH**

**Ravindra Peravali, Eduard Gursky, Daniel Marcato, Johannes Stegmaier, Helmut Breitwieser, Christian Pylatiuk, Masanari Takamiya, Andrey Kobitskiy, Jos van Wezel, Volker Hartmann, Gerd Ulrich Nienhaus, Ralf Mikut and Uwe Straehle**

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In recent years fish models have been increasingly adopted for identifying novel compounds and in *in vivo* testing of drugs and in toxicological studies. Specifically, the zebrafish (Danio rerio) embryo has emerged as a robust model for such investigations owing to its transparency, fecundity and genetic capabilities including transgenesis and gene knock-out. Furthermore, the importance of this model is reflected by the OECD’s developing and establishing rigorous guidelines for Fish Embryo Toxicity (FET) testing based on the zebrafish. Besides in-depth mechanistic studies, the zebrafish embryo model permits systematic screening of large numbers of compounds in parallel in a fast and unsupervised manner. To this end, the European Zebrafish Resource Center (EZRC) has exploited advances in imaging technologies, data storage and high-performance computing to establish screening platforms and pipelines for identifying and evaluating compounds using the zebrafish.
One of the bottlenecks in using zebrafish embryos for high-throughput studies is the manual handling and plating of the embryos. We present a “zebrafish sorting robot” that is capable of pipetting zebrafish eggs and larvae (up to 120 hours post fertilization (hpf)) into 96-and 384-microtiter plates and into petri-dishes. The zebrafish sorter is the first component of all our screening platforms. We present four specific imaging platforms that are aimed at performing chemical screens in a high-throughput and high-content manner. The first is an automated and intelligent microscopy platform that is developed on an Olympus Scan^R microscope but can be adapted to any microscope. This platform has the capability to automatically detect different Regions-of-Interest (ROIs) in zebrafish embryos and then perform high-throughput and high-resolution imaging without human intervention. The second platform is based on a robotic imaging system. A robotic arm equipped with a high-resolution camera is used to image developmental phenotypes both from a morphological and behavioral perspective. This system is capable of unsupervised data acquisition from 0 – 5 days post-fertilization (dpf) of zebrafish embryos. The third is a Photomotor Response (PMR) platform that is used to study the effect of psychotropic drugs on the behavior of zebrafish embryos. This automated platform captures the behavior of embryos (treated with neuroactive substances) prior to, during and after presenting a series of stimuli. Finally, we present a state-of-the-art Digital Scanned Light Sheet Microscopy (DSLM) platform that is used for studying embryonic development at high spatiotemporal resolution over long periods of time. Importantly, all the platforms presented include specialized data analysis pipelines that automatically extract quantitative phenotypic read-outs in real-time. We discuss the mathematical algorithms that are used in such data analyses. To facilitate such high-throughput and high-content screens we present the LSDF (Large Scale Data Facility) our data storage infrastructure that has on-line storage and archive capacity for several peta-bytes.

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**SL-75**

*Track: Medical Imaging*

**MICROSCOPIC IMAGING OF LIVING CELLS, AUTOMATIC TRACKING AND THE DESCRIPTION OF THE KINETICS OF THE CELLS FOR IMAGE MINING**

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Live-cell assays are used to study the dynamic functional cellular processes in High-Content Screening (HCA) of drug discovery processes or in computational biology experiments. The large amount of image data created during the automatic microscopic imaging screening requires automatic image-analysis procedures that can describe these dynamic processes. One class of tasks in this application is the tracking of cells. We describe in this talk a fast and robust cell tracking algorithm applied to High-Content Screening in drug discovery or computational biology experiments. We developed a similarity-based tracking algorithm that can track the cells without an initialization phase of the parameters of the tracker. The similarity-based detection algorithm is robust enough to find similar cells although small changes in the cell morphology have been occurred. The cell tracking algorithm can track normal cells as well as mitotic cells by classifying the cells based on our previously developed texture classifier. Results for the cell path are given on a test series from a real drug discovery process. We present the path of the cell and the low-level features that describe the path of the cell. This information is used for further image mining based on clustering and decision tree induction in order to obtain the desired information.

**Keywords:** Cell tracking, similarity-based cell tracking, microscopic image analysis, description of the kinetic of the cells, high-content analysis, computational cell biology, image mining.
A floating skeleton concept postulating a hydrostatic connection of the synovial capsules covering the joints [1] was experimentally validated in a controlled in vivo study [2]. It was discovered that pressure is transmitted between synovial joints (Fig. 1b). Such a paradigm is in contrast with a general convention about a joint capsule as an isolated container [3] with in-joint pressure independent of the pressures in the other capsules as illustrated in Fig. 1a.

Biomechanical rationale for hydraulic connection of the joints is a reduction of the pressures applied to the contacting surfaces of the bone heads for protecting the cartilages.

The concept provides for a new insight to the mechanisms of joint diseases and can be used in development of the new rehabilitation strategies or for enhancing the existing therapies.

REFERENCES


ONE POT SYNTHESIZED POLYMERIC NANOFORMULATION FOR TARGETING MICROTUBULES, TYR KINASES AND IMAGING FOR HEPATOMA THERAPY

Radhika Poojari, Rohit Srivastava and Dulal Panda

Hepatoma is the fifth malignant form of cancer worldwide. Till date, systemic treatment of hepatomas has not been effective in most cases and its clinical therapy is a major challenge. Many conventional antitumor drugs are non-selective for hepatoma cells and cause undesirable side effects. Therefore, it is important to search for new therapeutic modalities and novel therapeutic targets to generate effective treatment modalities for this fatal disease. Nanomedicines that can target both microtubules and kinases may provide new avenues to treat hepatoma. We have developed a one pot synthesized polymeric nanoformulation (OPPNF) comprising of microtubule inhibitor, tyrosine kinase inhibitor and an imaging probe quantum dots against human hepatoma cells. The real-time imaging of quantum dots in hepatoma cells showed accelerated internalization. OPPNF exhibited potent inhibition in hepatoma cell proliferation, clonogenicity, induced strong G2/M phase block, enhanced apoptosis induction and antiangiogenesis in comparison to free drugs. OPPNF strongly promoted the microtubule bundling, multinucleation, and inhibited the activation of downstream protein tyrosine kinase, ERK1/2 in hepatoma cells. These findings provide a significant insight into the intrinsic molecular interplays of OPPNF in hepatoma cells. One pot synthesis mediated OPPNF system integrates several avenues in a single nanoscale-platform for dual-drug delivery and high sensitivity quantum dots imaging for hepatoma therapy.

QUICK DISSOLVING OR LONG LASTING ELONGATED MICROPARTICLES FOR ENHANCING TOPICAL DRUG DELIVERY IN SMALL OR LARGE AREAS

Tarl Prow

Over the last 5 years we have been developing a novel transdermal drug delivery enhancement technology based on elongated microparticles called ForodermTM. This platform technology consists of high aspect ratio microparticles that can improve the transdermal delivery profile for a wide range of payloads including small molecules, peptides, proteins, vaccines, nutraceuticals and cosmeceuticals. We have explored quick dissolving microparticles and long lasting materials for long term delivery. The microparticles are not attached to any solid support allowing application to large or small areas of skin. Penetration of the stratum corneum by the microparticles creates pathways for the delivery of a range of bioactive including higher molecular weight compounds. We use 3-D printed applicators that have microtexturing engineered for optimal delivery. Our goal is to characterize cosmeceutical payload delivery using elongated microparticle formulations that maintain skin barrier function. We discuss our findings in excised human skin and volunteers.
OPTICAL FOURIER PHASE CONTRAST MICROSCOPY

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Phase contrast microscope is an extremely useful device for teaching and research. It is widely used to view high-contrast images of transparent specimens, such as living cells (without staining) in culture and thin tissue slices. As a result, the dynamics of ongoing biological processes can be observed and recorded in high contrast. Recently we developed novel Fourier phase contrast microscopy technology, a simple, inexpensive, all-optical, user-friendly and self-adaptive technique. It exploits monochromaticity, intensity and phase coherence characteristics of a low power laser and photo-induced birefringence of a nematic liquid crystal. Monochromaticity facilitates precisely defined deviated light and also provides well-resolved Fourier plane mapping of spatial frequencies (object information). Intensity of the laser source makes object features bright and clearly visible. High degree of phase coherence preserves the phase retardation introduced by the liquid crystal. When the liquid crystal cell is placed at the Fourier plane, low spatial frequencies at the center are intense enough to induce local liquid crystal molecules into isotropic phase whereas high spatial frequencies on the edges are not so intense and remain in the anisotropic phase resulting in $\pi/2$ phase difference between high and low spatial frequencies in real time. Moreover, by using a laser line notch filter (NF), brightfield+fluorescence, phase+fluorescence, and edge enhanced+fluorescence features of Drosophila embryo are imaged at once without the need for digital image registration and fusion. The phase information was obtained using the Fourier phase contrast microscopy technique, and fluorescence was imaged using trans-fluorescence illumination. This comprehensive microscope has the capability of simultaneously providing both structural and functional information of biological specimens in a streamlined simplified design with a single optical path. We recently licensed this technology to a company.
**SL-127**

**Track:** Genomics

**CONSTRAINTS OF DRUG RESISTANCE IN *MYCOBACTERIUM TUBERCULOSIS* – PROSPECTS FOR PHARMACOLOGICAL REVERSION OF ANTIBIOTIC SUSCEPTIBILITY**


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Emergence of multidrug resistant strains of *Mycobacterium tuberculosis* (Mtb) threatens public health around the world. This problem is aggravated by the crisis with design and introduction of new antibiotics against tuberculosis. Reversion of drug susceptibility looks as a promising alternative way to overcome the problem. Analysis of distribution of drug resistance mutations in the global Mtb population revealed a strong dependence of drug resistance on multiple other polymorphic alleles. Moreover, many drug resistance mutations were incompatible with each other possibly due to fitness cost accumulation. We hypothesized that the antibiotic resistance is dependent on general genomic context of microorganisms and thus targeting of multiple proteins or metabolic pathways may alleviate drug resistance or significantly reduce viability of mutant strains in the population. First, the hypothesis was confirmed by *in silico* calculation of linkage disequilibrium and R2 co-evolution coefficients for all reported genomic polymorphisms in Mtb population. Then, the hypothesis was confirmed by population genomic comparison of isolates of a multidrug resistant strain Mtb SCAID 187.0 (CP012506), which were reverted to drug sensitive variants by a new anti-tuberculosis nanomolecular complex FS-1. Successful clinical trial of FS-1 demonstrated prospect of the approach of antibiotic susceptibility reversion to combat multidrug resistant tuberculosis.

**SL-136**

**Track:** CNS Drug Discovery & Therapy

**COOPERATIVE RNA MODULATION OF NEURODEGENERATIVE DISEASE TRANSCRIPTS TO IMPROVE IRON HOMEOSTASIS WHILE ALSO PROVIDING ANTI-AMYLOID EFFICACY**

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We identified a potent neuroprotective activator of translation of the mRNA for the heavy subunit of the iron-storage protein ferritin in the network of mRNAs encoding iron-associated proteins. This iron homeostatic network includes the neurodegenerative Alzheimer’s disease (AD) specific amyloid precursor protein (APP) and the prion protein (PrP), which exhibit a role in iron efflux from neurons. PrP and APP mRNAs are iron-dependently translated via uniquely folded sequences that are homologous to the canonical Iron-responsive Element (IRE) RNA stem loops in the 5’ untranslated regions (5’UTR) of L- and H-ferritin mRNAs. As proof-of-concept for RNA based therapeutic approaches to cure neurodegenerative diseases, we had published that the APP 5’UTR directed FDA pre-approved drugs N-acetyl cysteine (antioxidant and iron chelator) and paroxetine (SSRI) had generated anti-amyloid efficacy in vivo in the brains of the TgCRND8 transgenic mice. This was also the case for the high throughput screened (HTS) drug JTR-009, as a benzimidazole that inhibited APP 5’UTR directed translation and prevented amyloid buildup to a high degree of selectivity.

Our small molecule lead was designated as ‘BL-1’, as a benzimidazole, that was first identified after an HTS
screen for 5'UTR inhibitors of PrP mRNA conducted at the Broad Institute (Cambridge, MA). Several experiments then proved that BL-1 was a selective translation blocker of APP as well as the co-seeding PrP. Secondary Western blot assays demonstrated that BL-1 modulated iron-responsive RNA binding protein events at these IRE-like sequences. BL-1 was found to be trophic since it activated translation of the ferritin light and heavy chains to safely store iron and prevent toxic buildup of iron-catalyzed oxidative radicals. BL-1’s capacity to promote safe storage of intracellular iron likely serves to prevent ferroptosis and slows down cellular aging. BL-1 was highly selective to IRE-like targets since this benzimidazole did not change the expression of a battery of metabolic proteins (i.e., GAPDH, LDH and cis-aconitase) and β-actin and β-tubulin levels were unchanged.

BL-1 limited tau phosphorylation without influencing tau and alpha-synuclein expression in neuronal cells lines and it improved cognitive performance of mice that underwent control cortical impact injury (CCI) (CCI is known to activate an AD-like pathology of increased amyloidosis, tau phosphorylation and increase brain iron burden). In collaboration with the Laboratory for Drug Discovery and Neurodegeneration (BWH, Harvard) we will medicinally diversify BL-1 as our lead small molecule activator of ferritin translation into a drug that will combat conditions of iron overload in the brain, improve neuronal health and boost cognition in established mouse models for AD.

Supported by grants from Aria and QR Pharmaceuticals, Alzheimer’s association (Zenith), and NINDS/NIH.

**SL-102**

*Track: Pharmaceutical Research & Development*

**HOLISTIC DRUG TARGETING**

**Anuradha Roy**

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Single target-single drug paradigms have long dominated the drug discovery and development landscape. While preferential drug specificity towards a target is effective against diseases that are monogenic, the administration of single drugs has been less successful against the widely prevalent diseases affecting large population groups like cancer, cardiovascular diseases, metabolic syndromes and neurological disorders. Majority of these complex diseases are multifactorial and are modulated by genetics, environment, age and sometimes, gender. Although drug combinations directed against two or more targets are widely employed in treatment of some diseases (cancer, AIDS), the new found realization of the successful outcomes attributed to polypharmacology of marketed drugs or of new molecular entities opens a new emerging paradigm for targeting multifactorial complex diseases.

**SL-16**

*Track: Recent Advances in Patient Treatment and Care*

**UNDERMINED BY ALTERED EPIDEMIOLOGY: CHANGING CONCEPTS IN THE MANAGEMENT OF BILHARZIAL URINARY BLADDER CARCINOMA IN EGYPTIAN POPULATION**

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**Introduction:** The objective is to validate the new clinicopathological features of bilharzial and non-bilharzial urinary bladder carcinoma in Egyptian population. These features are caused by altered epidemiology, and proposed to have reflection on management.
**Materials and Methods:** Timely contributions of leading Egyptian experts in bladder cancer in the last 4 decades were reviewed. Additionally, 102 patients were studied in 2 subsets A&B based on a pre-planned treatment modality: cystectomy facing transurethral resection plus radiotherapy. Observation on gross and microscopic features and their reflection on treatment decision are recorded.

**Results:** An overview of studies published in the last 4 decades is given, demonstrating a striking change in the characteristic features of bladder carcinoma in Egypt, more obvious in 2007 and after. Sixty percent of patients had their tumors in a bilharzial bladder, while 35% had their tumours in a non bilharzial bladder, where walls demonstrated the classical cystoscopic features of the disease. Group A patients were treated by cystectomy carrying 7.7% perioperative mortality, whereas patients in group B received radiotherapy preceded by transurethral resection.

**Conclusions:** Bladder cancer in Egyptian patients has lost its peculiar features imposed by bilharzial cystitis, shifting towards traditional types suitable for organ preserving management.

**Keywords:** Bilharzial cystitis, bladder carcinoma, carcinoembryonic antigen, cystectomy, trimodality therapy.

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**SL-21**

**Track:** Cancer Targeted Drug Delivery

**NOVEL ANTICANCER COMPOUND [TRIFLUOROMETHYL-SUBSTITUTED PYRAZOLE N-NUCLEOSIDE] TRIGGERS MITOCHONDRIA-DEPENDENT APOPTOSIS AND INHIBITS FLT3 ACTIVITY TO INDUCE DIFFERENTIATION IN ACUTE MYELOID LEUKEMIA CELLS**

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Anticancer properties of chemically synthesized compounds have continuously been optimized for better efficacy and selectivity. Derivatives of heterocyclic compounds are well known to have selective antiproliferative effect against many types of cancer. In this study, we have investigated the mechanistic aspects of anticancer properties of the indigenously synthesized anticancer molecule G-11, [1-[(2″,3″,4″,6″-Tetra-O-acetyl-β-D-glucopyranosyl)-4-(3′-trifluoro-methylphenylhydrazono)-3-trifluoromethyl-1,4-dihydropyrazol-5-one], in HL-60 cell line. We demonstrated that cytotoxic effect of G-11 is mediated by caspase-dependent apoptosis. However, the involvement of mitochondrial dysfunction induced by G-11 was independent of caspases. G-11 triggered generation of ROS, caused disruption of mitochondrial transmembrane potential, increased release of cytochrome c to the cytosol, and altered the expression of Bcl-2 and Bax proteins. These results suggest significant involvement of intrinsic apoptotic pathway.

Furthermore, G-11 was able to cause selective cytotoxicity and induce differentiation in the acute myeloid leukemia HL-60 cells. G-11 was to exert cytotoxic effect on hematological (Jurkat, U937, K562, HL-60, CCRF-SB) and solid tumor (MCF-7, HepG2, HeLa, Caco-2) cell lines, with IC50 values significantly lower than noncancerous cells (HEK-293, BJ and Vero) and normal peripheral blood mononuclear cells. G-11 induced differentiation of HL-60 cells to granulocytes and monocytes/macrophages by inhibiting the activation of FLT3 (CD135 tyrosine kinase). ITD-FLT3 mutation found in many acute myeloid leukemia patients could also be targeted by G-11 as exhibited by its inhibitory effect on MOLM-13 and MV4-11 cell lines. Molecular docking studies suggest the involvement of Leu616, Asp698, Cys694 and Cys828 residues in binding of G-11 to FLT3. This study comprehensively details the possible mechanisms of action of a novel heterocyclic compound which could find its potential use as an anticancer agent.
NATURE OPEN LIBRARY: AN OPEN INNOVATION INITIATIVE TO BOOST THE EXPLORATION OF NATURAL SUBSTANCES IN LIFE SCIENCES

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The decline in approved therapeutics is leading the pharma industry to redefine its drug discovery strategies. One outcome is the initiation of intercompany and academia collaborations to drive innovation. Pharma organizations are aiming to provide support in areas they are strongest in, and propose open access to core assets in return for enterprise. Open Innovation offers greatest chance of increasing productivity and in recent years, corporate libraries have so been used as tools to promote innovation, in order to encourage external involvement in enhancing drug discovery.

Natural products are a largely untapped resource, not only in pharma, but in animal health, agronomy, and nutrition among other. As part of an Open Innovation strategy and to foster the valorization of natural products in Life Sciences, Pierre Fabre Laboratories announced that they are launching “Nature Open Library”, their first Open Innovation initiative based on expertise on natural products. “Nature Open Library” will allow Pierre Fabre to share their private plant’s collection as well as their expertise in natural substances with industrial players and innovative projects initiators, for research, development and industrialization of plant active ingredients in all Life Sciences domains.

Pierre Fabre Laboratories provide access to their private plant collection, one of the most important in the industry, numbering over 15,000 classified samples including edible and pharmacopoeia parts of plants (with the aim of developing functional foods or nutraceuticals) but also numerous uncommon species of interest in drug discovery. This collection covers high taxonomic ranks to ensure a large botanical diversity (90% of plant Orders and 60% of plant Families), assuming that it would generate a rare library of natural substances. This collection has been developed in accordance with biodiversity access regulations (Rio Convention and Nagoya Protocol) and is managed through a total Quality Management system (Botanical Expertise Pierre Fabre). Thousands of plants extracts of worldwide origin are thus available for screening. Pierre Fabre Laboratories propose also collaboration with their interdisciplinary teams mastering the entire phyto-industrial value chain (from botanists and phyto-chemists to regulatory specialists) and will help in the further development of products (prescription medicines and consumer health care products).

In the frame of this Open Innovation initiative, some innovative results (new natural compounds and potential new herbal drugs) based on joint partnerships and collaborations between Pierre Fabre and French academic institutions will be presented and discussed.

Through this unique Open Innovation initiative “Nature Open Library” and by opening new fields of exploration for natural products that lead to innovative discoveries, Pierre Fabre Laboratories will help its future partners to boost their innovative process.

RATIONAL DESIGN AND SYNTHESIS OF A NOVEL MEMBRANE BINDING NAV1.8 SELECTIVE INHIBITOR WITH IN VIVO ACTIVITY IN PAIN MODELS

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Voltage-gated sodium channels (Nav), including subtype Nav1.8, are emerging as promising therapeutic targets to treat chronic pain. However, as these channels are intimately involved in almost all aspects of physiology, only the most selective inhibitors are suitable as drug leads. We have recently isolated µO-conotoxin, MIVIA, which inhibits Nav1.8 with high potency through interaction...
with the Nav1.8 channel voltage sensor domain. µO-conotoxin peptides are extremely hydrophobic and difficult to synthesize. In light of this, we have pioneered a novel sophisticated approach to obtain synthetic MfVIA, allowing us to produce analogues of µO-conotoxin to conduct pharmacological characterization of µO-conotoxin peptides.

Peptide-interaction with the voltage sensor domain is likely driven by the peptide initially inserting into the cell membrane surrounding this domain. With this in mind, analogs with improved membrane-binding properties compared to MfVIA were designed. One of these analogs showed a striking improvement in selectivity towards NaV1.8 over all the other NaV subtypes, including the skeletal muscle subtype NaV1.4. Therefore we believe to have found the first peptide drug lead with potential to selectively target Nav1.8.

Synthesis, structure-activity in vitro results, membrane-binding interactions and in vivo results from animal pain studies will be discussed, highlighting that MfVIA binding sites on Nav1.8 and Nav1.4 are distinct and that selectivity for Nav1.8 over Nav1.4 can be achieved resulting in peptides with proven efficacy in validated animal pain models.

**SL-144**

*Track: CNS Drug Discovery & Therapy*

**CHARNOL BODY AS A NOVEL BIOMARKER OF ZIKA VIRUS INDUCED MICROCEPHALY**

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Charnoly body (CB) was discovered initially in the developing undernourished rat cerebellar Purkinje neurons and in the intraterine Domic Acid-exposed mice hippocampal and hypothalamic neurons. The incidence of CB is increased with the severity of nutritional and environmental neurotoxic insult. We discovered CB as a universal biomarker of cell injury in nanomedicine and chronic drug addiction. CB was detected in various cellular and animal models of fetal alcohol syndrome, Parkinson’s disease, Alzheimer’s disease, vascular dementia, chronic drug addiction, and during intraterine exposure to environmental neurotoxins such as Kainic Acid, Domoic Acid, Acromelic Acid, PCBs and Lead. At the ultrastructural level, CB appears as a pleomorphic, electron-dense multi-lamellar, quasi-crystalline, stack of degenerated mitochondrial membranes causing progressive neurodegeneration in highly vulnerable neurons of the developing brain and may be induced by Zika Virus infection during intraterine life from infected parents. CB is a pre-apoptotic biomarker of compromised mitochondrial bioenergetics and is formed in response to intraterine infection, nutritional stress, environmental toxins, and/or drugs of abuse due to free radical overproduction and mitochondrial genome down-regulation. Accumulation of CB at the junction of axon hillock impairs axoplasmic flow of various enzymes, neurotransmitters, hormones, neurotropic factors (NGF, BDNF), and mitochondria at the synaptic terminals to cause cognitive impairment, early morbidity, and mortality accompanied with or without microcephaly. Early events in CB formation including: ΔΨ collapse, down-regulation of mitochondrial ubiqunone-NADH-oxidoreductase, and 8-OH-2dG can be detected as CB rudiments to evaluate epigenetic modulation of DNA methylation and histone acetylation following cellular injury with or without microbial infection. During chronic phase, CB can be detected at the ultrastructure level in the platelets, lymphocytes, neurons, and in any highly vulnerable cell. Antioxidants such as MTs inhibit CB formation as free radical scavengers by regulating zinc-mediated transcriptional activation of genes involved in growth, proliferation, and differentiation as we discovered in gene-manipulated human dopaminergic (SK-N-SH and SHY5Y) cells and in mouse models of neurodegeneration and multiple drug abuse. Hence novel drugs may be developed to prevent CB formation or enhance charrholagophy as a basic molecular mechanism of intracellular detoxification during acute phase and CB antagonists to avert microcephaly by employing CB as an early, sensitive and specific biomarker to detect, prevent and effectively treat microcephaly. The Zika Virus is a mosquito-transmitted infection related to dengue, yellow fever, and West Nile virus. Currently, it remains unknown how Zika Virus infection causes microcephaly and there is no vaccine available against its infection, which was first detected in Pernambuco (Brazil) in May 2015. About 24 locations mostly in the Caribbean, Central America and South America have been affected by Zika Virus infection. The children exposed to Zika Virus infection may become victims of microcephaly and burden to society rest of their life. It is proposed that Zika Virus infection in utero compromises mitochondrial bioenergetics to enhance free radical overproduction and lipid peroxidation in the highly vulnerable developing neurons to enhance CB formation and apoptosis; which may eventually induce microcephaly. Hence early therapeutic interventions to inhibit CB formation by nutritional rehabilitation, antioxidants, and healthy life-style choices (including personal and environmental hygiene) and refraining from drugs of abuse including smoking and alcohol may go a long way in the prevention and/or treatment of Zika Virus-induced or other forms of microcephaly in utero.
Charnoly Body-Induced Microcephaly

Various risk factors including (i) fetal alcohol, environmental neurotoxins (poly-chlorobiphenyls: PCBs, Lead: Pb, and mercury, Hg), and Zika viral infection alone or in combination may induce CB formation in the developing neurons to cause apoptosis, and eventually microcephaly in utero. Environmental protection, personal hygiene, well-nourished diet, and antioxidants may attenuate CB formation to prevent microcephaly.

NOVEL THERAPEUTIC INTERVENTION FOR Pancreatic CANCER USING SYNTHETIC CURCUMIN ANALOG UBS109

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Pancreatic ductal adenocarcinoma (PDA) is the fourth most common cause of cancer death, in part because a large majority of patients present with non-resectable advanced disease. The inherent biology of the disease makes it not only uniformly but also rapidly lethal: the overall 5-year survival for PDA is less than 5%, with a median survival of 4–6 months.

Curcumin is a common constituent of the daily diet in India and is believed to effectively prevent most cancers. We have synthesized over 100 monocarbonyl analogs of curcumin (MACs) such as EF24 and UBS109 and tested their activity against several cancer cell lines. We identified UBS109 as a key lead compound. We have demonstrated that UBS109 exhibits strong anti-cancer activity against pancreatic cancer and colon cancer cells, and show superior activity compared to gemcitabine and fluorouracil (5-FU) which are the current standard regimens.

Cytotoxic potency of UBS109 outmatches that of gemcitabine, HSP90 inhibitor (STA-9090), Akt inhibitor (MK2206) and p38 MAPK inhibitor (SB23580) against four human pancreatic cancer (PC) cell lines expressing full-length tissue factor (fTF) and alternatively spliced TF (asTF) at different levels. We have likewise confirmed that UBS109 inhibits pancreatic cancer xenograft and colon cancer xenografts with equal or better efficacy than the oxaliplatin and 5-FU combination. We tested four PC cell lines that express different levels of tissue factor since pancreatic cancer frequently induces thromboembolic complications.

Cytotoxic activity ranking follows: UBS109 > EF24 > HSP90 inhibitor > Akt inhibitor (MK2206) > gemcitabine > p38 MAPK inhibitor (SB203580). All agents were dosed from 0.0009 to 20 μM. MACs inhibit tumor growth in PC tumor xenografts. Importantly, UBS109 and EF24 do not kill normal cells at the same concentration range used for pancreatic cancers up to 20 μM.

UBS109 is an anti-cancer agent that inhibits both tumor growth in PDA tumor xenografts and desmoplasia in PDA that develop as a consequence of inflammatory reactions between the tumor and microenvironment. Desmoplasia causes PDA tumors to be hard and firm, compresses blood vessels and inhibits drug delivery into PDA tumors by increasing the intra-tumoral pressure. We have demonstrated that UBS109 inhibits desmoplasia in PDA as manifested by inhibition of the hyaluronic acid-binding protein (HABP), α-smooth muscle, and HSP90.
Mechanisms of action of MACs include:

a) MACs bind the sulfhydryl group of cysteine in glutathione (GSH), thereby oxidizing the thiol and inducing oxidative stress, mitochondrial membrane depolarization, and apoptosis.

b) MACs inhibit inflammatory reactions of NF-κB by suppressing IKK-α and IKK-β, thereby preventing desmoplasia that arises from the inflammatory reaction between the tumor and microenvironment. MACs, such as UBS109, inhibit the downstream effectors of NF-κB such as COX-2, inflammatory cytokines, VEGF, and fITF and asTF which promote tumor invasion and metastasis.

c) MACs are DNA hypomethylating agents in PDA tumor xenografts.

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**SL-38**

**Track:** Hot Topics in Natural Products

**ANTIBACTERIAL ACTIVITY OF ENDOPHYTIC Fungal EXTRACT OF MORINGA OLEIFERA**

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**Background:** Endophytes make symbiotic relationship with their host plant may be through intergeneric exchange of genetic information, thus may produce some bioactive compounds or their derivatives which were originally reported from their host plants. Thus endophytes are an exciting and relatively untapped source of novel compounds. The causative agent of infectious diseases are developing resistance toward present drugs. Hence, isolation of new effective compounds from natural source gives us an opportunity to develop new drugs. Endophytes are biological factories to produce bioactive compounds which are natural, inexpensive, safe, reproducible, unlimited and weather/season independent instead of using medicinal plants in huge amount. However, one major challenge in drug discovery lies in developing strategies to efficiently recover highly bioactive strains.

**Material and Methods:** A medicinal plant _Moringa olifera_ (family Moringaceae) is used in Ayurvedic traditional medicine. has been used as the source for endophytes in this study. _Moringa olifera_ plants growing within and around the campus premises of Banaras Hindu University, Varanasi (25.5° N 82.9° E, elevation 85 m) were selected for study. The source plant materials as leaves, stem and roots were surface sterilized and transferred to PDA media for endophytes isolation. The isolated endophytic strains were re-cultured for pure strain and the pure separated strains were inoculated in flask and incubated in BOD cum orbital shaker for mass cultivation. The filtered broth was then extracted with ethyl acetate three times. The organic phase was evaporated to dryness under reduced pressure using a rotary evaporator to constitute the crude broth extract. The antibacterial activity of endophytic fungal extracts was determined by disc diffusion method against human pathogenic Escherichia coli (ATCC 25922) gram negative and S. aureus gram positive (ATCC 25323). Light microscopy & SEM was done for morphologically identification of active strain. The preliminary phytochemical screening was done for host specific chemicals using standard protocols.

**Results:** A total 15 promising endophytic fungal isolates were recovered from different parts of _Moringa olifera_ in which 6 strains were isolated from leaves, 5 from stem and 4 from roots. Fungal isolates were grouped in 5 fungal genera Out of these strains, MO-L3 was most effective against gram positive and gram negative bacteria, however, MO-S5 was moderately effective and MO-L8 & MO-S1 were less effective. Alkaloids, flavanoids, polyphenols and steroids were positive while tannin was absent.

**Conclusion:** Our results suggest that isolated endophytes may be a source of new antimicrobial source to combat with drug resistance bacteria.

**Keywords:** Fungal endophytes, Antibacterial Activity, _Moringa olifera_ and bioactive strains.
SL-129

Track: Enabling Technologies

COMPOUND SERIES AND FAVORITES: A MEDICINAL CHEMISTRY STORY TELLING TOOL AT NOVARTIS

Timothy J. Smith

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Small-molecule drug discovery project teams currently use the idea of chemical series to organize their thinking and data. The series definition is clear to the project team, but it is rarely captured. As the project progresses the team learns about the properties of these series, identifies issues and makes decisions on whether to continue to work on or discontinue a series. This valuable information is captured ad-hoc in slides used for project updates or just stays with the scientists. At the level of the individual project teams, there is substantial overhead associated with tracking and using scaffolds to organize and present their data.

We developed a tool that would capture in dynamic graphs that thread of history from screen to therapeutic entity and the valuable problem solutions along the way. Once captured, the searchable and sharable information builds a knowledge space that informs new and similar med-chem leads as well as giving the researchers an easy tool to connect to other critical data systems. The ultimate advantage of integrated information is to accelerate innovation and benefit from our institutional knowledge.

Our tool was designed to share chemistry-specific project information, including:

- Key advances—and setbacks—in a series
- Relationships between structures
- Searchable scaffolds
- Rationales and decisions made on a series
- Integrate directly with key systems
- Graphical view of the med-chem story

The presentation of the conception, development and deployment of our Compound Series and Favorites tool may help the audience find new approaches to development and use of their institutional knowledge and learn from our experience developing a new narrative tool for the medicinal chemistry space.

SL-101

Track: Drug Discovery in Pre-clinical Research

DESIGN, SYNTHESIS AND ANTICANCER EVALUATION OF NOVEL PYRAZOLE AND PYRAZOLE[1,5-A]PYRIMIDINE DERIVATIVES

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Pyrazole derivatives play an important role among antitumor agents because of their good inhibitory activities against a number of crucial enzymes involved in cancer treatment. The pyrazolopyrimidine scaffold is also considered as an isostere to the purine nucleus and hence exhibits promising antitumor activity by acting as ATP competitive inhibitor for many kinase enzymes. In this study, the newly synthesized compounds were screened for in vitro anti-breast cancer activity, (MCF-7). Synthesis of 31 novel pyrazoles and pyrazolo[1,5-al]pyrimidines, was carried out. Among the 31 synthesized pyrazole and pyrazolo[1,5-al]pyrimidine derivatives compounds VIIIb and Xa elicited potent anticancer effects against MCF-7, comparable to the reference drug, doxorubicin.

Preliminary research on the mechanism of action of the most active compounds showed that the inhibition might be through S phase cell cycle arrest. Moreover, molecular modeling simulation of the most active compounds into the active site of CDK2...
(Cyclin dependent kinase 2) was performed in order to predict their affinities toward these enzymes. In addition, generation of 3D pharmacophore hypothesis and quantitative structure activity relationship (QSAR) models were combined to explore the structural requirements controlling the observed cytotoxic properties.

### SL-33

**Track: Anti-Infectives**

**STRUCTURE-BASED DISCOVERY OF NOVEL DNA GYRASE B INHIBITORS**


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The emergence of bacterial resistance to most of the clinically used antibiotics and the urgent need for potent antibacterials with broad spectrum of efficacy and improved safety profile has revived the research in this field. One of the well established targets is the DNA gyrase B [1], a topoisomerase with an ATPase activity. Starting from the available structural information and using structure-based design approach we identified a series of novel (i) 4,5'-bithiazole-2,2'-diamines [2], (ii) 4,5 dibromopyrrolamides and (iii) 4,5,6,7-tetrahydrobenzo[1,2-d]thiazoles [3] as ATP competitive DNA gyrase B inhibitors. Details of a nanomolar inhibitor 4,5-dibromo-pyrrole-benzamide binding mode were revealed by high-resolution crystal structure of the complex with DNA gyrase B [4].

**REFERENCES**


### SL-86(a)

**Track: Medical Imaging**

**ADVANCED APPROACHES TO DIAGNOSE AND TREAT THE CHRONIC AUTOIMMUNE DISORDERS: MULTIMODAL MOLECULAR IMAGING**

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Pathology and dynamics of particular cells and the molecular components of immune system is still challenging to be traced within living organisms. The techniques of molecular imaging (MI) are promising tools to monitor the immune system at work, to improve or allow personalized diagnostics and treatment, especially of the autoimmune diseases. In this study some possible targets for MI and biosensing are discussed. The personalized medicine, in addition to bioinformatics-based systemic approach, requires extensive research and novel high-throughput technologies like next generation of imaging, biosensing experimental systems based on microfluidics, nanotechnology, femtochemistry, superresolution (STED, STORM, PALM, SOFI, etc.), label-free imaging, spectroscopy (including TCSPC), MRI, multimodal optical methods, acoustic imaging through ultrasonic waves, nuclear medicine methods like SPECT and PET. Moreover, dedicated designs of modular Lab-on-Chip solutions are of high demand to perform multipurpose cell measurement and give a possibility to flexibly interact with sensed objects. These approaches are further supported through means of computational molecular biology and bioinformatics. Several aspects of in-silico solutions will be also discussed.
AN UPDATED MODEL OF PHARMACY AND TRANSLATIONAL MEDICINE EDUCATION TO GROW DRUG DESIGNERS OF THE NEWEST GENERATION

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Predictive, Preventive and Personalized Medicine (PPPM) as the Healthcare of the Future represents an innovative model for advanced healthcare and robust platform for relevant industrial branches for diagnostics and pharmaceutics. However, rapid market penetration of new medicines and technologies demands the implementation of reforms not only in biopharma, but also in education. Therefore, the problem of the updated education of specialists in bioengineering, drug design and affiliated fields is becoming particularly urgent, and it requires significant revision of training programs and curricula. Modernization and integration of widely accepted standards require consolidation of both the natural and medical sciences that may become the conceptual basis for the biopharma education. The main goal of this training is not simply to achieve advanced training and expansion of skills, but to provide development of novel multifaceted approaches to build academic schools for future generations. So, it becomes obviously that a higher, secondary and primary education as a TRIO should be integrated into the circuit! Based on current trends and own experience, we have made the first steps towards reshuffling the canonical educational tandem "School-University" and restructuring of Specialized Groups (with targeted disciplines) to get the mentees to be involved into having the existing healthcare system advanced and stepped forward. Moreover, non-canonical approach has been used to create a team of young researchers and biopharma students which has been recognized as The International Research Team of Youngsters under the aegis of EPMA, Brussels, EU, and ISPM, Tokyo, Japan. This model of multistage training has included (1) the 1st level of education-familiarize of schoolchildren with biopharma and drug discovery; (2) the 2nd level of education-deep study of fundamental and applied aspects of drug design; and (3) the 3rd level of education-study of interdisciplinary aspects of bioengineering and drug design among post-graduate students. Thus, integration of the primary and secondary education provides: (1) development in the chosen direction; and (2) optimization of the jointly set activity of a student and the teacher within a PAIR or a TANDEM (mentor-mentee). The need for teachers to be competent in all areas of professional practice has never been greater. So, a phrase “What Does It Mean to Be a Professional?” would attribute to a schoolchild, the child's family, the mentoring teacher and the microenvironment, for sure! The above-mentioned has pre-determining value, because under the disintegration of the world community expressed the competition in quality of the scientific intellect dramatically increases. The same occurs in the areas of quality of all of three segments of the educational process, i.e., Pre-College (secondary school), University and Graduate.

Keyword: Curriculum, Biopharma, drug design, drug discovery, bioengineering, education.

STUDY OF ANTITUMOR EFFICACY OF CISPLATIN IN COMBINATION WITH HORMONAL DRUGS FOR AN ASCITES OVARIAN CANCER MODEL IN WISTAR RATS

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Aim: To study antitumor activity of triptorelin-agonist of gonadotropin-releasing hormone and exemestane-inhibitor of aromatase in monotherapy and in combination with cytostatic drug cisplatin on the model of receptor-positive for estrogens and progesterone transplantable malignant ascites ovarian tumor (OT), to assess tumor response to treatment-treatment pathomorphosis and VEGF expression in tumor cells using different combinations of cytostatic and hormonal drugs.
Materials and Methods: 72 female Wistar rats, which underwent intraperitoneal transplantation of ascites OT, by 5×106 cells per animal, have been involved in the study. Rats were divided into 8 groups, 9 rats in each group: group 1-control, animals received physiological solution intraperitoneally and orally; group 2-rats, which were administered cytostatic cisplatin intraperitoneally; group 3-animals, which were treated with triptorelin intraperitoneally; group 4-rats, which were administered exemestane orally; group 5-animals, which received combination of cisplatin and triptorelin; group 6-rats treated with combination of cisplatin and exemestane; group 7-animals, which were administered combination of cisplatin, triptorelin and exemestane; group 8-animals, which received combination of triptorelin and exemestane. Histological study with assessment of treatment pathomorphosis in OT and immunohistochemical study have been carried out to analyze VEGF expression in OT cells. Survival of animals in the studied groups has been evaluated.

Results: Among animals treated in regimen of monotherapy (groups 2, 3, and 4), the most pronounced antiangiogenic activity in OT has been observed on application of hormonal drugs (triptorelin-39.4 and exemestane-33.9%, р<0.01), the highest grade of treatment pathomorphosis in OT has been observed at treatment with cisplatin (relative part of viable tumor tissue (RPVTT)-11.7%, р<0.01). Combination of triptorelin and exemestane has amplified antiangiogenic activity in OT (12.2%, р<0.01), but has not significantly changed rates of treatment pathomorphosis (RPVTT-22.1%, р<0.05) and survival of animals (32.2%, р<0.01) as compared with the same rates in rats treated by these hormonal drugs in monotherapy. Combination of cytostatic agent with triptorelin or exemestane has demonstrated significantly high rates of treatment pathomorphosis (RPVTT-10.1 and 16.2%, respectively) and antiangiogenic activity in OT (21.4 and 15.0%, respectively) as well as the highest survival of animals (100.0 and 85.7%, respectively) as compared with the same one in rats treated in regimen of monotherapy with cisplatin, triptorelin, exemestane or by combination of hormonal drugs. Among animals treated by combination of cytostatic drug with triptorelin, two were cured, and among rats, which received cisplatin and exemestane, one animal was cured.

Conclusion: Triptorelin and exemestane increase antitumor activity of cisplatin in respect to the malignant ascites OT and significantly increase survival of animals, especially when triptorelin and cisplatin are used in combination.

Keywords: Transplantable ascites ovarian tumor, rat, cisplatin, triptorelin, exemestane, treatment pathomorphosis, VEGF, survival.

SL-37
Track: Anti-Infectives

ASSESSMENT OF TIGECYCLINE PRESCRIPTION AND PATIENTS OUTCOMES AT THREE DIFFERENT HOSPITALS IN SAUDI ARABIA

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Purpose: To investigate tigecycline prescription and patient outcomes in the Kingdom of Saudi Arabia (KSA).

Methods: A retrospective observational study was conducted in three KSA government hospitals, between January, 2013 and May, 2014. The patients were identified from electronic prescription records; data were retrieved by trained researchers.

Results: Thirty-seven patients who received tigecycline were included (mean age, 52.5 years; range, 17 92): 51.4% were female. Tigecycline was prescribed for sepsis (59.5%), pneumonia (21.6%), and/or intra-abdominal infections (13.5%). The majority of the patients (86.5%) were prescribed tigecycline in intensive care unit (ICU) and the remaining patients were in the general medical ward. APACHE II score at the beginning of treatment was 16.8 ± 4.3, indicating severe disease. Susceptibility testing revealed 22 different bacterial pathogens, most commonly Acinetobacter baumannii (20 patients) and Klebsiella pneumoniae (14 patients). A significant proportion (56.7%) was polymicrobial and 16.2% involved suspected resistant pathogens. Sixteen patients recovered (5 on tigecycline alone, 5 with additional antimicrobials, and six switched to alternatives) while 21 patients died (nine on tigecycline alone, 12 with additional antimicrobials).
Conclusion: The study revealed that tigecycline prescription was conducted according to marketing authorizations and national guidelines. Infection severity/stage and comorbidities may influence patients’ response, and explain some of the poor outcomes.

Keywords: Kingdom of Saudi Arabia, prescription patterns, mortality, tigecycline, antimicrobial.

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**SI-111**

**Track:** Pulmonary Drug Discovery & Therapy

**ESTRADIOL METABOLISM: PHARMACOLOGICAL TARGET IN PULMONARY HYPERTENSION**

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Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by proliferation of endothelial cells and formation of occlusive (OL) and plexiform lesions (PL). The fact that this disease is more common in women (women: men ratio = 3-4:1) suggests that estrogens may importantly contribute to the pathophysiology of PAH. Since our first report (J Cardiovasc Pharmacol 2005; 46:430) that 2-methoxyestradiol (2ME; major non-estrogenic metabolite of E2, product of 2-hydroxylation pathway) attenuates the development and progression of MCT-induced PAH, it has become increasingly clear that estradiol and its metabolic precursors and metabolites can exhibit both detrimental and protective effects in PAH. In this regard, we have shown that 2ME, its metabolic precursor 2-hydroxyestradiol (2HE), and synthetic analog 2-ethoxyestradiol have protective and/or therapeutic effects in monocrotaline, hypoxia-, alpha-naphthylthiourea- and bleomycin-induced PAH. Recently we have demonstrated that compared to male rats, females develop more severe angioproliferative PAH. 2ME is dehydrogenated by type-2 17β-hydroxyestradiol dehydrogenase (17-HSD2) to 2-methoxyestrone (2ME1), a metabolite with no biological activity. However, in vivo 2ME1 may be converted back to 2ME2 by type-1 17β-HSD (17-HSD1).

Therefore, we examined the effects of estradiol (E2), ovariectomy (OVX), E2 synthesis inhibitor Anastrozole, 2ME and its inactive metabolic precursor 2ME1 in our female model of accelerated and severe angioproliferative PAH. All animals received (20-100mg/kg/s.c) of VEGF antagonist Sugen5416 (20-100mg/kg/s.c) and were exposed for 3 weeks to hypoxia (10%O2), followed by 0-3 weeks of normoxia (Su+Hx).

In intact female (F) rats, Su+Hx induced severe PAH with numerous OL and PL and sporadic presence of grade 6 lesions. Ovariectomy reduced PH and OL, yet increased the number of PL and tended to increase RV hypertrophy. In OVX rats, preventive treatment with E2 had mixed effects in regard to PAH, pulmonary vascular lesions and right ventricle (RV) remodeling, whereas rescue treatment with E2 exacerbated the development of PAH and pulmonary vascular lesions, yet, reduced RV remodeling. Ovariectomy reduced PH and OL, yet increased the number of PL and tended to increase RV hypertrophy. Anastrozole, an inhibitor of extra-gonadal E2 synthesis, reduced PAH and number of OL and PL and had no effect on RV remodeling. Preventive treatment with 2ME had moderate beneficial effect on disease, while rescue treatment reduced PAH and number of OL and PL. In OVX rats, 2ME1 significantly retarded the progression of disease, reduced OL and tended to reduce PL and markedly reduced RV remodeling.

The current study suggests potential therapeutic effects of non-estrogenic E2 metabolites in PAH and warrants further evaluation of E2 metabolism modulators in PAH.

Keywords: Pulmonary hypertension, estradiol metabolism, 2-methoxyestradiol.
SL-54

Track: Hot Topics in Drug Targets

PARTIAL INHIBITION OF MITOCHONDRIAL FUNCTION AVERTS THE DEVELOPMENT OF ALZHEIMER’S DISEASE

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Alzheimer’s Disease (AD) presently affects more than 5 million Americans with numbers expected to grow. This is a terrible epidemic with no effective treatment and with multiple failed clinical trials focused on prevention of amyloid beta production. Alternative approaches and novel molecular targets are urgently needed. Decrease in mitochondrial function is traditionally associated with the worsening health. Surprisingly, emerging data including our own suggest that partial inhibition of mitochondrial activity using small molecules or genetic manipulation that affects the activity of electron transport chain, could be beneficial promoting health and lifespan, and alleviating the development of neurodegenerative diseases.

I will discuss our new data that partial inhibition of mitochondrial Complex I with small molecule compounds represents safe and efficacious therapeutic approach for Alzheimer’s Disease (AD). This treatment prevented the development of cognitive and behavioral phenotype in three preclinical animal models of AD (APP, PS1 and APP/PS1 mice) when animals were treated in utero for life (14 months) or at pre-and symptomatic stages of the disease. Neuroprotection was associated with the augmented cellular bioenergetics, increased neuronal resistance to oxidative stress, reduction in soluble and insoluble Aβ and levels of pTau, restoration of axonal trafficking and synaptic activity in vivo. Using computational biology and multiple assays, we identified mitochondrial Complex I as the molecular target of our small molecules. I will discuss current stage of this drug discovery project, its translational validation, stages of hit to lead optimization, safety and selectivity data regarding new compounds developed using rational design.

SL-19

Track: Bioactive Lipids

EFFECTS OF SYSTEMIC INFLAMMATION ON SERUM ALBUMIN BINDING CAPACITIES

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Albumin is critically important in binding and transporting a wide range of life-supporting substances including bioactive lipids and a variety of pharmacologic agents. Albumin can be structurally modified by oxidation and ligand-binding in acute and chronic phases of a variety of disease states, and such modifications can significantly impair the binding capacities and transport functions that albumin has under normal healthy conditions. The effects of structural modifications on albumin binding capacity are difficult to determine by analyzing serum or plasma samples in a clinical setting. We recently developed two fluorescent assays that specifically determine the binding activities of albumin with fatty acids and phospholipids in serum and plasma. Our assays showed that oxidation of and pre-binding of fatty acids and/or lyso-phospholipids to albumin could alter and deplete albumin’s normal binding capacity. Our investigations also showed that the normal binding capacities of serum albumin obtained from patients with sepsis in a critical care unit setting were either completely or largely depleted, even after adjusting for serum albumin content, which we presume to be due to albumin binding to cell membrane breakdown products of fatty acids and lyso-phospholipids when a massive level of cell death occurs. Our assays may be useful to determine binding capacities of serum albumin under normal conditions and during episodes of critical illness when deliveries of nutrients, essential elements, and drugs that depend on albumin for transport are needed to enhance recovery from severe systemic illness.
**SL-151**

*Track: Proteomics & Bioinformatics*

**STRUCTURAL BASED APPROACH TO EVALUATE MAPK PATHWAYS: A NOVEL TARGET FOR DRUG DISCOVERY**

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Cell-signaling in the c-Raf downstream pathways have been explored because genetic variants discovered in any genes in this pathway play a central role in human cancers. Different members of the MAP kinases belong to family of Ser/Thr protein kinases, and localizes between cytoplasm and nucleus. Noting the cellular localization, this pathway can be divided into two functional cascades RAF-MEK1-ERK2 and ERK2-RSKs. The genes present in both of the cascade shuttle between cytoplasm and nucleus through the functions mediated by protein–protein interactions (PPIs). Few amino acids present at the interfaces of both the cascade helps in shuttling them between cytoplasm and nucleus. Protein-protein interactions present in different pathways of MAPK play very important role in cell-signaling. Considering the role of MAPK in dissecting the signaling mechanism, we have performed multidisciplinary in-vitro, in-silico and biophysical approach to unravel the functions associated to MEK1/ERK2/RSKs pathways. Nevertheless, large numbers of small molecule inhibitors are identified to explore signaling mechanism in MAPK pathways, but the drug that target specific cancer with less toxicity is still far from reach. The in-silico docked small molecules into the structures of MAPKs can help in cell-signaling and furthermore designing the better inhibitors.

**SL-113**

*Track: Cancer Targeted Drug Delivery*

**ENZYME CATALYZED DECOMPOSITION OF 4-HYDROXYCYCLOPHOSPHAMIDE: THE KEY FOR UNDERSTANDING THE HIGH CANCERO SELECTIVITY OF OXAZAPHOSPHORINE CYTOSTATICS**

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According to general doctrine canceroselectivity of Cyclophosphamide is based on different activities of the 4-hydroxy cyclophosphamide (OHCP) detoxifying cellular enzyme aldehyde dehydrogenase in tumor and normal cells. Aldehyde dehydrogenase converts the OHCP tautomere aldophosphamide (ALDO) to the non cytotoxic carboxyphosphamide. Due to different activities of the detoxifying enzyme more cytotoxic phosphoramid mustard (PAM) is spontaneously released from OHCP/ALDO in tumor cells. PAM unfolds its cytotoxic activity by forming intrastrand and interstrand DNA crosslinks. This hypothesis is supported by *in vitro* experiments which show inverse correlations of aldehyde dehydrogenase activity and sensitivity of tumor cells against activated congeners of cyclophosphamide like mafosfamide which hydrolyses within a few minutes to OHCP. In protein free rat serum ultrafiltrate however free OHCP and its coexisting tautomer ALDO are stable compounds. Its half life in protein free rat serum ultrafiltrate (pH7, 37°C) is more than 20 h. Contrary to protein free ultra filtrate in whole serum ALDO is enzymatically decomposed to PAM and 3-hydroxypropionaldehyde (HPA) within minutes. The decomposing enzyme was identified as 3’-5’ phosphodiesterase, the Michaelis constant for which was determined to be 10-3 M in human serum.

A two step mechanism for the mechanism of action of OHCP/ALDO is discussed. During the first step, the DNA is damaged by alklylation by PAM. During the second step the cell containing damaged DNA is eliminated by apoptosis, supported by HPA.
CHEMOTHERAPY OF HUMAN CYSTIC ECHINOCOCCOSIS IN BULGARIA

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Introduction: Echinococcosis is a chronic disease in humans. Thirty six years ago a two-years-long multicenter clinical trial on the treatment of human cystic echinococcosis with benzimidazole carbamates started in five centers (Beirut, Paris, Roma, Sofia and Zurich).

Materials and Methods: Chemotherapy was introduced in 1979 for the treatment of echinococcosis in Bulgaria and 408 patients was treated. The patients are with single and multiple echinococcosis (secondary disseminated cysts, relapses, inoperable cases, with contraindications for surgery, cases intraoperatively ruptured, residual cysts). The treatment response was based on objective criteria provided by imaging methods-US, X-ray, Computed tomography, confirmed by serological methods (ELISA, indirect hemagglutination, immunofluorescent test, latex agglutination).

Results: Cyst changes, which characterized the cyst responses, are criteria for determining the final chemotherapeutic effectiveness in patients. The initial change in cysts were observed at the end of 1st month therapy (detachment of endocyst). The subsequent changes (hyperechoic/hyperdense appearance, size reduction), detected in all cysts in following albendazole therapy are considered as a damage of hydatid cysts. There were no serious side effects related to the applied drugs.

Keywords: Liver cystic echinococcosis, chemotherapy, Albendazole.

ITPKA AS A TARGET FOR TUMOR THERAPY

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As ectopic expression of the neuronal inositol-1,4,5-trisphosphate-3-kinase A (InsP3Kinase) in tumor cells increases the metastatic potential, InsP3Kinase is an interesting target for tumor therapy. Recently, we have identified a membrane-permeable InsP3Kinase inhibitor (BAMB-4) exhibiting an IC50-value of 20 µM. Here we characterized a new InsP3Kinase inhibitor which shows a 130-fold lower IC50 value (157 ± 57 nM) as compared to BAMB-4. We demonstrate that this nitrophenolic compound, BIP-4, is non-competitive to ATP but competitive to InsP3, thus exhibits a high selectivity for inhibition of InsP3Kinase activity. Docking analysis suggested a putative binding mode of this molecule into the InsP3Kinase active site. Determination of cellular uptake in lung cancer cells (H1299) revealed that 6% of extracellular BIP-4 is internalized by non-endosomal uptake, showing that BIP-4 is not trapped inside endo/lysosomes but is available to inhibit cellular InsP3Kinase activity. Interestingly, we found that BIP-4 mediated inhibition of InsP3Kinase activity in the two lung cancer cell lines H1299 and LN4323 inhibited proliferation and adhesion at IC50 values of 3 µM or 2 µM, respectively. InsP3Kinase inhibition did not alter ATP-induced calcium signals but significantly reduced the level of Ins(1,3,4,5,6)P5. From these data we conclude that the inhibitory effect of BIP-4 on proliferation and adhesion of lung cancer cells does not result from alterations of calcium but from alterations of inositol phosphate signals. In summary, we reveal that inhibition of cellular InsP3Kinase by BIP-4 impairs proliferation and adhesion and therefore BIP-4 might be a promising compound to reduce the metastatic potential of lung carcinoma cells.
RNA BINDING PROTEINS INTERACT WITH TAU TO MODULATE PATHOLOGY AND DISEASE PROGRESSION

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Introduction: RNA binding proteins have emerged as one of the key groups of proteins that contribute to disease pathogenesis, pathology and progression. Mutations in proteins such as TDP-43 and FUS cause motor neuron diseases, and sporadic cases of amyotrophic lateral sclerosis and frontotemporal dementia (FTD) exhibit abundant TDP-43 pathology. Involvement of RNA binding proteins in neurodegenerative diseases is thought to derive from the inherent tendency of these proteins to aggregate, forming various types of RNA granules, including stress granules. We previously observed that RNA binding proteins also associate with tau pathology in Alzheimer’s disease, FTDs and animal models of tauopathy.

Methods: We use neuronal cell lines, primary cultured neurons, and animal models of tauopathy (PS19, Tg4510) to investigate the role of TIA1 in tau pathophysiology and toxicity. For the in vivo studies, we examined PS19 mice (overexpressing human P301S tau) on Tia1+/+ or Tia1 +/-. Mice were assessed at 3 and 6 months of age by a combination of immunohistochemical, biochemical, and behavioural approaches.

Results: We now report that tau contributes to the biology of RNA binding proteins in vitro and in vivo, and that RNA binding proteins modulate the pathophysiology of tauopathies. Analysis of the protein interactome network for TIA1, a RNA binding protein, demonstrates a striking dependence on the presence of tau, with tau deletion reducing the number of proteins interacting with TIA1 and inhibiting its ability to translocate into the dendritic arbour. Conversely, TIA1 modulates the misfolding and aggregation of tau. Over-expressing TIA1 in cultured hippocampal neurons induced tau misfolding and aggregation in stress granules. Knockdown or deletion of TIA1 inhibited tau misfolding and prevented the toxicity of P301L tau in cultured hippocampal neurons. Protection by TIA1 was also evident in vivo.

Discussion: These results indicate that tau contributes to the neurobiology of RNA binding proteins. The results also demonstrate that RNA binding proteins, such as TIA1, modulate the pathophysiology of tauopathy. We propose that the pathological interaction of RNA binding proteins with tau contributes to disease progress, which places tauopathies in the spectrum of diseases linked to RNA binding protein dysfunction.

CLINICAL RESEARCH OF NATURAL INGREDIENT "DLK-2" ON AD (ALZHEIMER'S DISEASE) PATIENTS' COGNITIVE FUNCTION AND SLEEP CURATIVE EFFECT

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Objective: Figuring out and verifying the effectiveness of DLK"s on Sleep Apnea Syndrome (SAS) and AD by using analysis on MMSE and "PSQI" tests.

Methods: Using before and after control study. Selecting 20 patients who were diagnosed as AD. After 20 days of medical treatment by using extracted polysaccharide ingredient from a kind of Dioscoreaceae plants, observe and compare the scores of scale of those patients.

Results: After twenty-day clinical trial, analysis on MMSE and "PSQI" tests results of before-after dosing revealed that patients who all attained criterion of AD had cognition injured in different degrees before dosing, while, their cognition has ameliorated after dosing and scores of scale have also increased. According to statistical results, before-after
comparison of the total score and average score was \( p=0.239775 \) and \( p=0.226561 \) respectively. Although both of which were not of significant differences, from the view of clinical manifestation on AD, dosing time of 20 days has brought out the significant amelioration.

**Conclusion:** DLK-2 had significantly improved the cognitive level and sleeping disorder of patients in a short time without side effects. With a striking result of clinical manifestation, as an extract of natural substance, DLK-2 is indisputably eligible to be developed into a functional food or nutritional supplement with safety and effectiveness.

**Keywords:** Natural nutritional supplement, AD, MMSE and "PSQI" tests, natural extracts.

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**SL-155**  
**Track:** Drug Delivery & Targeting

**ELONGATED SILICA MICROPARTICLES FOR ENHANCED DELIVERY OF TAILORABLE NANOEMULSION AS A POTENTIAL PLATFORM FOR TRANSDERMAL DRUG DELIVERY**


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The purpose of this research was to evaluate the combination of elongated silica microparticles (EMP) and tailorable nanoemulsions (TNE) to control topical delivery of hydrophobic drug surrogates. The microparticles penetrate through the epidermis and stop at the dermal-epidermal junction (DEJ). TNE is unusually stable because the oil core allows high loading levels and the surface properties can be easily controlled. In this study we incorporated a fluorescent lipophilic dye, DiI, as a hydrophobic drug surrogate into TNE for visualization with microscopy. In addition, the core droplet of TNE was packed with pharmaceutical grade lipid (glycerol) instead of DiI and imaged by coherent anti-Stoke Raman scattering (CARS) microscopy to characterize the delivery of lipid in freshly excised human skin. We compared four different coating approaches to combine EMP and TNE. These data showed that a freeze-dried formulation with alginate cross-linking showed 100% of the detectable TNE were retained on the EMP. When this dry formulation of EMP-TNE was applied to excised, living human abdominal skin, the EMP penetrated to the DEJ and we observed that the controlled release of TNE thereafter. This formulation resulted in a sustained release profile, whereas a freeze dried formulation without crosslinking showed an immediate burst type of release profile. DiI could be detected as deep as 60 µm into the skin showing a potential usage of TNE as a hydrophobic drug carrier in combination with a physical penetration enhancing technology. These data show that a dry, slow release formulation containing EMP coated with TNE can effectively deliver a hydrophobic payload deep into the human epidermis and controllably release that payload.

**Keywords:** Transdermal delivery, Nanoemulsion, Elongated microparticles

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**SL-192**  
**Track:** Biologics

**EFFECT OF AZADIRACHTA INDICA (NEEM LEAVES) ON HEMATOLOGICAL PARAMETERS & SERUM BIOCHEMICAL PROFILE IN COMMERCIAL BROILERS CHICKENS**

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Study was conducted to assess the effects of Azadirachta indica admixed in poultry feed on weight gain performance, hematological values, immune modulations, and toxic effects in broiler chickens. The birds were divided into 3 groups and four sub-groups of each i.e. A1, A2, A3 and A4; B1, B2, B3 & B4 and C1, C2, C3 and C4, respectively. The birds of groups A, B and C were fed with poultry feed with powder of neem leaves @ 2 gm, 4 gm and 6gm per kg feed at different days of age
respectively. Difference b/w weekly weight gain in birds of groups A1, B1 and C1 was non-significant (P>0.05) however the difference b/w weight gain in treated and control groups was significant (P<0.05). Herb treated birds from day 0 of their life showed more weight gain. There was no difference in the hematological indices b/w all of the treated groups and the control groups. Treated birds showed increased antibody titers (P<0.05) against ND and IBD viruses. With the increase of neem leaves values of ALP and AST showed decreasing trend. Serum creatinine and uric acid values decreased slightly. Higher the concentration of the herb, lower the cholesterol value. The organ body weight indices showed no significant difference. Gross pathological lesions were absent in liver, spleen, kidneys and thymus. No histopathological changes were observed in liver, spleen, kidneys and thymus in treated birds.

**Keywords:** Broiler chickens, neem leaves, weight gain.

**SL-43**

**Track:** Protein and Peptide Sciences

THE DISCOVERY OF SMALL MOLECULE PEPTIDE DRUGS AND THEIR POTENTIAL THERAPEUTIC AND PREVENTIVE EFFECTS

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After nearly 10 years of research, we found dozens of small molecular peptides in fermented milk products. Our researches show that these small molecular peptides have a variety of biological activities and could serve as new potential peptide drugs in disease therapy and prevention.

Based on previous knowledge, only molecules with big molecule weights such as insulin and thymopeptide tend to have therapeutic effects. We discover however, that dozens of small molecular peptide with molecular weight under 1000 Da have strong biological activities in immune regulation, anti-inflammatory, antioxidant and anti-aging. Our gastrointestinal digestion simulation experiment and intracellular extracellular test results show that some short peptide, such as DELQ, QEPV and LPLP can penetrate the cell membrane and play biological activities inside of the cell. Therefore, we believe that unlike the macromolecular polypeptide drugs which interact with small compounds and function outside of the cell, these potential short peptide drugs can move into the cell and function from inside.

**Keywords:** Polypeptide, fermented milk, preventive effect.
**PO-7**

*Track*: Pharmaceutical Research & Development

**COMPUTER SIMULATION FOR ACTION OF DRUGS WITH PARTICULAR EMPHASIS ON PRIMARY PHARMACOPHORE DRUG REACTION WITH SICK PARTS OF REACTIVE GROUPS**

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Electronic simulation or computer simulation of activity of the reactive, active or passive group or a receptor target for the pharmacophore on parts of the drug in three-dimensional space. Experimental theoretical determination of the reactive components as drug and active molecular groups of sick parts in body or foreign agents. It does not matter whether it is a bacteria, virus, cancerous part or allergen, as well as autoimmune antigen, principle is the same. Pharmacophore drug, as the main active part, is placed in a different three-dimensional situation-mentioned reactions, with molecules or reactive groups. Particular problems are in addition to these primary pharmacophore, secondary and tertiary pharmacophore. Also problem is in other than the reactive group of the pharmacophore as secondary and tertiary reactions with other reactive sites. Until now, the most tested antibiotics in bacterial infections confirmed, but the principle is the same for all as viruses, fungi, allergens, antigens, autoimmune disease or malignancies. It is possible to predict the side effects if we recognize all reactive groups, and even the outcome of treatment, only for this we require even more sophisticated computer programs. It is also possible to design drugs and its specific pharmacophore before experimental tests on animals, and later in adult volunteers. A particular challenge is the pediatric pharmacological testing of drugs, side effects in the child population, which represents for me the biggest challenge in science. Time will show the undoubted value of these computer tests which will be improved as well as their own drugs with effective pharmacophore, including targeted action in a sick part of organism.

**Keywords**: Simulation, Computer, Pharmacophore, Drug, Reactive groups.

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**PO-50**

*Track*: Pharmaceutical Research & Development

**THE EFFECT OF TREATMENT WITH CALCIUM CARBONATE OR ALPHA METHYLDOPA ON SERUM LEVELS OF THE ELEMENTS (CALCIUM, MAGNESIUM, IRON, COPPER AND ZINC) IN WOMEN WITH PRE-ECLAMPSIA**

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The etiology of pre-eclampsia is still not exactly known. The change in the levels of various elements in women’s serum and its relation to the aggravation of the hypertensive complication of pregnancy may play a role. This study was conducted to investigate the possible effects of treatment with calcium carbonate in mild-, and α-methyldopa in moderate- pre-eclampsia on the serum levels of calcium, magnesium, iron, copper, and zinc and the relation to the development of such medical condition.

Forty-five women in the third trimester of pregnancy were selected to participate in this study. The study was approved by the Scientific Committee of the College of Pharmacy-Baghdad University. Informed consent was obtained from each woman. They were classified into three groups: normotensive pregnant control group, their mean systolic blood pressure (115.33 ± 5.4) mmHg and diastolic blood pressure (78.66 ±5.46) mm Hg; pregnant women with mild pre-eclampsia,
their mean systolic and diastolic blood pressure were, respectively (140.83±2.60) mmHg and (91.70±2.85) mmHg, they received calcium carbonate 500 mg twice daily; pregnant women with moderate pre-eclampsia, mean -systolic blood pressure (155.00 ± 8.40) mmHg and -diastolic blood pressure (102.50 ± 6.10) mmHg, they received α- methyldopa 250 mg tablet three times daily. Pre-eclamptic women received their specific treatment until the day of delivery. Blood pressure, fetal heart rate and other clinical investigations were checked every two weeks by the obstetrician. Serum levels of (calcium, magnesium, iron, copper, and zinc) were measured before and after one month of starting of each treatment.

There was significant elevation in the levels of systolic-, and diastolic- blood pressure in mild and moderate pre-eclamptic women compared to normotensive pregnant. The levels were significantly reduced after one month of treatment with calcium carbonate or α-methyldopa. Serum calcium level was significantly reduced in mild- and moderate- pre-eclampsia compared to normal pregnancy which is significantly increased after each treatment compared to pre-treatment level. Serum magnesium level was non-significantly different in mild pre-eclampsia compared to normal pregnancy which was also non-significantly different after one month of treatment with calcium carbonate; while in moderate pre-eclampsia, serum magnesium level was significantly reduced compared to normal pregnancy and it was significantly increased after α-methyldopa therapy. There was significant increase in serum levels of iron and copper in both cases of pre-eclampsia compared to normotensive pregnant controls. Serum -iron level was significantly reduced, with a non- significant reduction in the -copper level after one month of treatment with calcium carbonate in mild pre-eclampsia compared to pre-treatment levels. In moderate pre-eclamptic women, treatment with α-methyldopa produced non-significant differences in serum iron and copper levels after one month of treatment. Serum zinc level was non-significantly different in mild pre-eclamptic women; while in moderate pre-eclamptic women, there was a significant reduction in the level of serum zinc compared to normal pregnancy. No significant changes in the levels of serum zinc were observed after one month of treatment with either calcium carbonate in mild or α-methyldopa in moderate pre-eclamptic women compared to pre-treatment levels.

In conclusion, this study revealed that changes in serum elements of women with pre-eclampsia might be possible contributors in the etiology of this condition. The study also indicated the beneficial effect of both calcium carbonate in controlling -mild and α-methyldopa in -moderate pre-eclampsia by reducing blood pressure, and improving the deterioration in serum levels of elements.

Keywords: Pre-eclampsia, calcium, magnesium, iron, copper, zinc.

PO-49

Track: Nutraceutical Drug Discovery & Therapy

CASUES OF NON-ANTIBODY-MEDIATED SKIN DISORDERS ASSOCIATED WITH HYPERHOMOCYSTEINEMIA TREATED WITH HIGH DOSE FOLIC ACID, VITAMINS B6 AND B12

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Published reports show daily folic acid (FA) (5-7 mg) with vitamins B6 (100 mg) and B12 (1000 mcg) improves psoriasiform contact dermatitis [1-2] and palmar plantar pustulosis [4]. Psoriasis cases have been presented that flared on 1-2 mg daily FA, B6 and B12 yet improved when the folic acid dose was increased to 4-7 mg [5, 6]. Five mg FA, B6 and B12 were added to patients on 16 weeks of adalimumab, 2 of 7 patients’ psoriasis worsened. Both had body mass indices under 24 and baseline vascular endothelial growth factor levels at or above 140 pg/ml [3, 6].

Lower doses of FA can be pro-inflammatory through creation of monomeric endothelial NOS. High doses can be anti-inflammatory through anti-inflammatory conjugated eNOS, BH4 recycling and deactivation of peroxynitrite derived radicals.

Homeocysteine (Hcy) reduces expression of VEGF-A and VEGFR-2. Reducing Hcy with 1- 2 mg daily FA may promote psoriasis by allowing VEGF effect to act unopposed.
Reducing or stopping these high FA doses may place a patient at risk for comorbid events due to the passage through pro-inflammatory FA levels. The safety of stopping this therapy requires study.

REFERENCES

PO-16

Track: Pharmaceutical Research & Development

BIOTRANSFORMATION: A TOOL FOR THE DISCOVERY OF NOVEL BIOACTIVE COMPOUNDS

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Biotransformation has been extensively used for the structural modifications of organic compounds by whole cell cultures of fungi or bacteria, isolated enzymes, and animal and plant cells. Biotransformation is employed to produce new compounds that can be used as pharmacophores for new drug discovery. The reactions catalyzed through biotransformation are regio- and stereoselective. Such types of reaction are rarely feasible through conventional chemical synthesis. Oxandrolone (1) is a synthetically used dehydrotestosterone derivative with low androgenic and anabolic effect. Five new and one known compounds were obtained from the microbial transformation of 1 with Macrophomina phaseolina and Cunninghamhamella blakesleeana. Etonogestrel (7) is used as a hormonal contraceptive. Microbial transformation of contraceptive compound 7 with Cunninghamhamella blakesleeana and Cunninghamhamella echinulate yielded three new and two known metabolites. Etonogestrel and its transformed products were evaluated by a β-glucuronidase inhibitory assay, metabolites 9 and 11 were found to be active against β-glucuronidase with IC50 values of 222.8 ± 5.60 and 13.972 ± 0.125 μM, respectively, as compared to the standard D-saccharic acid 1, 4-lactone (IC50 = 45.75 ± 2.16 μM). β-Glucuronidase enzyme is a target for drug discovery against number of diseases, such as inflammation, and rheumatoid arthritis. These results indicated that biotransformation is an approach that can produce new bioactive compounds for existing pharmacophores.
REFERENCES


PO-41

Track: Anti-infectives

STUDY OF THE REACTIONS OF MICROORGANISMS IN RESPONSE TO THE MAGNETITE NANOPARTICLES

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The influence of basic physical factors caused by magnetite nanoparticles (constant magnetic field and sorption) on microorganisms by examining the reactions of the intensity of free radical lipid peroxidation (FRLP) and bacteriostatic action was studied. It was well established that the magnetite nanoparticles caused unequal reaction in intensity of FRLP on different groups of microorganisms. It was determined that the most significant factor that influenced on the ultimate indicator of the intensity of luminescence on Candida albicans, Escherichia coli and Pseudomonas aeruginosa was constant magnetic field which induced by nanoparticles. On the contrary, sorption was the most significant factor on staphylococcus aureus. It was found that the rate of consumption of free radicals lipid reduced reliably on all microorganisms after the processing by magnetite nanoparticles. The results of microbiological studies of Escherichia coli, Klebsiella pneumoniae and Staphylococcus aureus showed that bacteriostatic effect was detected after exposure by magnetite nanoparticles. Visually, it was detected by decreasing the number of colonies on the nutritious medium in comparison with the control. It was revealed an interesting fact that saline NaCl, which had previously been processed by magnetite nanoparticles also significantly had a marked bacteriostatic effect on the studied microorganisms. This effect could be explained by mechanism of change the polarization structure water of microorganisms by magnetite nanoparticles. It was discovered that degree of expression of bacteriostatic action which induced by magnetite nanoparticles had correlation with marks of reactions intensity of FRLP. Maximum bacteriostatic effect on Staphylococcus aureus was expressed in second variant application of magnetite nanoparticles where mechanism of sorption was more significant than action of the magnetic field. On the contrary, maximum bacteriostatic effect on Escherichia coli and Klebsiella pneumoniae was revealed in third variant, where time exposition of contact with microorganism’s nanoparticles and, consequently, action of a constant magnetic field was determinative.

Keywords: Magnetite nanoparticles, microorganisms, free radicals peroxidation lipids, polarization structure, bacteriostatic effect.
**PO-76**

*Track: Drug Discovery in Preclinical Research*

**NEW SMALL-MOLECULE INHIBITORS OF THE CD40-CD154 COSTIMULATORY INTERACTION**

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The CD40-CD154 costimulatory interaction holds critical roles in autoimmune diseases including type 1 diabetes (T1D). Although neutralizing antibodies targeting CD154 proved effective in animal models of various autoimmune diseases, their clinical applicability was hindered by side effects likely to be related to their protein nature. Starting from the chemical space of the first small-molecule organic dye inhibitors of CD40-CD154 interaction discovered recently in our lab, we have now designed, synthesized, and tested a series of novel drug-like poly-aromatic compounds. Binding experiments using a cell-free ELISA-type setup confirmed sub-micromolar inhibitory potency for the several compounds. Inhibitory activity has been also confirmed in cell assays including inhibition of CD154-induced activation in CD40 NF-κB sensor HEK-Blue cells as well as human B cells. Corresponding IC50s were in the ten micromolar range, well below cytotxic levels. Thus, these novel compounds provide proof-of-principle evidence for the possibility of small molecule inhibition of costimulatory protein-protein interactions, and they can serve as starting point for further lead optimization for our immune-focused drug discovery program.

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**PO-9**

*Track: Pharmaceutical Research & Development*

**THE DUAL EFFECT OF EB101 VACCINE: A PROMISING STRATEGY FOR PREVENTING AND TREATING ALZHEIMER’S DISEASE**

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Vaccination has become one of the most promising immunotherapeutic approaches in the prevention and treatment of Alzheimer's disease (AD) hallmarks, especially the use of active immunization strategies with specific conformations of these proteins has yielded promising results in animal models. However, these prototypes have been clinically unsuccessful when preventing neuroinflammation. Therefore, a new paradigm is needed by using new immune-agents against AD-like pathology, a notion supported by our recent successful active immunotherapy results, with S1P/niosome-based adjuvant that induce Th2-only while inhibiting Th1 immunity. We show the experimental results of using the Aβ 1-42 vaccine (EB101) in AD-mouse models and the potential benefits of Aβ 1-42 delivered in a novel immunogen-adjuvant composed of niosomes-containing sphingosine-1-phosphate (S1P) that induces regardless of the antigen a safe and effective antibody response, while preventing damaging neuroinflammation and ameliorating pathological degeneration. Chronic administration of EB101 to AD transgenic mice led to a dual immunotherapeutical effect as preventive, before Aβ plaques development, and treatment action by the significant reduction in amyloid-β accumulation in both cortical and hippocampal regions when measured by different imaging and biochemical methods. Therefore, immunization with EB101 has proven neuroprotective effect to prevent and control AD-like neuropathology in a significant manner by halting disease progression without developing behavioral deficits in transgenic mice.
**PO-38**  
*Track: Pharmaceutical Research & Development*

**IN VITRO AND IN VIVO ANTI-TUMOR EFFECTS OF E-CONGERINE-10423®**

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The aim of the present study was to investigate the antitumor effect of E-Congerine-10423®, an extract obtained from Conger conger, in both in vitro and in vivo models. *In vitro* studies were performed against HL-60 (promyelocytic leukemia), HS 274.T (breast adenocarcinoma), HS 313.T (lymphoma), H2126 (lung adenocarcinoma), WM 115 (melanoma), HS 281T (breast adenocarcinoma), Caco-2 (colorectal adenocarcinoma), HT-29 (colon adenocarcinoma) and SW-480 (colon adenocarcinoma) human tumor cell lines. The highest level of growth inhibition was observed in Caco-2 (66, 75.8, 88.1%), HT-29 (56, 73, 876), and SW-480 (38.5, 61.6, 78.6%), with respect to untreated cells, while the results of the expression of genes associated with apoptosis indicated a down-regulation of Bcl-2 in all cell lines. *In vivo* studies were performed in DSS-induced mice models of colitis. Morphological and histopathological changes in the colonic mucosa were evaluated, where adenocarcinoma and cryptal cells of the dysplastic epithelium showed cathepin-β, COX-2 and BCL-2 expression, together with increased production of IFN-γ. In our model, the optimal dose-response was the 10% E-Congerine-10423® concentration, where no histological alterations or mild DSS-induced lesions were observed. These results indicate that E-Congerine-10423® displays a powerful anti-inflammatory effect in DSS-induced colitis, acting as a chemopreventive agent against colon carcinogenesis. Taken together these results suggest that E-Congerine-10423® contains small bioactive peptides that might play a key role against the apoptotic triggering process in pre-tumor cells.

**PO-37**  
*Track: Nutraceutical Drug Discovery & Therapy*

**NEUROPROTECTIVE EFFECTS OF ATREMORINE IN MPTP MOUSE MODEL OF PARKINSON’S DISEASE**

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Parkinsonian-like states have been generated in mice by the administration of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) to study the effects of an herbal-derived nutraceutical compound, atremorine, in Parkinson’s disease (PD) related neuropathology and behavior. The disease is caused by the progressive degeneration of dopaminergic neurons in the substantia nigra, and although numerous therapeutic strategies have been developed to protect neuronal damage, no effective treatment for PD has been validated so far. Here, we tested the preventive and therapeutic neuroprotective effect on the C57BL/6 parkinsonian mouse model by repeated MPTP injections. In addition to behavioral analysis, nigrostriatal dopaminergic neurons and inflammation biomarkers were directly quantified in mice brain regions by specific antibody-antigen binding methods of immunohistochemistry. The affected neuronal populations and behavior limitations induced by MPTP was significantly mitigated in mice when treated with atremorine-rich diet. Differences in the atremorine content in diet induced therapeutically degrees of neuropathological and behavioral improvements, based on the progressive beneficial effects observed in nigro-striatal dopaminergic neurons of MPTP mice. Therefore, results highlight the contribution of atremorine’s neurotrophic/protective factors as exogenous molecules to preserve the midbrain neurons against degeneration and therefore conserve or restore normal movement in parkinsonian models. Our data demonstrates that atremorine promotes neuroprotection and behavioral recovery in the injured MPTP mouse brain by modulating expression levels of tyrosine hydroxylase, glial proteins, apoptosis and endogenous dopamine concentrations important to the reestablishment of basal ganglia function.
**PO-30**

**Track:** Drug Discovery in Preclinical Research

**HIGH THROUGHPUT ASSAYS FOR MEASURING THE αVβ6 INTEGRIN-MEDIATED TGF-β ACTIVATION**

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TGFβ regulates developmental processes such as cell adhesion, migration, and proliferation, as well as epithelial-mesenchymal transition. In addition, TGFβ regulates immune functions. Abnormal regulation of TGFβ contributes too many pathological disorders, including cancer and fibrosis, among others. Interestingly, TGFβ is synthesized as latent form, its activation can be regulated by αVβ6 integrin. Evidence suggests that αVβ6 integrin is also regulated in many pathological conditions. The pathological regulation of TGFβ and αVβ6 integrin gives rise to opportunities in therapeutic interventions, so does the unique aspect of αVβ6 integrin-mediated TGFβ activation. Although binding assays for simulating this activation process are widely reported, these assays can be miniaturized to speed up compound discovery and to save reagent cost. Here we describe the development of 1536 well assays for measuring human and mouse αVβ6 integrin function using HTRF technology from Cisbio international. The assays are robust and high throughput. The assays are useful for the identification and optimization of inhibitors of αVβ6 integrins, as demonstrated using published compound CWHM-12.

**Keywords:** Integrin αVβ6, TGF-β Activation.

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**PO-27**

**Track:** Pharmaceutical Research & Development

**TMF AND GLYCITIN ACT SYNERGISTICALLY ON KERATINOCYTES AND FIBROBLASTS TO PROMOTE WOUND HEALING AND ANTI-SCARRING ACTIVITY**

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Scope: Keratinocyte-fibroblast interactions are critical for skin repair after injury. During the proliferative phase of wound healing, proliferation, migration, and differentiation of these cells are the major mechanisms leading to tissue remodeling, and both cell types secrete TGF-β, which promotes tissue remodeling. We have previously reported that glycitin, a major soy isoflavone, stimulates dermal fibroblast proliferation [1], and the phytochemical, TMF, induces migration of HaCaT keratinocyte cells [2]. We therefore investigated whether these compounds display synergistic effects on skin cells during wound healing in vitro and in vivo.

Methods and Results: Our results show that co-treatment with TMF and glycitin synergistically promotes the proliferation and migration of both keratinocytes and dermal fibroblasts, with a 1:1 ratio of these compounds showing the greatest efficacy in our co-culture system. This keratinocyte-fibroblast interaction occurred via the secretion of TGF-β, and the induction of differentiation and proliferation was confirmed in both indirect, and direct, co-culture assays. In an excisional wound animal model, mice treated with a 1:1 ratio of TMF and glycitin (G:T=1:1) showed faster wound closure and regeneration than even the positive control drug, as measured by collagen content, epidermal thickness, and scar width. Further, in a burn scar animal model, both the G:T=1:1 group and the TMF-treated group showed better scar reduction and faster tissue remodeling than all other groups.

Conclusion: These data indicate that two isoflavones, TMF and glycitin, act synergistically to promote wound healing and anti-scarring and could potentially be developed together as a bioactive therapeutic for wound treatment.
Keywords: Wound healing, flavonoids, keratinocyte.

PO-24
Track: Pharmaceutical Research & Development

AURAPTENE, A MAJOR COMPOUND OF SUPERCritical FLUID EXTRACT OF PHalSAK (CITrus Hassaku Hort ex Tanaka), INDUCES APOPTOSIS THROUGH THE SUPPRESSION OF mTOR PATHWAYS IN HUMAN GASTRIC CANCER SNU-1 CELLS

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The supercritical extraction method is a widely used process to obtain volatile and nonvolatile compounds by avoiding thermal degradation and solvent residue in the extracts. In search of phytochemicals with potential therapeutic application in gastric cancer, the supercritical fluid extract (SFE) of phalsak (Citrus hassaku Hort ex Tanaka) fruits were analyzed by gas chromatography-mass spectrometry (GC-MS). Compositional analysis in comparison with the antiproliferative activities of peel and flesh suggested that auraptene as the most prominent anticancer compound against gastric cancer cells. Auraptene induced the death of SNU-1 cells through apoptosis, as evidenced by the increased cell population in the sub-G1 phase, the appearance of fragmented nuclei, the proteolytic cleavage of caspase-3 and poly (ADP-ribose) polymerase (PARP) protein, and depolarization of the mitochondrial membrane. Interestingly, auraptene induces an increase in the phosphorylation of Akt, which is reminiscent of the effect of rapamycin, the mTOR inhibitor that triggers a negative feedback loop on Akt/mTOR pathway. Taken together, these findings provide valuable insights into the anti-cancer effects of the SFE of the phalsak peel by revealing that auraptene the major compound of it induced apoptosis in accompany with the inhibition of mTOR in SNU-1 cells.

Keywords: Auraptene, Apoptosis, Supercritical Fluid Extract, mTOR, Gastric Cancer SNU-1 cells.

PO-4
Track: Pharmaceutical Research & Development

EXPLORING THE MOLECULAR MECHANISM OF SMOKING-INDUCED NON-SMALL CELL LUNG CANCER

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The total of 80% cases of lung cancer were associated with smoking, whose molecular mechanism was still not well understood yet. We aimed to explore the molecular mechanism of smoking-induced lung cancer with systems biology approach.

We extracted gene-chips of 50 smoking-induced lung cancer samples and 50 normal samples from GEO database, and protein-protein interactions and protein sub-cellular localization data from HPRD database. Differentially co-expressed gene modules were found with WGCNA and DiffCoEx packages and annotated with GeneTrail. Protein expressed network of different modules were built.

Seven modules were found, and three of them contained significant pathways. Chemokine signaling, Cytokine-cytokine receptor interaction and Endocytosis were in one module. Spliceosome, Pyruvate metabolism and inflammatory response were in another module. And Ribosome signal pathway was in one module. DAB1, COPS5, CUL3 proteins stimulated Ras, PI3K, NF-κB pathways. DAB1 in chemokine pathway activated JAK3 pathway. The regulatory process ribosomal protein, such as RPL5,
activated p53 and Hedgehog signal pathways with CUL3, NACA, and TPT1 in the encoded process. COPB5, activated byAkt1, regulated gene expression by activating NF-kB. Akt1 and MAPK could regulate gene expression by activating HMGB1. We refused that the protein DAB1, activated by GRK6, induced the PI3K/Akt1 and JAK/STAT signaling pathway.

**Keywords:** Smoking, non-small cell lung cancer, gene co-expression network, signal pathway, inflammation.

**ACKNOWLEDGEMENTS**

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**PO-5**

*Track: Hot Topics in HIV Research*

**NEW HIV REVERSE TRANSCRIPTASE INHIBITORS - MOLECULAR MODELLING, SYNTHESIS AND BIOLOGICAL STUDIES**

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Nucleoside reverse transcriptase inhibitors (NRTIs) are still interesting category of anti-HIV medicines that require further exploration of mechanism of action and pathways for synthesis of new, more effective molecules. In our research we focused not only on nucleoside analogs but also on derivatives including C60 fullerene moiety. In the molecular modelling studies, as prerequisite for rational design of synthesis and prediction of biological properties, we use both quantum chemical (Density Functional - DFT) methods, and molecular mechanics approach for docking molecules to the molecular targets. The comparison covers both subcomponents that display significant biological activity and final egzohedral conjugates with C60 fullerene cage. As template compounds the zidovudine, stavudine and lamivudine were selected.

**Keywords:** HIV, reverse transcriptase inhibitors, fullerenes.

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**PO-68**

*Track: Translational Medicine*

**A STUDY ON THE KNOWLEDGE, ATTITUDE, AND PRACTICE OF GENERIC MEDICINES AMONG THE DOCTORS IN A TERTIARY CARE TEACHING HOSPITAL IN NORTH EAST INDIA**


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**Background:** Prescription drug spending is increasing and out-of-pocket expenses 80% of total health-care expenditures. Generic drugs are typically less expensive than brand-name drugs with same therapeutic effect but many doctors hold negative views of generics and resist prescribing.

**Aims:** To evaluate the knowledge, attitude and practice of doctors regarding generic medicines and to explore the factors hindering and favoring generic drug prescribing if any. Study design: Cross-sectional questionnaire-based study in a tertiary-care teaching hospital. Methodology: All doctors working in the hospital during the study period were participated and filled up the structured and pre-validated questionnaires and analyzed.
**Results:** A high proportion of doctors had negative perceptions of generics. Doctors believed generics were of inferior quality and caused more side effects but cheaper than brand name drugs. The majority of respondents believed that their prescribing decision is influenced by lots of factors.

**Conclusion:** These results suggest that there are a significant number of doctors concerns about the efficacy, safety and quality of generics and this negative perceptions are likely to be barriers to a wider acceptance of generics. In order to have a better understanding of generic, the doctor must be well-informed about the generic during their academic career resulting in savings to healthcare budgets.

**Keywords:** Generic medicines, Knowledge, Attitude, Practice, India.

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**PO-34**

*Track: Pharmaceutical Research & Development*

**SYNTHESIS OF NEW 1-(1H-IMIDAZOL-4-YL)-1H-1, 2, 3-TRIAZOLES AND THEIR FUNGICIDAL AND ANTIBACTERIAL ACTIVITIES**

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Azole antifungal agents including imidazole and triazole derivatives are an important class for fighting fungal diseases. Imidazole derivatives, such as bifonazole, clotrimazole, econazole and miconazole were the first group of azole antifungal agents used in clinical practise in the 1970s.

The main purpose of our investigation was to obtain new molecules containing 1H-imidazole and monosubstituted or 1,4-disubstituted 1H-1,2,3-triazole rings which would show considerable fungicidal activity and to test some of those molecules against both Gram-negative and Gram-positive bacteria. The set of new hybrids was prepared in 9 steps by using most financially affordable nitromethane, paraformaldehyde and tert-butylamine as start materials. The 1, 4-disubstituted triazoles were obtained by addition of azides to substituted acetylenes. Most of the synthesized compounds were screened *in vitro* for their antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum*, *Fusarium moniliforme*, *Fusarium graminearum*, *Sclerotinia sclerotiorum*, *Venturia inaequalis*, *Bipolaris sorokiniana*, *Cryptococcus neoformans* and *Candida albicans*. The antibacterial activity was tested against key pathogens, *E. coli*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *S. aureus*. Some of the compounds demonstrated significant activities rates.
THE USE OF PLANTS AND FUNGI TO PRODUCE NOVEL COMPOUNDS IS WELL DOCUMENTED

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The use of plants and fungi to produce novel compounds is well documented. Natural products have accounted for an estimated 40% of prescription-based drugs in the United States. Specifically, fungi are recognized as extraordinary producers of unique metabolites and compounds. They can enzymatically create complex molecules that traditional, synthetic, organic chemistry is incapable of producing. Thus fungi represent an understudied area of biological organisms capable of producing structurally complex compounds with the potential for therapeutic use. We have used a systematic approach to isolate a strain of Phoma brasiliensis which produces metabolites demonstrating cytotoxic properties. Further, to investigate the mechanism of cell death we have employed several genotoxic endpoints. Mutation frequency and DNA fragmentation data suggest DNA double strand break damage. The double strand DNA break damage sensing and response pathway was investigated by immunoblot analysis. We conclude that an as yet unidentified compound(s) is causing double strand DNA breaks leading to apoptosis. Further characterization of the metabolite(s) is needed to identify the precise chemical mechanism of DNA interaction. Nonetheless, triggering cell death through the double strand break repair pathway continues to be an attractive therapeutic strategy in the treatment of cancer.

Keywords: Triggering, therapeutic, DNA.

STRUCTURE-BASED PREDICTION OF HIV NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR RESISTANCE

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Resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) is a leading cause of HIV treatment failure. Often included as a combination therapy, NNRTIs are chemically diverse entities that bind an allosteric pocket of target reverse transcriptase (RT). Several new NNRTIs incorporate flexibility in order to compensate for lost interactions with amino acid conferring mutations in RT. Unfortunately, even these successful inhibitors, such as diarylpyrimidines etravirine and rilpivirine, are affected by mutations in RT. In order to aid drug design efforts, it would be powerful to pre-evaluate NNRTI compounds in development using structure-based and computational methods. As proof of concept, we applied a residue scan and docking strategy retrospectively to HIV RT and found that computational estimations of changes in free binding energy and stability are predictors of resistance to rilpivirine. Interestingly, both calculations and models predict rilpivirine resistance to variants with a clinically relevant lysine to proline mutation at the 101 position of RT (RT (K101P)). An additional predetermined crystal structure of RT (K101P) in complex with an NNRTI compound in development also provides molecular insight to the resistance mechanism. In our future work, we will investigate this strategy prospectively for resistance prediction of new inhibitors in development.

Keywords: HIV, NNRTI, drug resistance, antivirals, crystal structures.
PO-12

Track: Medical Imaging

DEVELOPMENT OF BLOOD-BRAIN BARRIER PERMEABLE NITROXIDE-BASED THERANOSTIC PROBES

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Theranostics is a future medical strategy that combines therapeutic and diagnostic capabilities. We are presently attempting to develop theranostics probes to better understand the redox biology of the brain diseases, and recently we have synthesized a compound by connecting nitroxide contrast agents, which can be used for contrast agents in MRI, to anti-inflammatory drugs, ibuprofen, ketoprofen and theophylline, in a high yield. In the present study, these newly synthesized theranostics probes were applied to brain disease model mice for diagnostic and therapy. Using electron paramagnetic resonance (EPR) imaging and MRI, we examined detail distribution and kinetics of these theranostics probes in mouse heads. EPR images of mouse heads clearly indicated these probes can enter the brain by passing through the blood brain barrier, resulting in contrast enhancement in mouse brain. This contrast enhancement persisted much longer than a small pyrrolidine nitroxide, and the half-lives of these probes in mouse brain were more than 30 min. additionally, the therapeutic effects of these probes were evaluated in septic mouse brains by a biochemical assay. The obtained results clearly showed that the nitroxide-based theranostics probes worked as therapeutic drugs and as contrast agents in both MRI and EPR imaging.

Keywords: Imaging theranostics oxidative stress.

PO-39

Track: Pharmaceutical Research & Development

SYNTHESIS AND BIOLOGICAL EVALUATION OF PHOSPHOGLYCOLIPID (PGL-1) ANALOGUES

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Two phosphoglycolipid (PGL) analogues were isolated and purified from thermophilic bacteria Thermus oshimai, Thermus thermophilic, Meiothermus ruber, and Meiothermus taiwanensis. Structural determination revealed their structure to be 2'-O-(1, 2-diacyl-sn-glycero-3-phospho)-3'-O-(α-N-acetyl-glucosaminyl)-N-glyceroyl alkylamine (PGL-1), and 2'-O-(2-acylalkydio-1-O-phospho)-3'-O-(α-N-acetylglucosaminyl)-N-glyceroyl alkylamine (PGL-2). In prointerleukin-1β (proIL-1) induction experiments on human THP-1 monocytes, it was revealed that PGL-1 could stimulate the release of proIL-1 while PGL-1 instead showed a weak inhibition on the function of PGL-1. Isolated PGL-1 from different species of bacteria showed different lengths of fatty acids attached to the glycerol moiety and showed different potency in biological function.

In this project, we propose to develop a total synthesis for PGL-1, to synthesise analogues with different chain lengths in order to study the effects of the fatty acid chain length on the biological function of PGL-1.
**PO-48**

*Track:* Protein and Peptide Sciences

**IMMUNE-MODULATING EFFECTS OF PRE-TREATED MILK-DERIVED BIOACTIVE PEPTIDE QEPV ON LPS-INDUCED INFLAMMATION**

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Milk-derived bioactive peptides are isolated from fermented dairy products. One of the milk-derived bioactive peptides, Gln-Glu-Pro-Val (QEPV) is evaluated on its function. Our results show that QEPV has significant immune-modulating effects both in vitro and in vivo. Pre-culturing with QEPV can promote the proliferation of mouse lymphocytes, of which, the expression of pro-inflammation cytokines such as IL6/IL12 are significantly reduced, while expression of anti-inflammation cytokine IL-10 is enhanced. Transcription levels of iNOS and COX-2 genes also decrease. QEPV can also inhibit LPS-induced inflammation by regulating the release of NO and the producing of INF-γ, IL-12 and PGE2 in mice that are pre-injected with QEPV. Overall, QEPV has significant immune-modulating effects on lymphocytes and contributes to inflammation treatment as a functional food ingredient.

**Keywords:** Polypeptide, fermented milk, lymphocyte, LPS, inflammation.

**PO-52**

*Track:* Anti-Cancer Drug Discovery

**FLUORESCENT DYES AS CANCER DRUG DISCOVERY TOOLS IN THE P53 PATHWAY**

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The p53 protein is a critical tumor suppressor that functions as a transcription factor in cells to maintain genomic integrity and safeguard against cancer. This is achieved through the regulation of molecular pathways which results in specific cellular outcomes (DNA repair, growth arrest, senescence, and apoptosis). In many human cancers where the p53 response is attenuated, different strategies can be employed to augment p53 activity, depending on the p53 status. Anti-tumoral effects can be elicited in wildtype p53 expressing cells by inhibiting the Mdm2-p53 negative feedback loop to stabilize p53 protein levels, or by restoring wildtype transcriptional functions to mutation-inactivated p53 molecules (which accounts for above 50% of all cancers). We describe here, the synthesis and application of different classes of fluorescent probes (molecular rotors and aggregation-induced emission dyes) used in various approaches to interrogate p53-Mdm2 interaction as well as p53 sequence-specific DNA binding in in vitro, and cell-based systems. These techniques can be harnessed as useful tools in the areas of cancer diagnostics, drug discovery platforms as well as understanding p53 basic biology.

**Keywords:** Fluorescence probe, p53, mutant p53, drug discovery, cancer therapeutics.
PO-71

Track: CNS Drug Discovery & Therapy

TACRINE (10)-HUPYRIDONE, A NOVEL DUAL-BINDING ACHE INHIBITOR, POTENTLY BLOCKS AB OLIGOMERS-INDUCED COGNITIVE IMPAIRMENTS AND NEUROTOXICITY POSSIBLY VIA INHIBITING THE FORMATION OF AB OLIGOMERS

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Tacrine (10)-hupyridone (A10E), a novel synthesized dual-binding acetylcholinesterase inhibitor, is derived from tacrine and huperzine A, an active Chinese medicinal component. In this study, we have evaluated the neuroprotective effects of A10E on β-amyloid (Aβ) oligomers-induced neurotoxicity both in vitro and in vivo. Aβ oligomers were injected into the hippocampal regions to induce cognitive impairments in mice. It was found that A10E (0.3-0.6 mg/kg i.p. daily) significantly attenuated Aβ oligomers-induced cognitive impairments by using novel object recognition and Morris water maze tests. We have further demonstrated that A10E (0.1-1 μM) effectively blocked Aβ oligomers-induced neuronal apoptosis in SH-SY5Y cells. Most importantly, we have shown that A10E potently inhibited the formation of Aβ oligomers by using dot blot assay.

Taken together, our results have shown that A10E attenuated Aβ oligomers-induced neurotoxicity possibly via the inhibition of Aβ oligomers formation, which offers a novel molecular insight into the potential application of A10E in AD treatment.

ACKNOWLEDGEMENT

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Keywords: Alzheimer's disease, Aβ oligomers, Novel dimer, AChE inhibitor.

PO-47

Track: Protein and Peptide Sciences

MORPHOLOGY, ANTIOXIDANT AND ANTIHYPERTENSIVE PROPERTIES OF α-CASEIN TREATED WITH UV-C AND FAR-IR RADIATIONS

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α-casein is the most important bioactive protein in bovine milk. After treated with UV-C at 11.8 W/m² and far-infrared radiation (FIR) at 500 W, the morphology, antioxidant and antihypertensive activity properties changed in different levels. The AFM results indicate the surface of untreated α-casein sample with a relatively consistent size in general and evenly distribution. Ra and Rmax value of untreated α-casein was 0.21nm and 3.10nm respectively. UV-C (15 min) showed the increase of Ra and Rmax value to 0.30nm and 5.24nm. FIR (15 min) increased the Ra and Rmax value to 0.31nm and 5.13nm. The antioxidant and antihypertensive activities of α-casein increased after UV-C and FIR treatments. The DPPH and ABTS value of untreated α-casein was 21.26% and 55.95%. UV-C (15min) and F-IR (15min) caused the most significant increase in antioxidant activity compared with control and 5min treatments. The ACE-inhibitory activity of both UV-C and FIR treatments increased from 40.07% (control). Ultra-performance liquid chromatography-tandem mass (UPLC-MS/MS) spectrometry analysis showed the different levels of increase and decrease of released peptides related to those bioactivities. The peptide related with antihypertensive activities increased significantly after UV-C and FIR treatments compared with control sample. UV-C (15min) treatments efficiently changed the morphology and increased the antioxidant and antihypertensive activities of milk.

Keywords: UV-C, far-IR, α-casein, antioxidant, antihypertensive, UPLC-MS/MS.
**PO-43**  
Track: Pharmaceutical Research & Development

**NOVEL POLYMER SELF-ADJUVANTING VACCINES WITH STRONG OPSONIC ACTIVITY AGAINST GROUP A STREPTOCOCCUS**

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Vaccination is one of the most cost-effective public health interventions available. The development of effective vaccines has dramatically reduced the morbidity and mortality associated with infectious diseases. Peptide-based vaccines are designed to carry the minimum required antigen to trigger the desired immune responses; however, they are usually poorly immunogenic and require appropriate delivery system. Recently, developments in GAS vaccines have primarily focused on the peptide-based approach, which target the GAS major virulent factor, the M-protein. Peptides, B-cell epitope (J14) derived from group a streptococcus (GAS) M-protein and universal T-helper (PADRE), were conjugated to a series of linear and branched polyacrylates. All produced conjugates formed submicron-sized particles and induced a high level of IgG titres in mice after subcutaneous immunisation. These polymer-peptide conjugates demonstrated high opsonisation capacity against GAS clinical isolates. We have successfully demonstrated that submicron-sized polymer-peptide conjugates are capable of inducing strong humoral immune responses after single immunisation.

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**PO-66**  
Track: Drug Delivery & Targeting

**TRANSDERMAL DELIVERY SYSTEM OF SMALL INTERFERING RNA USING LIPOSOMES AND FUNCTIONAL PEPTIDES**

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Intradermal small interfering RNA (siRNA) delivery is difficult because of two barriers encountered in the skin, intercellular lipids in the stratum corneum and tight junctions in the granular layer. We have reported that the application of AT1002 peptide can open tight junctions reversibly and increase intradermal siRNA delivery at the skin.

In this study, to improve the siRNA delivery into the skin, we developed an intradermal siRNA delivery system combined with liposomes and AT1002.

We observed the distribution of FAM-labeled siRNA in the back skin of tape-stripped normal mice and subcutaneous tumor of skin cancer-like mice treated with FAM-siRNA using the liposomes and AT1002, and measured the brightness by confocal laser microscopy.

The fluorescence of the liposome and AT1002 solution was observed not only in the epidermis but also in the deeper dermis area and within the skin and the tumor, unlike the other groups. This result indicated that liposome and AT1002 accelerate transdermal siRNA delivery widely and effectively. Thus, combination of liposome and AT1002 is expected to be an excellent transdermal siRNA delivery carrier.

**Keywords:** Transdermal delivery, siRNA, peptide, liposome.
PO-35

Track: Chemistry

PALLADIUM SUPPORTED ON CERAMIC FOAM AS A CATALYST FOR HYDROGENATION IN ORGANIC SYNTHESIS


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Hydrogenation is widely-used reaction in the organic synthesis, and Pd is a very common heterogeneous catalyst for hydrogenation. Pd is usually supported on carbon or Al₂O₃ powder. In our work we used Pd supported on ceramic foam. Ceramic foam is well known material for filters but it has been rarely used as catalyst support before. The main ceramic foam component α-Al₂O₃ covered by sol γ-Al₂O₃ with pores no less than 70–95% was used as catalyst carrier, readily permeable to air and water. This catalyst carrier was impregnated by Pd(NO₃)₂ and heated at 450 °C to afford PdO-coating catalyst. PdO was hydrogenated to metallic Pd by hydrogen at 50–55 °C, yielding the targeted catalyst with 0.1–3.5% Pd/6% γ-Al₂O₃. These catalysts with different amount of Pd were studied as a replacement of Pd/C catalyst in primary and secondary amines and alcohols synthesis, heterocyclic compounds preparation and unsaturated hydrocarbons catalytic reduction. It was shown that Pd supported on ceramic foam is highly effective for reducing aromatic compounds with such functional groups as NO₂, NOH and CN and could be used in aliphatic compounds hydrogenation in some cases. Unsaturated hydrocarbons, including cyclic, were reduced on these catalysts with high yields but aromatic bonds never have been reduced in any conditions. These catalysts are easily regenerated and could be use no less than 50 times without activity decreasing.

PO-73

Track: Chemistry

SPECTROSCOPY OF THE TYROSINE KINASE INHIBITOR AG-1478: AN EXPERIMENTAL AND THEORETICAL STUDY

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We studied the photophysics of a tyrosine kinase inhibitor, AG-1478, both experimentally and theoretically. The AG-1478 UV-Vis absorption spectrum exhibited two characteristic overlapping bands at 330 nm and 340 nm respectively. Two local minima structures in the theoretical potential energy surface were revealed through rotation of the C-N linker between anilinyl and quinazolinyl moieties. The energy difference between the planar conformer and the twisted conformer was estimated to be 1.58 kcal/mol. Time-dependent Density Functional Theory (td-DFT) approach with B3LYP/6-311+G (d) level of theory revealed that the 330 nm peak was associated with the planar conformer while the 340 nm peak was due to the twisted conformer. The observed fluorescence spectra of AG-1478 were found to be very sensitive to polarity and hydrogen bonding strengths of the solvent and exhibited high values of stokes shift (4536 - 9210 cm⁻¹). Taken together, these results showed how the absorption spectrum is sensitive to conformation and the fluorescence spectrum is sensitive to environment. Hence, our findings may assume relevance in understanding the structure and environment of AG-1478 in the ATP pocket of a target protein.

Keywords: Solvatochromism, UV-Vis spectroscopy, TD-DFT, tyrosine kinase inhibitor, AG-1478.
**PO-45**

*Track: Hot Topics in Natural Product*

**CELLULAR ANTI-OXIDANT ACTIVITY AND MUTAGENICITY OF FRUIT EXTRACTS OF WAN KHAN MAK (AGLAONEMA SIMPLEX BL.)**

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Wan Khan Mak (WKM; Aglaonema simplex Bl.) has been widely used in recent years because of its anti-aging and longevity properties. Nevertheless, there is still no studies of ethno-pharmacological properties or toxicity of WKM. This study aimed to investigate the cellular anti-oxidant activity and mutagenicity of the Wan Khan Mak 95% ethanol macerated extract (KMEM) and 95% ethanol fresh fruit extract (KMEF). The results revealed that both KMEM and KMEF effectively attenuated tBuOOH-induced intracellular oxidative stress in RAW264.7 cells using the DCFH-DA fluorescent probe. The percent inhibition of DCF fluorescent emission of 125 µg/ml and 500 µg/ml KMEF was 38.84% and 73.82%, respectively, and the inhibition was significantly higher than that of corresponding concentrations of KMEM (32.72% and 65.41%, respectively) (p<0.05). Moreover, KMEM and KMEF have no mutagenicity as evaluated by the Ames assay. Overall, the results suggest that WKM is a good source of natural antioxidant and is presumed to be safe for long-term usage.

**PO-79**

*Track: In-silico Drug Design and In-silico screening*

**IN SILICO DESIGN OF NOVEL COMBINATORIALLY GENERATED NBTIS AS POTENTIAL DNA GYRASE INHIBITORS AGAINST VARIOUS STAPHYLOCOCCUS AUREUS MUTANT STRAINS**

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Although intercalating agents such as quinolones proved their therapeutic success as antibacterials for more than 40 years, the emergence of new forms of quinolone-caused resistance in bacteria is continually growing. To alleviate this problem, a new class of antibacterials is urgently needed and recently novel bacterial topoisomerase inhibitors (NBTIs) were found as particularly important. Based on 67 experimentally evaluated NBTIs against wild-type (WT) DNA gyrase originating from *Staphylococcus aureus*, a predictive QSAR model was initially constructed and validated, which was later used for *in silico* prediction of biological activities for an in house designed compounds library of 548 novel drug-like NBTI combinatorial analogs. To evaluate the influence of gyrA alterations on NBTIs resistance, various mutant homology models were constructed, while their selectivity was assessed and validated relative to WT enzyme by structure-based virtual screening of known NBTIs. Surprisingly, M121K mutant model was recognized as the most selective one due to an additionally established cation-pi interaction between Lys121-NH3+ (not found in WT) and aromatic moiety of NBTIs right-hand site fragment, which finding was additionally supported by VS of our combinatorially generated NBTIs. Moreover, we identified several attractive, synthetically feasible building-blocks that could enable the development of new NBTIs.

**Keywords:** NBTIs, intercalating agents, DNA gyrase, mutants, bacterial resistance.
PO-17
Track: Pharmaceutical Research & Development

NOVEL BISNAPHTHALIMIDOPROPYL (BNIP) DERIVATIVES INDUCE OXIDATIVE STRESS THAT TRIGGER DNA DAMAGE IN TRIPLE NEGATIVE HUMAN BREAST CANCER CELLS

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Advances in the development and applications of novel DNA intercalators in drug design have created new opportunities for anticancer compound development. A series of novel bisnaphthalimidopropyl (BNIP) derivatives, bisnaphthalimidopropyl-piperidylpropane (BNIPPiProp), bisnaphthalimidopropyl- ethylenedipiperidine (BNIPPiEth) and (trans-(trans))-4,4’-methylenebis-cyclohexylamine (trans, trans-BNIPDaCHM) were synthesised, characterised and studies for their DNA binding and anticancer activities against human breast cancer MDA-MB-231 cells. Fluorescence binding/UV binding studies were used to determine their DNA binding properties. Cytotoxicity evaluation was performed by 3-(4, 5-Dimethylthiazol-2-yi)-2, 5-diphenyltetrazodium bromide (MTT) assay. All compounds induced cell death (1.4-2.3 μM) after 24 hours treatment, with trans, trans-BNIPDaCHM being the most promising candidate. Further evaluation of the cellular DNA content after 24 hours treatment with BNIPs showed induction of sub-G1 cell cycle arrest, indicative of apoptotic cell death and confirmed by studies on the externalization of phosphatidylserine residues in MDA-MB-231 cells. In addition, intracellular reactive oxygen species levels were increased after 4, 8 and 12 hours treatment with BNIP derivatives, while DNA damage studies showed a significant upturn in the number of DNA strand breaks in MDA-MB-231 cells. The above findings, relating to oxidative stress, form the basis to explore further BNIPs as potential treatment for triple negative breast cancer cells.

PO-32
Track: Anti-Cancer Drug Discovery & Therapy

CHARACTERIZATION OF HISTONE LYSINE METHYLTRANSFERASE AND DISCOVERY OF NSD2 INHIBITORS

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Methylation of lysine 36 on histone H3 (H3K36me2) by histone lysine methyltransferase (NSD2) constitutes one of the major chromatin regulatory mechanisms [1]. Overexpression of NSD2 has been genetically linked to multiple myeloma in various cancers [2]. Despite these findings, no drug candidate has been developed to date.

Our computational analysis of homology model of NSD2 revealed two druggable binding sites – the S-adenosylmethionine (SAM) and substrate binding pockets. Further biochemical and biophysical characterization of the SAM binding to NSD2 was performed. Subsequent efforts towards developing inhibitors of NSD2 led to the discovery of ligands binding in the low micromolar range. The structure-activity-relationship, as well as proposed binding site and mode will be detailed during presentation.

REFERENCES


PO-74
Track: Pharmaceutical Research & Development

NIR FLUOROPHORES FOR IN VIVO ADRENAL GLAND IMAGING

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The adrenal glands (AGs) are relatively small yet require definitive identification during their resection, or more commonly, their avoidance. To enable image-guided surgery involving the AGs, we have developed novel near-infrared (NIR) fluorophores that target AGs after a single intravenous injection, which provided dual-NIR image-guided resection or avoidance of the AGs during both open and minimally-invasive surgery.

PO-69
Track: Pharmaceutical Research & Development

CHEMICALLY AND BIOLOGICALLY STABLE NIR FLUOROPHORES FOR TRACKING OF LIVE CELLS

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In vivo cell tracking is imperative to understand how specific cell types perform in the body under the host defense mechanism. The ability to monitor localization and behavior of administered cells for a long period of time using high-resolution in vivo optical imaging techniques would provide useful information in the treatment of diseases. Currently, long-term live cell trafficking is limited due to the lack of available fluorophores in the near-infrared (NIR) wavelengths with stable optical and physicochemical properties. In this study, the first fixable NIR fluorophore, CTNF126, was synthesized with high extinction coefficients and quantum yields, excellent cell permeation and retention, and high stability in chemical treatment for histology. The chemical structure of CTNF126 allows sequestering inside the lysosome for a long period of time, preventing efflux elimination of dyes, thus outperforming all commercially available visible-wavelength fluorophores.
SIGNIFICANCE OF IMMUNOGLOBULIN E IN UMBILICAL BLOOD IN RELATION TO AN ALLERGIC FAMILY HISTORY, IT’S RELATION TO SEASONALITY, IMMUNITY AND POSSIBILTY OF PRE- AND POSTNATAL CONSEQUENCES. THE REMARKABLE SUBSEQUENT EFFECTS OF ALTERING GASTROINTESTINAL FLORA IN TREATED NEWBORNS

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We have examined 4312 samples of umbilical blood taken from children born into families with a positive history of allergy in one or both parents from 1998-2014. Newborn were divided into 3 groups: 2005-2007, 2008-2009, 2010-2014. The results revealed that allergy is strongly linked with family history (p≤0.0001). We also detected differences in seasonality, especially with regards to pollen allergies. High values of umbilical IgE, together with a positive family history of allergy an indication for inclusion of patients into the treated group, which, during the years of 2005-2014 where treated with Colinfant Newborn (a lyophylized non-pathogenic strain of E. coli). Normalisation of IgE was seen in 90% of patients with previously increased levels. IgG and IgA at the first and the third year of life were also normalized (p≤0.0001). This also corresponded with an entirely negligible subsequent morbidity of the monitored group of children (up to 4 years of life) when compared with the control group.

DISCOVERY OF NOVEL DIARYL PYRIMIDINE-TYPE DERIVATIVES AS POTENT HIV-1 NNRTIS

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In continuation to explore the resilience of novel HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) to the highly mutable viral strains, two most representative diarylpyrimidine derivatives (DAPYs) of the second generation of NNRTIs, etravirine (ETR) and rilpivirine (RPV) have been approved by US FDA for anti-HIV therapy in recent years. Based on the newly established pharmaophore model for DAPYs by our group, in combination of structural biology, computer-aided drug design (CADD) and medicinal chemistry strategies of bioisostermism, molecular hybridization, scaffold hopping and designed multiple ligands, a focused library of DAPY-type derivatives has been constructed to test their anti-HIV activities. More than one hundred compounds were found to display remarkable inhibition of wild-type (wt) HIV-1 (IIIB) strain at low nanomolar concentrations, which were far more potent than NNRTI drugs nevirapine (NVP) and delavirdine (DLV). Additionally, several analogues exhibited potencies against HIV-1 double mutant strain RES056 (K103N/Y181C, the most common mutant HIV-1 strain in clinical) at sub-micromolar concentrations. Especially, one compound showed extraordinary antiviral activities against wt and six mutant HIV-1 strains, which is now undergone systematic preclinical studies. These encouraging results prompted us to make further optimizations on DAPY scaffold to discover next generation of NNRTIs.
Owing to their high specificity and relatively lower toxicity, HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) have become standard components of HAART (highly active antiretroviral therapy) regimens [1]. Indolylarylsulfones (IASs) represented by lead compound L-737126 (Fig. 1), are a class of NNRTIs endowed with prominent anti-HIV-1 activity [2]. The binding mode revealed by the crystallographic structure and molecular modeling study of IASs in complexes with RT was detailedly inspected, and it was found 2-carboxamide group exactly pointed to the newly found “entrance channel” of NNRTI binding pocket (NNIBP). The entrance channel has been proven to tolerate a wide variety of substituents distinctly improving antiretroviral potency of IASs. Thus, a novel series of IAS derivatives containing a piperidine group targeting the entrance channel of NNIBP was designed and evaluated for their anti-HIV activities. The antiviral results showed that most compounds displayed marked inhibitory activity against the wild-type HIV-1 IIIB and some common mutant strains. Besides, one compound exhibited better potency against Y188L HIV-1 strain than L-737126. Additionally, sixteen inhibitors were found to be more potent than L-737126 against F227L/V106A double mutant HIV-1 strain. These inspiring results indicated that installation of piperidine containing substituent for IASs into the entrance channel of NNIBP is effective.

Fig. (1). Structure of lead compound L-737126.
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**PO-28**

*Track: Chemistry*

**SYNTHESIS, ANTIMICROBIAL EVALUATION, MOLECULAR MODELING AND QSAR STUDIES OF N-ALKYL-3-HYDROXYPYRIDINIUM SALT SERIES; THE EFFECT OF THE HYDROXYL MOIETY**

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Disinfectants and antiseptics are extensively exploited in health care settings for a variety of topical and hard-surface applications. Presently, they constitute an essential part of infection control practice, which particularly aids in the prevention of devastating nosocomial infections occurring within hospital facilities. In this study, we have carried out a combined experimental and computational investigation to elucidate several bred-in-the-bone ideas sticking out in rational design of novel cationic surfactants as antibacterial agents. Our argumentation is grounded on the synthesis and analysis of five 3-hydroxypyridinium salts differing in the length of N-alkyl side chain. We have performed a chromatographic analysis to evaluate the compounds' lipophilicity, biological in vitro tests against panel of pathogenic bacterial and fungal strains, and computational simulations using molecular mechanics and advanced quantum chemical methods. Herein, the majority of the prepared 3-hydroxylated substances showed notably lower potency than the parent pyridinium structures, although the compound 1-dodecyl-3-hydroxypyridinium bromide proved distinctly better antimicrobial activity comparing to the other homologs. Focusing on this anomaly, we have made an effort to reveal the optimal conditions for boosting the activity through molecular dynamics simulation of the interaction between the bacterial membrane and 1-dodecyl-3-hydroxypyridinium bromide.

Supported by the Project Health Research Agency NV15-31847A.

**Keywords:** 3-hydroxypyridinium salts, antimicrobial activity, molecular modeling, QSAR.

**PO-58**

*Track: Pharmaceutical Research & Development*

**ENHANCING DOXORUBICIN IMMUNE CELL ACTIVATION AND CANCER CELL TOXICITY WITH DICHLOROACETATE ADMINISTRATION: A COMBINATION THERAPY OF CANCER**

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Despite recent advances in cancer therapy, treating solid cancer is still very difficult. This difficulty can be explained by the heterogeneity of cancer cells within the tumor microenvironment, the down regulation of the patient's immune system and the timing of diagnosis is usually late. Because a single treatment modality is usually insufficient for the complete elimination of cancer cells, new therapeutic strategies from various aspects are needed. Doxorubicin (DOX) is a potent chemotherapeutic drug and is widely used as a treatment of choice for solid tumors as well as lymphomas and some leukemias. DOX is known to interact with DNA by intercalation and thus inhibits macromolecular biosynthesis. On the other hand, dichloroacetate (DCA) is one of the new, promising anticancer drugs. DCA inhibits pyruvate dehydrogenase kinase and thus restores normal mitochondrial function and enables cancer cells to undergo apoptosis. Previously, we have shown that DOX and DCA enhance the production of anti-tumor cytokines; IFN-γ and IL-12 from
spleen cells. Therefore herein, we studied if the combination of DOX and DCA are more effective than either one alone in enhancing the production of anti-tumor cytokines and enhancing cancer cell killing in vitro. The results showed that the combination of DCA with DOX significantly enhanced the production of IFN-γ and IL-12 from cultured spleen cells more than either drug alone. Secondly, each drug produced significant MCA fibrosarcoma killing and when both were combined the killing of MCA fibrosarcoma was higher than either one alone. Furthermore, adding spleen cells to the DCA and DOX at a concentration of 10 mM and 10µM, respectively, significantly increased killing of MCA fibrosarcoma cells. These data supports that having the combination of DCA with DOX is more effective in modulating anti-tumor cytokines and killing MCA fibrosarcoma cells. However, in vivo cancer models are warranted to test that the combination effect of DCA and DOX are more effective than either one alone.

**PO-57**

*Track: In Silico Drug Design and In Silico Screening*

PROBING COMBINATORIALLY GENERATED NBTIs BINDING TO THE STAPHYLOCOCCUS AUREUS DNA GYRASE INTERCALATING SITE: A 6D-QSAR PSEUDORECEPTOR MODELING CONCEPT

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Bacterial type II topoisomerases have proven to be very effective targets for intercalating agents such as 6-fluoroquinolones (6-FQs). Unfortunately, 6-FQs-related problem of resistance in bacteria is continually growing and novel antibacterial alternatives targeting the bacterial DNA gyrase replication/transcription machinery are certainly welcomed. Novel bacterial topoisomerase inhibitors (NBTIs) are a new class of antibacterials that show promise in combating bacterial resistance. Here we report a novel series of combinatorially generated NBTIs as potential *Staphylococcus aureus* DNA gyrase inhibitors. To predict their binding mechanism and quantify their binding affinity, 6D-QSAR pseudoreceptor modeling concept was employed for construction of a spatial *S. aureus* NBTIs binding-pocket (NBTI-BP) surrogate populated with quasi-atomistic properties, thereby emulating the key NBTI-BP amino acid residues for affinity. Grounded on the latterly confirmed in vitro NBTIs experimental data, a NBTI-BP surrogate model was constructed and validated ($r^2=0.908$, $q^2=0.905$; $p^2=0.842$, predictive $r^2$) that properly reproduces the corresponding properties of the key amino acids for NBTIs binding and affinity (Ala68, Val71, Asp83, and Met121), additionally confirmed and quantified ($K_i [\mu M]$) by flexible molecular docking calculations. We believe that these findings will significantly contribute to the on-going design of new potent NBTIs against various bacterial resistant strains.
PO-67
Track: Innovative Drug Discovery and Nanotechnology

ACYCLOVIR RELEASE STUDY USING PSEUDBOEHMITE – TESTS IN VIVO

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After conducting various experiments using nanoparticles pseudoboehmite for drug delivery system in in vitro assays for atenolol, Glucantime® and acyclovir, the conclusion reached that pseudoboehmite can be used for this purpose. In addition, toxicity study of pseudoboehmite was conducted on Wistar rats and the results showed that this material is not toxic. The objective of this research is the synthesis and characterization of pseudoboehmite by the sol-gel process and its use in drug delivery system for acyclovir. The pseudoboehmite was characterized by the following techniques: X-ray diffraction, scanning electron microscopy. Differential thermal analysis, thermogravimetric analysis and nitrogen adsorption isotherms. After synthesis of pseudoboehmite, in vivo tests were performed using Wistar rats to compare the release of acyclovir with and without the addition of pseudoboehmite. The administration of acyclovir and acyclovir / pseudoboehmite was performed in wistar rats by gavage. To determine the concentration of acyclovir in the blood of the rats, high performance liquid chromatography was used. The result shows that addition of pseudoboehmite increased the content of acyclovir in the plasma of wistar rats after 3 hours administration.

Keywords: Pseudoboehmite, drug delivery system, acyclovir, nanoparticles.

PO-42
Track: CNS Drug Discovery & Therapy

TACRINE - TROLOX HYBRIDS: A NOVEL CLASS OF CENTRALLY ACTIVE, NON-HEPATOTOXIC MULTI-TARGET-DIRECTED LIGANDS EXERTING ANTICHOLINESTERASE AND ANTIOXIDANT ACTIVITIES WITH LOW IN VIVO TOXICITY

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Coupling of two distinct pharmacophores - tacrine and trolox, endowed with different biological properties, afforded 21 hybrid compounds as novel multifunctional candidates against Alzheimer's disease. Several of them showed improved inhibitory properties towards acetylcholinesterase (AChE) in relation to tacrine. These hybrids also scavenged free radicals. Molecular modeling studies in tandem with kinetic analysis exhibited that these hybrids target both catalytic active site as well as peripheral anionic site of AChE. In addition, incorporation of the moiety bearing antioxidant abilities displayed negligible toxicity on human hepatic cells. This striking effect was explained by formation of non-toxic metabolites after 1 h incubation in human liver microsomes system. Finally, tacrine - trolox hybrids exhibited low in vivo toxicity after i.m. administration in rats and potential to penetrate across blood-brain barrier. All of these outstanding in vitro results in combination with promising in vivo outcomes highlighted derivative 7u as the lead structure worthy of further investigation.

This work was supported by Health Research Agency (no. NV15-30954A), MH CZ-DRO (University Hospital Hradec Kralove, no. 00179906) and by the grant of Ministry of Defense (Long Term Organization Development Plan - 1011).

Keywords: Alzheimer's disease, Acetylcholinesterase inhibitors, Tacrine, Oxidative stress, Antioxidants, Trolox, MTDLs.
IN VITRO ANTIMYCOBACTERIAL ACTIVITY AND CYTOTOXICITY OF ANTITUBERCULAR PLANTS TRADITIONALLY USED IN EASTERN REGION, GHANA

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Mycobacterium tuberculosis, the prominent causative agent of tuberculosis, is one of the leading causes of human mortality and morbidity caused by infective microorganisms [1]. Several medicinal plants are used traditionally to treat tuberculosis in Ghana [2]. The current study was designed to investigate the antimycobacterial activity and cytotoxicity of crude extracts from five selected antitubercular plants.

The microplate alamar blue assay (MABA) was used for antimycobacterial studies while the MTS assay was used for cytotoxic studies. Correlation coefficients were used to compare the activity of crude extracts against nonpathogenic strains and the pathogenic Mycobacterium tuberculosis subsp. tuberculosis. Minimum inhibitory concentration values as low as 0.1563 mg/mL against M. tuberculosis; Strain H37Ra (ATCC® 25177™) were recorded. Cytotoxicity of the extracts varied, and the leaves from Solanum torvum Sw. (Solanaceae) had the most promising selectivity index. Activity against M. tuberculosis; Strain H37Ra was the best predictor of activity against pathogenic Mycobacterium tuberculosis subsp. tuberculosis (correlation coefficient= 0.8). The overall results of the present study provide supportive data on the use of some medicinal plants for tuberculosis treatment. The leaves of Solanum torvum are a potential source of anti-TB natural products and deserve further investigations to develop novel anti-TB agents against M. tuberculosis.

REFERENCES


NEW CARE AND TREATMENT OF PULMONARY HEMOSIDEROSIS WITH A SOLUTION OF MAGNESIUM CHLORIDE HEXAHYDRATE: FIRST RESULTS

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Our research focused on patients with pulmonary hemosiderosis (EP) and patients with multiple sclerosis (SM). In particular, we had significant clinical results on a patient with pulmonary hemosiderosis, who had diagnosed since childhood (four years). In the course of fourteen years, despite the treatments and the many transfusions in hospitals, the patient's clinical situation was not good as blood counts (haemogram). In the last year, we have discovered that treatment with oral solution of magnesium chloride hexahydrate (CME) in two months and without any transfusion gave significant results. The magnesium salts bound to organic matrices (type magnesium “pidolate”) have no specific activity on this type of diseases while the series of our analytical and bibliographic investigations show that only the magnesium chloride hexahydrate acts with significant efficacy and immediacy on this pathologies (as evidenced by clinical examinations). This is demonstrate by the course of the sequences of hydration of magnesium chloride hexahydrate up to its complete
solubilization. In fact in support of our thesis we had the study of Nobel Laureates Pons and Fleischmann on low energies. This studies were confirmed by the Nuclear Research Centre (CERN) in Geneva in 1974 that communicated to the laboratories of Batavia and Argonne, in the US, that nuclear reactions (atomic explosion) took place even at low energies due to neutrinos and that even the existence of neutral currents are explained by biphasic mechanism [1]. In the first phase the enzyme (magnesium activated according to our hypothesis) changes the molecular structure of the cell, making it more sensitive to the action of neutrinos; in the second phase of the neutrino enters the nucleus of another element (usually hydrogen or oxygen) by activating the process. It is clear that only magnesium chloride hexahydrate in its unity and molecular complexity has significant effect on diseases set herein. We know that the chlorine ion also regulates the functions of the brain (appearance extensively studied by the Centre Neuro Psychiatric Sciences of Lausanne with work published in the journal: "Nature Communications"). In fact, it is necessary to chlorine when you need to run properly on the nervous system because it causes a change in the type of receptor "Gaba" [2]. Chlorine ion also changes the electrical behavior of the cells, slowing down the activity. This mechanism is useful in case of alterations of cerebral functions: when, for example, neurons work not correctly. Chlorine ion corrects neurons orientation.

Keywords: Pulmonary hemosiderosis, magnesium chloride hexahydrate, new care, receptor Gaba, chlorine ion.

REFERENCES

PO-60
Track: Pharmaceutical Research & Development

DEVELOPMENT OF ANTIBODY AS CARRIER INCORPORATING PLATINUM-BASED AGENT FOR TARGETED THERAPY OF COLORECTAL CANCER

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Using the combination of Panitumumab, a monoclonal antibody, and oxaliplatin, a Pt-based drug, is known to be effective for patients with colorectal cancers (CRC) in clinical. It is thought that Panitumumab can efficiently bind to epidermal growth factor receptor (EGFR), inhibiting cell growth. Pt-based drug can cause DNA damage, inducing cell death. Synergistic effect is found when Panitumumab and Pt-based drug are combined. However, new strategy to cure patients with CRC is to be explored. Therefore, we designed and created a novel nanoparticle, named Pt-Pan (N). Pt-Pan (N) is self-aggregated from Panitumumab conjugated Dichloro (1, 2-diaminocyclohexane) platinum (II) (DACHPt), named Pt-Pan. It is noted that panitumumab in Pt-Pan (N) can serve as tumor-targeted drug delivery vehicles, efficiently facilitating EGFR-overexpressed CRC cells to take up Pt-based drug. After evaluation of in vitro cytotoxicity, cellular uptake and binding, it is proven that Pt-Pan (N) has good ability to bind to EGFR overexpressed on CRC cells, resulting in more cancer cell death. After evaluating the in vivo tumor inhibition, it is found that Pt-Pan (N) could help achieve outstanding antitumor efficacy. In sum, our findings suggest that Pt-Pan (N) could replace the use of combination of Panitumumab and oxaliplatin and help achieve optimal anticancer efficacy for CRC treatment in clinical.

Keywords: Panitumumab, DACHPt, Oxaliplatin, colorectal cancers (CRC).
THE RESOLUTIVE PROPERTIES OF SUPERMAPO® TREATMENT ALLOW THE ARREST OF ONGOING INFLAMMATION

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Immune-mediated inflammatory diseases have in common a dysregulation of the immune response that cannot be controlled to resolve and stop. Resolution of inflammation is a powerful process involving a numerous of factors which can act on many inflammatory actors. A critical step of inflammation resolution is efferocytosis of apoptotic effector cells by phagocytes which produce factors allowing the arrest of inflammation and initiating tissue healing. We develop a technology allowing us to reproduce this process and produce a biological complex drug composed of resolutive factors. Such factors, injected once in inflammatory experimental models of arthritis, colitis, Crohn disease or experimental autoimmune encephalomyelitis, allowed the long term arrest of ongoing inflammation, clinically and biologically. So far we identified that this drug called SuperMApo® is able to favor highly specific regulatory T cell generation as well as reprogramming of antigen presenting cells that then demonstrated protolerogenic properties. In particular, macrophages and plasmacytoid dendritic cells sorted from SuperMapo®-treated animals are able to favor Treg polarization from naïve T cells for instance. SuperMApo® is under development for further preclinical regulatory evaluation and should provide an innovative opportunity for the treatment of chronic inflammatory diseases and in particular Rheumatoid Arthritis and Crohn disease.

SHIKONIN DERIVATIVES TARGETING STAT3 SH2 DOMAIN INDUCE ANTITUMOR EFFECTS

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Signal transducer and activator of transcription 3 (STAT3) is constitutively activated in various human cancers and has been validated as a therapeutic target for tumors. In our recent work, we utilized in silico approaches combining scaffold growth, docking and molecular dynamics to design a series of shikonin derivatives. The compounds were synthesized and evaluated for their pharmacological profile. Among all the entities, PMM-172 showed the best anti-proliferation activity and decreased STAT3 activity in a dose-dependent manner. Also PMM-172 could induce poly (ADP ribose) polymerase cleavage and activate caspase 3. Besides, PMM-172 suppressed both interleukin 6-inducible and constitutive STAT3 phosphorylation and blocked the nuclear translocation of STAT3 in MDA-MB-231 cells. Further, PMM-172 downregulated the expression of STAT3 downstream target genes cyclin D1, Bcl-XL, Bcl-2 and survivin. Moreover, PMM-172 suppressed MDA-MB-231 tumor growth and STAT3 activities in xenografted mice model. Overall, these results indicate that the antitumor activity of PMM-172 is related to the inhibition of STAT3 signaling in breast cancer cells.

Keywords: STAT3, shikonin derivatives, in silico design, anticancer.
**PO-20**

*Track: Inflammation and Immunology*

**EVALUATION OF URINARY INTERLEUKIN-8 LEVELS IN PATIENTS WITH SPINAL CORD INJURY**

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**Background:** Interleukins are a kind of cytokines and have been identified as soluble proteins which regulate inflammatory and infectious responses. Interleukin 8 plays an important role in the chemotaxis and operation of leukocytes and is locally produced in infected tissues and it is seen in abundance in the urine of individuals with Urinary Tract Infection.

**Material & Methods:** Midstream sterile urine sampling were conducted which varied in different patients who admitted in SCI research center. The samples were tested and examined to determine the level of IL-8 by ELISA method. The commercial kit used for this study was an R & D kit built in Germany.

**Results:** The average level of IL8 was 369.59 pg/ml and 75.42 pg/ml in male and female patients respectively. In the current project, out of the 97 patients under study, 87 (89.7%) were IL-8 positive (>10 pg/ml) and 10 patients were IL-8 negative.

**Conclusion:** It is recommended that SCI patients, irrespective of their SCI severity or the presence or absence of UTI symptoms, have their urinary IL-8 levels measured on a routine and periodic basis. Timely and effective diagnosis and treatment of UTI can prevent the irreversible complications caused by frequent UTI and resistance to treatment in this group of patients.

**Keywords:** Interleukin 8, spinal cord injury, urinary tract infection.

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**PO-29**

*Track: Pharmaceutical Research & Development*

**USE OF SIGNATURE GENOMIC POLYMORPHISMS OF MYCOBACTERIUM TUBERCULOSIS FOR CLADE IDENTIFICATION AND EVOLUTIONARY INFERENCES**

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Tuberculosis is responsible for 1.5 million of deaths annually around the globe. Severity of the disease and propensity of the bacteria to develop antibiotic resistance depend on the pathogens’ affinity to different genetic variants of *Mycobacterium tuberculosis* (Mtb) termed clades. Clades have had distinguishable geographic provenances but nowadays admixed Mtb infections are registered around the world. Because of significant public health implications, multiple Mtb genomes have been sequenced that allowed large scale evaluation of multiple non-synonymous single nucleotide polymorphisms (SNP) for their clade discrimination powers. A computer program for robust identification of the Mtb clades based on submitted sequence data in different file formats including raw DNA reads generated by the next generation sequencing technologies was made publically available at http://mtbclade.bi.up.ac.za/. Analysis of distribution of signature SNP in functional genes elucidated possible driving forces of the Mtb clade diversification. It was found that the Mtb pandemic was preceded by a period of existence of multiple independent clonal lines of Mtb transmitted mostly from parents to children. Increased human population density caused the Mtb pandemic that had started independently in Africa and Asia. Contributions of the genetic drift and positive selection of mutations towards evolution of the Mtb clades were considered.
STUDY OF MECHANISM OF ACETAMINOPHEN TOXICITY

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Acetaminophen (APAP) belongs among mostly used antipyretics and analgesics. It is a safe drug at therapeutic doses. However, after overdose, it can cause cell impairment that may lead to acute liver and/or kidney failure. Although the toxicity has been studied widely, its entire mechanism remains unknown. To introduce specific treatment of APAP overdose, new approaches have been requested but no alternative to N-acetylcysteine treatment rather have been found. To elucidate some other mechanisms of toxicity, we focused on study of APAP toxicity in detail. We used human proximal tubular kidney and epithelial lung cells that were incubated with acetaminophen. We tested the changes in cellular viability (WST-1), redox state (glutathione and ROS levels), morphological changes after treatment with acetaminophen. We found dose dependent relation between dose and viability decrease. Interestingly, we found that also activation of apoptosis may be linked with APAP treatment (p < 0.01) what could be a new promising target for acetaminophen overdose treatment. We conclude, our finding should be also evaluated in consideration of possibilities for acetaminophen treatment. This project was supported by the grant TG02010058.

Keywords: Acetaminophen, acetaminophen toxicity, cell death.

SATURIN - ANTIDIABETIC HERBALREMEDY


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A chemical investigation of plant Satureja hortensis L. - garden savory (GS) has been carried out. It is established that the GS is rich in phenolic compounds. Flavonoids apigenin, luteolin, luteolin-glucoside, luteolin-glucuronide, luteolin-rutinoside, isorhamnetin and phenylcarbonic acids - chlorogenic acid and rosmarinic acid were isolated from the leaves of the plant. The total content of flavonoids and phenylcarbonic acids in GS is 1.6-1.7%. The leaves of GS contain up to 1% essential oil consisting mainly of thymol and methyl carvacrol.

Dry aqueous extract of GS leaves, which retains the full range of substances of raw plant material, has been obtained. Pharmacological investigation of the GS extract was carried out on intact animals and animals with experimental alloxan diabetes. Antidiabetic Arfazetine was chosen as a reference drug. The study revealed that the GS extract exhibits hypoglycemic activity significantly reducing blood sugar levels and is safe in the long run. Drug dosage form named Saturin - capsules containing 0.33 g of dried aqueous extract of GS leaves, has been developed.

Clinical trials of Saturin confirmed its efficacy in diabetes mellitus type 2. The drug is approved for use in type 2 diabetes either independently or in combination with other hypoglycemic agents. Saturin is manufactured at the Experimental and Production Facility of the Institute of Pharmacology.

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PO-59

**Track:** Cancer Targeted Drug Delivery

**ANTIPROLIFERATIVE ACTIVITY OF THE NOVEL ISOINDIGO 5'-BR IN HL-60 CELLS IS MEDIATED BY APOPTOSIS, DYSREGULATION OF MITOCHONDRIAL FUNCTIONS AND ARRESTING CELL CYCLE AT G0/G1 PHASE**

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Our new compound, 5'-Br [(E)-1-(5'-bromo-2'-oxoindolin-3'-ylidene)-6-ethyl-2', 3, 6, 9-tetrahydro-9-dioxo-1H-pyrrolo[3, 2-f] quinoline-8-carboxylic acid], had shown strong, selective antiproliferative activity against different cancer cell lines. Here, we aim to comprehensively characterize the mechanisms associated with its cytotoxicity in the human promyelocytic leukemia HL-60 cells.

**Method:** We focused at studying the involvement of apoptotic pathway and cell cycle effects.

**Results:** 5'-Br significantly inhibited proliferation by inducing caspase-dependent apoptosis. Involvement of caspase independent mechanism is also possible due to observed inability of z-VAD-FMK to rescue apoptotic cells. 5'-Br was found to trigger intrinsic apoptotic pathway as indicated by depolarization of the mitochondrial inner membrane, decreased level of cellular ATP, modulated expression and phosphorylation of Bcl-2 leading to loss of its association with Bax, and increased release of cytochrome c. 5'-Br treated cells were found arrested at G0/G1 phase with modulation in protein levels of cyclins, dependent kinases and their inhibitors. Expression and enzymatic activity of CDK2 and CDK4 was found inhibited. Retinoblastoma protein (Rb) phosphorylation was also inhibited whereas p21 protein levels were increased.

**Conclusion:** These results suggest that the antiproliferative mechanisms of action of 5'-Br could involve apoptotic pathways, dysregulation of mitochondrial functions and disruption of cell cycle checkpoint.

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PO-78

**Track:** Translational Medicine

**ADVERSE DRUG REACTIONS DUE TO CANCER CHEMOTHERAPY IN A TERTIARY CARE TEACHING HOSPITAL**


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**Background:** An adverse drug reaction (ADR) is defined by World Health Organization (WHO) as “Any response to a drug which is noxious, unintended and occurs at doses used in man for prophylaxis, diagnosis or therapy”. There is paucity of data regarding the safety profile of cancer chemotherapy in North-eastern India.

**Aims:** The objective of the present study was to evaluate the pattern of ADRs occurring in cancer patients treated with chemotherapy in a tertiary care hospital in North-east India.
Study Design: Hospital based prospective observational study to monitor Adverse Drug Reactions in Oncology department of NEIGRIHMS.

Methodology: Total of 119 cases were analysed. Reports were analyze for temporal causal relation of the suspected adverse reactions with the offending drug.

Results: ADRs were constipation, nausea and vomiting, alopecia and haematological changes. Suspected drugs were Cisplatin, Paclitaxel, 5-FU, Cyclophosphamide. Premedication drugs were Pheniramine maleate, Ranitidine, Dexamethasone and Granisetron.

Conclusion: Less nausea and vomiting cases in our patients owing to successful premedication and good diet. Uncommon ADRs like constipation seen in our patients which needs further evaluation.

Keywords: Cancer chemotherapy, adverse drug reactions, premedications.

PO-21
Track: Pharmaceutical Research & Development

OPEN INNOVATION IN DRUG DISCOVERY: USING SPECIALIZED LIBRARIES TO DRIVE INNOVATION

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In recent years, corporate libraries have been used as tools to promote innovation, in order to encourage external involvement in enhancing drug discovery.

The clear and steady decline in approved therapeutics is leading the pharma industry to redefine its drug discovery strategies. One outcome is the initiation of intercompany and academia collaborations to drive innovation. Pharma organisations are aiming to valorise their productivity, providing support in areas they are strongest in, by offering open access to core assets in return for enterprise. As part of this strategy and to foster the valorisation of natural products in Life Science industries, Pierre Fabre Laboratories announced that they are launching Nature Open Library, an Open Innovation program that will allow them to share their expertise with industrial players and innovative project initiators, for the research, development and industrialization of their plant assets. In this context, Pierre Fabre Laboratories provide open access to their private plant library, one of the most important in the industry, numbering over 15,000 classified samples, including some coming from rare species. The goal of this Open Innovation Initiative is to valorise the potential of their plant library by opening new fields of exploration that will lead to innovative discoveries in various fields such as pharmaceutical sciences (prescription medicines and consumer health care products), animal health, nutrition and agribusiness. Through Nature Open Library, Pierre Fabre Laboratories will help their future partners to boost their innovative process by giving them access to their plant extract libraries and to their interdisciplinary teams, experts in the entire phyto-industrial value chain, to building interactive relationships with mutual benefit.
PO-22

Track: Biology

EFFECT OF ADDING SALVIA OFFICINALIS EXTRACT IN DRINKING WATER TO PREVENT CHANGES IN BLOOD LIPIDS PROFILE UNDER HEAT-STRESS IN MICE

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Use herbs to reduce stress can play a key role in preventing damage due to heat stress have. The aim of this study was to evaluate the effects of the Salvia officinalis that is respected for its anti-stress effects. In the study 50 mature mice were divided into five groups including control, and four experimental groups (0,100, 200, 400 mg/kg). Mice were under heat stress (36±0.5°C) for four hours a day. At end of period, blood samples were prepared and blood lipid profiles, including: Cholesterol, triglycerides, HDL, LDL were evaluated. Based on the results obtained heat stress on cholesterol in the control group was significantly different from zero dose and group dose is 400 mg/kg extracts help reduce cholesterol (P<0.05). The results showed heat stress has led to an increase in blood LDL (P <0.05) and group 400 mg/kg extracts help reduce LDL (P <0.05).

The study showed, Salvia extract could reduce the effects of heat stress on blood cholesterol and LDL, also according to the results it can be concluded, heat stress by reducing the metabolism and sage herb can be used to extract the metabolism to the natural state changes in the patterns of blood lipids compensated.

Keywords: Heat stress, Garden sage extract, Blood lipid profiles.

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PO-18

Track: Clinical Trials and Regulatory Affairs

UTILIZATION OF CLINICAL TRIAL REGISTRY IN DRUG DISCOVERY RESEARCH PROJECTS ELSEVIER EVIDENCE-BASED MEDICINE, LEXISNEXIS RISK MANAGEMENT, INFOSYS

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Background: Systematic appraisal of completed and ongoing studies mitigates the risk of repeating clinical trials and reduces waste in the research aimed at drug development. A major barrier to evaluating and analyzing the breadth of information from clinical studies is the lack of standardization and normalization of the data.

Methods: We formatted and analyzed all human studies registered in clinicaltrials.gov as of May 2016. We applied standardization and normalization methods using Elsevier’s Merged Medical Taxonomy terms and the corresponding ICD 10 codes, EMBASE taxonomy and natural language processing methods. We performed systemic appraisal of completed and ongoing studies according to treatment allocation, masking of treatment status, early termination, and exclusion enrolled subjects from the analyses. We calculated treatment effect for more than 2 million hypotheses and provided the interpretation of drug effects according to statistical significance, direction, and magnitude of benefits and harms.

Results: We identified 97,042 drug studies including 56,041 completed and 7, 296 terminated studies. Poor recruitment was the most common reason for study termination. We identified the most common conditions under investigation and targeted age and gender groups (e.g. only 5% exclusively pediatric and 0.3% exclusively geriatric studies).
For 14,559 drug studies with the results posted in clinicaltrials.gov, we were able to analyze design (83% randomized trials) and sponsorship (63% with industry involvement), actual and anticipated enrollment status, regulation status according to the section 801 in the FDAA federal law (74%), and industry employment by principal investigators (12%). We analyzed the number of participants who were enrolled, completed or discontinued the study (due to death, adverse effects, physician decision and other factors). Interestingly, less than 1% of drug studies with posted results reported race and ethnicity of the enrolled participants.

**Conclusion:** Analysis of clinical studies registered in clinicaltrials.gov provides valuable information about bias in study design, recruitment and execution, attrition of the patients, baseline patient characteristics, variability in outcome definitions and assessment time. This information can improve efficiency in drug development process and assessment of comparative effectiveness and safety of pharmacological agents.

**PO-11**

*Track:* CNS Drug Discovery & Therapy

**DISEASE-SPECIFIC CHARNOLY BODY FORMATION IN NEURODEGENERATIVE AND OTHER DISEASES (THERAPEUTIC POTENTIAL OF ANTIOXIDANTS)**

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Down-regulation of mitochondrial genome in response to environmental neurotoxins, infections, and malnutrition augments Charnoly body (CB) formation in the most vulnerable developing or degenerating cell. CB appears as a quasi-crystalline, multi-lamellar, electron-dense, stacks of degenerated mitochondrial membranes due to free radical overproduction as a toxic inclusion if it is not phagocytosed efficiently as a molecular mechanism of intracellular detoxification.

Sequestration of lysosomal-resistant CB induces monoamine oxidase release and translocation protein (TSPO: 18kDa) delocalization to cause neurotransmitter (particularly Serotonin, Dopamine, and Norepinephrine) and steroid (sex) hormones imbalance, early morbidity, and mortality. Nonspecific induction of CB formation causes GIT disturbance, myelosuppression, and alopecia in response to multi-drug-resistant malignancies.

Accumulation of CB at the junction of axon hillock causes impairments in the normal axoplasmic transport of various enzymes, ions, hormones, neurotransmitters, neurotropic factors (NGF, BDNF), and mitochondria to cause synaptic terminal degeneration leading to cognitive impairments in PD, AD, and chronic drug addiction.

Metallothioneins (MTs) inhibit CB formation as potent free radical scavengers and provide Zinc-mediated transcriptional regulation of genes involved in cell growth, proliferation, differentiation, and development (Sharma and Ebadi 2013a, Sharma and Ebadi, 2014b). In addition, MTs serve as CB antagonists to prevent obesity.

Although MTs double gene knock out (MT<sub>dko</sub>) mice did not exhibit any overt clinical symptoms of Parkinsonism; these genotypes were mildly obese and lethargic as compared to MTs transgenic (MT<sub>trans</sub>) mice which were lean, thin, and agile. Chronic administration of 1-Methyl, 4-Phenyl, 1,2,3,6 Tetrahydropyridine (MPTP) induced severe body tremors, muscular rigidity, and complete immobilization in MT<sub>dko</sub> mice as compared to MT<sub>trans</sub> mice which could still walk with their stiff legs and erect tail, suggesting the neuroprotective role of MTs in PD.

Various antipsychotic drugs such as Chlorpromazine, Chlorprazine, Risperidone, Domeperidone, are generally antidopaminergic as these are dopamine D-2 receptor antagonists. These typical, first generation, antipsychotic drugs alleviate positive symptoms of schizophrenia as compared to next generation, atypical antipsychotic drugs, as Quetiapine, Olanzapine, Clozapine, which alleviate the negative symptoms of schizophrenia and act on dopamine D3 and D4 receptors preferentially. The atypical antipsychotic drugs do not induce extrapyramidal symptoms as typical antipsychotic drugs, but can cause agranulocytosis; hence periodic blood analysis is required. These drugs can also induce hepatotoxicity, hypertension, hyperglycemia, obesity, and diabetes due to the down-regulation of brain-region specific MTs and other antioxidants.
Chronic use of antipsychotic drugs can cause Parkinsonism associated with extrapyramidal symptoms. Although synaptic changes and adverse effects may take only hrs; these drugs require minimum 2-3 weeks to have their clinical effect. Chronic use of these drugs can induce reversible MOA-B specific CB formation to cause Parkinsonism associated with extrapyramidal symptoms; whereas discontinuation of these drugs eliminates these adverse symptoms due to efficient MAO-B-specific CB eradication through lysosome-mediated Charnophagy as a basic molecular mechanism of intracellular detoxification.

About 70-80% chronic drug addicts become victim to psychosis associated with schizophrenia due to excess and uncontrolled dopaminergic (DA-ergic) neurotransmission. Hence anti-dopaminergic drugs alleviate the most distressing symptoms of schizophrenia to a certain extent yet with adverse extrapyramidal symptoms. On the other hand, drugs which enhance the DA-ergic neurotransmission and/or DA-ergic agonists are used for the treatment of PD. Chronic use of these drugs induce hyper-sexuality and aggravate symptoms of schizophrenia in PD patients due to reversible MAO-A specific CB formation in the mesolimbic dopaminergic system. The symptoms of schizophrenia can be alleviated when these drugs are discontinued. Hence disease-specific CBs can be used as novel targets for the future development of antipsychotic, anti-Alzheimer, anti-parkinsonian, antidepressant, anti-diabetic, and anti-obesity drugs with minimum or no adverse effects as experienced with currently available drugs.

Particularly ROS scavenging antioxidants such as Resveratrol, Polyphenols, Lycopenes, Catchsin, Sirtuins, Rutuins, and several LSDs derived from natural foods, can easily pass through blood brain barrier without any serious adverse side effects and can modulate cellular epigenetic (histone acetylation, and DNA methylation) changes; hence can be used for the prevention and/or inhibition of CB formation involved in compromised mitochondrial bioenergetics, MAOs down-regulation, and TSPO delocalization. These therapeutic antioxidants have also anti-apoptotic and anti-inflammatory properties to protect the CNS and prevent and/or inhibit progressive neurodegeneration in PD, AD, ALS, HD, MS, chronic drug addiction, schizophrenia, diabetes, obesity and several other diseases of unknown etiopathogenesis through IL-10 induction and IL-6 repression.

Although wine has Resveratrol (250 µg/120 ml), it is insufficient to fulfil the daily requirement of 250 mg, which is 1000X more as compared to wine. More over wine contains nitrosamines which can cause cancer. In order to meet the daily requirement of Resveratrol from just wine, we may have to consume as many as 300 bottles of 120 ml of wine, which will definitely cause hepatotoxicity and neurotoxicity much earlier as compared to conferring the beneficial effects of Resveratrol derived from the wine. Hence natural sources of Resveratrol from natural foods or eating fresh grapes instead of wine will be more beneficial as a source of Resveratrol as generally publicized by the wine industries and misinterpreted by the consumers.

As there is limited scope of neuron-replacement therapy, therapeutic interventions with aforementioned antioxidants seems practically feasible as these can enter CNS freely without inducing any deleterious adverse effects; however, their adequate target delivery and reduced potency remains a significant therapeutic challenge.

PO-31

Track: Biologics

BIOMOLECULAR EVALUATION AND ASSESSMENT OF LIVER ENERGY CAPACITY IN RATS SUBMITTED TO PARTIAL HEPATIC ISCHEMIA AND TO LIVER PRECONDITIONING WITH LASER LIGHT

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Introduction: Biochemical and molecular markers such as intestinal or liver fatty acid binding protein (I-FABP or L-FABP) are being used for the detection of ischemic and reperfusion injuries mainly in the intestine and liver. I-FABP is found in the cytoplasm of small bowel enterocytes and L-FABP is found in the cytoplasm of hepatic, intestinal, renal and gastric cells.

Objective: To determine the protective effect of laser against hepatic injury in rats submitted to partial ischemia by analyzing mitochondrial function and L-FABP expression.
Method: Twenty-five Wistar rats weighing 200 to 300 g were divided into four groups (n=5): 1) Control (C), 2) Control + Laser (CL), 3) Partial Ischemia (PI), and 4) Partial Ischemia + Laser (PIL). PI was induced by clamping the hepatic pedicle of the middle and left lateral lobes of the liver (70% of hepatic tissue) with vascular microclips for 60 minutes. Laser light was applied to four different liver sites five minutes before the induction of PI at the dose of 22.5 J/cm². All animals were sacrificed after 30 minutes of reperfusion and blood and tissue samples were collected for serum aminotransferase (ALT and AST) determination, analysis of mitochondrial function, determination of malondialdehyde (MDA) and analysis of L-FABP. Data regarding serum ALT, AST and MDA were analyzed statistically by the nonparametric Mann-Whitney test (p<0.05) and data regarding L-FABP expression were analyzed by nonparametric one-way ANOVA, followed by the Tukey-Kramer post-test, using the Graph Pad Prism 5.0 software (Graph Pad Software Inc., LaJolla, CA, USA).

Result: Reduced mitochondrial function was observed in the PI group, especially ADP-activated state 3 respiration (PI vs C p<0.05), as well as reduced L-FABP expression (p<0.05). In group PIL the application of laser light prevented this reduction (p>0.05) in both mitochondrial function and L-FABP expression (p<0.05), with levels similar to those of group C being observed. Groups PI and PIL showed a similar increase in MDA (p>0.05).

Conclusion: The prophylactic application of laser light to the liver of rats submitted to partial ischemia proved to be effective as a liver protective factor, preventing changes in mitochondrial function and L-FABP expression.

Keywords: Laser, Ischemia, Rats.

PO-30
Track: Biologics

BIOMOLECULAR, MITOCHONDRIAL AND IMMUNOHISTOCHEMICAL ASPECTS OF LASER EFFECT ON LIVER REMNANT AFTER LARGE HYPOTERMIC PARTIAL HEPATECTOMY

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Objective: To evaluate the effect of laser on the LR of rats submitted to partial ischemia.

Method: Twenty Wistar rats weighing 200 to 300 g were divided into four groups (n=5): 1) Control (C), 2) Control + Laser (CL), 3) Liver remnant (LR), and 4) Liver remnant + laser (LRL). Partial liver ischemia was induced by clamping the hepatic pedicle of the middle and left lateral lobes of the liver (70% of hepatic tissue) using vascular microclips for 60 minutes. Laser light was applied five minutes before the induction of partial ischemia at the dose of 22.5 J/cm² to five different liver sites. All animals were sacrificed after 30 minutes of reperfusion for the study of the LR (30%), for serum determination of aminotransferases (ALT and AST), analysis of mitochondrial function, and determination of malondialdehyde (MDA). Data were analyzed statistically by the Mann-Whitney test (p<0.05) and by one-way ANOVA followed by the Tukey-Kramer post-test.

Result: Increased mitochondrial function was observed in the LR group but not in the LRL group, and increased MDA concentration was observed in the LRL group > LR. All animals showed a significant increase in ALT and AST levels.

Conclusion: Prophylactic application of laser light to the liver of rats’ submitted to partial ischemia reduced the energy capacity and increased the oxidative stress in the LR.

Keywords: Ischemia, Liver, Cold Ischemia, Laser, Mitochondria.
PO-62

Track: Inflammation and Immunology

DIOGENIN ANALOGUE-15 (26-(3’, 4’, AND 5’-TRIMETHOXYBENZYLIDENE)-FUROST-5EN-3β-ACETATE) ATTENUATE SKIN INFLAMMATION: AN IN VITRO AND IN VIVO STUDY

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Diosgenin is a C27 spiroketal steroidal sapogenin present in saponin form in the plants. Based on our previous report, we have explored the most potent lead diosgenin analogue-15 against the skin inflammatory condition using in vitro and in vivo bioassays. The treatment of diosgenin analogue-15 exhibited the significant inhibition of pro-inflammatory cytokine production and mRNA expression against lipopolysaccharide (LPS)-induced inflammation in J774A.1 macrophages cells in dose dependent manner without any cytotoxicity. Immunocytochemistry study also revealed that its pro-inflammatory inhibition response is due to the blocking of NF-κB activation. Efficacy and Safety of diosgenin analogue-15 was further explored in in vivo system using 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced skin inflammation in mice and primary skin irritation in rabbit. Its topical application markedly inhibited TPA-induced ear edema, pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β) production and oxidative stress (Lipid peroxidation and Nitric oxide) in ear tissue homogenate in a dose-dependent manner without any signs of primary skin irritation. These findings suggested that diosgenin analogue-15 may be explored in detail as a novel therapeutic candidate for the treatment of skin inflammation related condition.

Keywords: Diosgenin, Inflammation, Macrophages, Skin, LPS, TPA.

PO-26

Track: Hot Topics in Natural Products

EVALUATION OF CELLULAR ANTIOXIDANT ACTIVITY OF CHINESE HERBS TO BE USED AS FOODS WITH HEPATOPROTECTIVE POTENTIAL THROUGH REGULATING NRF2 PATHWAY

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The liver is the primary organ responsible for the major detoxifications and metabolic functions in the human body; however, severe liver failure caused by oxidative stress/inflammation induced by chemicals and non-alcoholic fatty liver disease always leads to death. Nrf2 is a master regulator to induce the expression of phase II detoxification/antioxidant enzymes. Some of Chinese herbs to be used as foods in Taiwan have hepatoprotective potential, including burdock root (BR), cassia seed (CS), lotus leaf (LL), or citrus peel (CP). We found that water extracts (WE, 0-25 μg/mL), ethnolic extracts (EE, 0-100 μg/mL), and ethnolic extracts of water extract residue (WREE, 0-100 μg/mL) of these Chinese herbs exhibited no cytotoxicity in HepG2 cells at 24 h in this study. Furthermore, we determined Nrf2 pathway induction activity of these extracts in HepG2-C8 cell line which is stably transfected with an antioxidant response element (ARE)-luciferase construct, and some extracts, such as BR-WE, BR-WREE, CS-WE, CS-EE, LL-WE, LL-EE, LL-WREE, and CP-WREE, showed stronger induction of ARE-luciferase activity at 24 h. A better understanding of the mechanisms how these extracts inhibit oxidative stress/inflammation related to liver injury in the future would open new avenues of approaches for the prevention of liver diseases in human.
MICROWAVE-PROMOTED SYNTHESIS OF MACROCYCLIC COMPOUND [3.3] (2, 2') 4, 4'-BITHIAZOLOPHANE EXHIBITING ANTI C-MET ACTIVITY

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Bithiazole group in bleomycin, an anticancer medicine, is known to play a role in recognition of DNA. We have synthesized bithiazole derivatives and evaluated some bioactivities of their compounds. In their bioactivities, a cleaving activity of plasmid DNA for the bithiazole derivatives was observed only in the presence of some metal ions.

On the other hand, the property of anticancer also has been researched for these compounds. Most of bithiazole derivatives didn’t show anticancer activities, however a bithiazolophane, including two bithiazoles in the macrocyclic molecule, showed anti c-Met activity among their activities.

In this study, we found out that the synthesis method of the c-Met inhibitor, 2,15-diaza-2,15-bis (butoxycarbonyl) [3.3][2,2')(4,4'-bithiazolophane) (1), on trying to synthesize bithiazoles using thioamide and 4-bromobutanedione by Hantzsch reaction and the reaction was promoted under microwave irradiation to produce (1) only for 30 seconds.

The bithiazolophane (1) was synthesized through 4 steps. First, amino group of dimethyl 2,2'-azanediylidiacetate (2) reacted with di-tert-butyl dicarbonoate and was protected by butoxycarbonyl group to give the N-Boc protected ester (3). Next, the use of ammonia aq. allowed a transformation of the ester (3) to the amide (4), which was converted into the thioamide (5) by treatment with Lawesson’s Reagent. Finally, the reaction of the thioamide (5) with 4-bromobutanedione easily gave the bithiazolophane (1) for 30 seconds under microwave irradiation. After optimization of the reaction conditions was carried out, the use of alumina gel as additives and EtOH as solvents under microwave irradiation in the reaction produced the target molecule (1) in 30% yield from (5). Furthermore this bithiazolophane (1) exhibited inhibitory activity (IC_{50} = 603 nM) only for c-Met among protein kinases. It will be reported in this conference that synthesis of (1) and its bioactivities in detail.
PO-54

Track: Pharmaceutical Research & Development

GRP/GRPR PATHWAY AFFECTS THE INVASIVENESS OF MURINE SYNOVIAL FIBROBLAST AND ALTERS PI3K/AKT PATHWAY

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Synovial fibroblasts (FLS) are the main cells involved in the mechanism of pathogenesis of rheumatoid arthritis (RA), presenting invasive and aggressive profile. The invasiveness of FLS is poorly understood, but it could be linked with intracellular pathways such as PI3K/Akt. Gastrin-releasing peptide (GRP) and its receptor (GRPR) are involved in the inflammatory response and in RA, FLS were isolated from the joints of mice with collagen-induced arthritis. Expression of GRPR in FLS was confirmed by immunocytochemistry and western blot (WB). FLS viability with GRP, RC-3095 (GRP antagonist) and with LY294002 (PI3K inhibitor) demonstrated no citoxicity. FLS invasiveness was measured using a Matrigel-coated transwell invasion system. GRP increased FLS invasion by nearly two-fold, compared with untreated cells, while RC-3095 reversed that effect. FLS treated with GRP+RC-3095 invaded similarly to control. LY294002 decreased FLS invasion compared with untreated cells and with GRP, and the same effect was observed with LY294002+GRP. Lastly, treatment with GRP increased phosphorylated AKT expression in FLS, analyzed through WB. This is the first study to identify the presence and activity of the GRP/GRPR pathway in FLS and to suggest a pathway related with PI3K/AKT. Thus, the GRP pathway is a potential therapeutic target on FLS for RA treatment.

PO-53

Track: Cardiovascular Drug Discovery & Therapy

CARDIO PROTECTIVE EFFECTS OF ROSMARINIC ACID ON ISOPROTERENOL-INDUCED MYOCARDIAL INFARCTION IN RATS

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Rosmarinic acid (RA) is a polyphenolic compound with considerable antioxidant activities. We aimed to investigate its cardioprotective effects in isoproterenol-induced myocardial infarction (MI). Male Wistar rats were assigned to 5 groups of control, isoproterenol, and treatments with 10, 20, 40 mg/Kg of RA. Myocardial infarction was induced by subcutaneous injection of isoproterenol (100 mg/Kg) once daily for 2 days. RA was injected intraperitoneally once daily, until the fourth day after MI induction. In fifth day the animals were anesthetized and hemodynamic and electrocardiographic parameters were recorded. After collecting the blood samples, the hearts were removed and weighed to measure the cardiac enlargement and were used for further histological studies and the level of Lactate dehydrogenase and malondialdehyde were measured in collected samples. Data were analyzed using One-way-ANOVA test. Isoproterenol induced MI and obvious cardiac damages. RA significantly reduced peripheral neutrophil percentage and inhibited electrocardiographic and hemodynamic changes in the infarcted hearts. It also significantly decreased the left ventricular end diastolic pressure and improved the ventricular contractility, compared to the isoproterenol group. Histopathological evaluations showed that RA significantly diminished the post-MI necrosis and fibrosis in myocardium and inhibited cardiac enlargement. It also revealed a considerable antioxidant activity in vitro. It can be deduced that RA can improve the cardiac performance and inhibit the myocardial damages post-MI, due to its antioxidative activity.

Keywords: Rosmarinic acid, myocardial infarction, Isoproterenol, antioxidant.
**PO-14**

*Track: Diabetes and Obesity Drug Discovery & Therapy*

**METFORMINIUM DECAVANADATE IMPROVE INSULIN RECEPTOR PHOSPHORYLATION AND GLUCOSE TRANSPORTERS IN TISSUES OF WISTAR RATS WITH DIABETOGENIC SYNDROME TYPE 1**

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Recently, the use of metal-based drugs as therapeutic agents has been increased. Its development and usage for the treatment of a variety of pathologies such as diabetes, cancer, rheumatoid arthritis, and inflammatory and cardiovascular diseases, have evolved strongly in the past two decades. Particularly, vanadium is a biometal capable of improving the metabolism of lipids and carbohydrates; also, it has been reported that some vanadium compounds possess insulin-mimetic activity. In this regard, our working group has developed a metforminium decavanadate compound [1, 2], which improve dysglycemia and dyslipidemia in rodent models with metabolic syndrome and diabetogenic syndrome type 1 and 2 (diabetes mellitus type 1 and 2, in humans). Recently, we studied metabolic pathways in liver, muscle, heart and kidney in rats with diabetogenic syndrome type 1. We found that the compound improved the insulin receptor phosphorylation, insulin-signaling in all tissues and contributed in GLUT’s expression (GLUT 2 and GLUT 4), as well as, stored triglycerides, but not in the glycogen reserve. These findings oblige us to delve into different pathways by which its effect is achieved.

**Keywords:** Diabetes type 1, Insulin Receptor, Metforminium Decavanadate.

**REFERENCES**


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**PO-10**

*Track: Anti-Cancer Drug Discovery & Therapy*

**ENHANCEMENT OF ANTITUMOR ACTIVITY OF THE OXAZAPHOSPHORINE CYTOSTATIC SUM-IAP BY N-METHYLFORMAMAMIDE**

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SUM-IAP has been developed with the aim to optimize therapeutic response and minimize toxic reactions of oxazaphosphorine cytostatics. In therapy tests in mice with advanced subcutaneously growing P388 leukaemia cells the primary tumor was successfully eradicated but animals died due to formation of lethal metastases. We supposed that high activities of SUM-IAP detoxifying enzymes caused metastasis formation in the liver. Therefore therapy tests with SUM-IAP in combination with cisplatin and N-methylformamide (NMF), which were not detoxified were carried out. The results of therapy tests with SUM-IAP plus cisplatin were as expected: No formation of metastases and long time survival of more than 100d was observed however the toxicity was increased as measured by decrease in body weight and the number in leukocytes. The results of the tests
in combination with NMF were surprising: With half the dosage of SUM-IAP compared to the experiments of in combination with cisplatin no metastases were found and long time survivors did not show signs of additional toxicity. NMF strongly enhances the antitumor activity of the oxazaphosphorine cytostatic SUM-IAP in mice with subcutaneously growing P388 leukemia cells by an unknown mechanism of action.

Keywords: Oxazaphosphorine cytostatics, SUM-IAP, N-methylformamide, cisplatin.

PO-13

Track: Anti-infectives

HUMAN CYSTIC ECHINOCOCCOSIS IN ENDEMIC REGIONS IN BULGARIA - PROPHYLACTIC ULTRASOUND EXAMINATIONS AND TREATMENT

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Introduction: Echinococcosis is a chronic disease in humans, with prolonged recurrent course of illness. In some cases no symptoms, but in others there is repeated surgical treatments and severe complications. High incidence of cystic echinococcosis (CE) reported in Eastern Europe was a reason for supporting international project, funded by the Seventh Framework Program of the European Commission - HERACLES.

Materials and Methods: Ultrasound examinations (US) were performed on 8602 people in four Bulgarian endemic regions for CE in two years period (2014 and 2015).

Results: Hydatid cysts were found in 70 patients, of which 44 were with post-operated cysts without relapse (CE4), 3 patients are post PAIR treated, 4 were treated in the past with albendazole (solid lesions). In 18 patients hydatid cysts were found for first time (CE1, CE2 and CE4). Relapses were detected in 3 patients operated in the past. Eight of people surveyed were operated because of a perceived extra-hydatid disease (pulmonary, cardiac, bone) without cysts in abdominal organs. From patients with active CE - 3 were operated, one have PAIR, one is treated 4 months with ABZ and after was operated, 4 have treatment with ABZ.

Conclusion: For the first time in endemic areas for CE in Bulgaria was carried out ultrasound screenings. Collection and analysis of accurate epidemiological and clinical data will give a reliable picture of the burden of this disease in Bulgaria, providing a statistically supported case series for future evaluation of efficacy and effectiveness of treatment.

Acknowledgements: The research was funded from the European Community’s FP7 under the grant agreement 602051 (Project HERACLES).

Keywords: Human cystic echinococcosis, ultrasound screenings, Bulgarian endemic regions for CE.
FROM DECONSTRUCTION TO RECONSTRUCTION: DESIGN FOR NEW BRAFV600E ANTAGONISTS BASED ON FBDD STRATEGY

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Dysfunctions of the components in Ras/Raf/MEK/ERK cascade are among the major causes of human cancers. Of note is that mutated B-Raf kinases are featured in 50-80% of melanoma and also involved in other somatic tumors. In our recent research, we retrieved the PDB database and acquired known B-Raf co-crystals with small molecular ligands. The complexes were gathered and superimposed, with the ligands thereafter deconstructed to generate fragments. Afterwards, the potency of fragments was estimated and employed as the metric to rank these fragments. Meanwhile, through a systematic analysis of the receptors, we explored the binding sites to provide structural information and guide the design process. The most potent fragments in different active pockets were then picked and recombined to furnish dozens of lead-like compounds. After removing the known chemotypes, the rest compounds were docked iteratively to estimate the binding affinity of these compounds. The best hit was thereafter synthesized and optimized preliminarily, with in vitro and in vivo assays depicting their pharmacological profile. The results suggested we have identified a novel scaffold which may be promising in the future study.

Keywords: Braf inhibitor, FBDD, fragments merging, in silico

EFFECT OF DIFFERENT OSMOLYTE CONCENTRATIONS IN THE L-ASPARAGINASE II ACTIVITY

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Drugs containing the enzyme L-Asparaginase II (ASNase II) are used for the treatment of Acute Lymphoblastic Leukemia (LLA). The enzyme hydrolysates L-asparagine, which is essential for the metabolism of malignant cells. Osmolytes are represented by sugars, polyols, free amino acids and their derivatives. These molecules present a protective behavior and favor the native form of macromolecules, being able of stabilizing proteins. The aim of this work was to analyze the effect of an increasing gradient of osmolytes in the specific activity of ASNase II from Erwinia chrysanthemi. The recombinant enzyme was expressed, purified and identified. The specific activity was measured in an increasing gradient of sucrose, sorbitol, urea, L- arginine and L-glycine (0, 15, 30, 45 and 60 mM) after the ASNase incubation for 24 h with the respective osmolyte solution, through Nessler method (Merck). The ASNase specific activity was, respectively, 41% and 43% higher in the presence of sorbitol or L- arginine 60 mM , while the other osmolytes resulted in lower values. We observed a similar enzyme activity profile for both of these molecules. Importantly, we found that the presence of osmolytes contributes to the improvement of L- asparaginase activity and specific concentrations are more efficient to be used.

Keywords: L- Asparaginase, Osmolyte, sorbitol, L- arginine.
**PO-2**  
*Track: Hot Topics in Natural Products*

MOLECULAR CLONING, STRUCTURAL CHARACTERISATION AND TARGETED ENGINEERING OF A NOVEL AMPHIBIAN ANTIMICROBIAL PEPTIDE FROM THE SKIN SECRETION OF THE TARSIER LEAF FROG, *PHYLLOMEDUSA TARSIIUS*

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Antimicrobial peptides (AMPs) in the skin secretions of amphibians, are fundamental components of a unique defence system, which has been developed to protect from microbial invasion. These polypeptides exhibit broad spectrum antimicrobial activity and have attracted attention as potential new antibiotic leads for the treatment of currently resistant bacterial infections. The medusins are a recently discovered AMP family from phyllomedusine leaf frog skin. They exhibit highly-conserved structural characteristics including the N-terminal hexapeptide sequence, LLGMIP-, and a C-terminal tetrapeptide amide sequence, -LSKLamide. Here, we report a novel medusin from the skin secretion of the tarsier leaf frog, *Phyllomedusa tarsius*, which was named, medusin-PT. The mature peptide was identified as encoded by cloned biosynthetic precursor-encoding cDNA, obtained by a RACE technique. Reverse phase HPLC of skin secretion and tandem mass spectrometry, confirmed both the presence and primary structure of medusin-PT (LLGMIPVAITAISALSKLamide). Chemically-synthetic medusin-PT exhibited antimicrobial activity only against the Gram-positive bacterium, *S. aureus*. However, after the cationicity and amphipathicity of medusin-PT was enhanced by engineering amino acid substitutions, a significant increase in antimicrobial activity against *S. aureus* as well as the appearance of activity against the Gram-negative bacterium, *E. coli* and the yeast, *C. albicans*, was observed. These data provide evidence that medusins may be promising candidates as novel antibiotic leads and that the targeted modification of a natural AMP can provide new insights in antibiotic design and development.

**Keywords:** Amphibian skin secretion, molecular cloning, antimicrobial peptides, medusins.

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**PO-63**  
*Track: Chemistry*

TOPOLOGICAL NANOSCIENCE MATERIALS OF GRAPHENE AND CARBON NANOTUBE COMPUTER 4D DISPLAY OPENGL TECHNIQUE ASSISTED WITH BLUETOOTH MODULE EQUIPMENT

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The aim objective of the presented OpenGL technique is to provide a platform for researchers as well as industrial professionals from all over the world to being presenting their research results of topological nanoscience materials such as Graphene and Carbon nanotube. And development activities in Materials Research and Application will be reviewed by technical computer 4D display OpenGL, that means 3 Dimensional computer movie displays with 1 Dimensional flexible positioning real-time changeable viewpoint. Additionally the unique points of presented research is being assisted with Bluetooth module equipment, regarding the remote assess mobile computing system i.e. Android OS Smartphone-type tablets.

**Keywords:** Topological nanoscience materials, graphene, carbon nanotube, computer display, OpenGL, Bluetooth module.
EXAMINATION OF CYTOTOXIC ACTIVITY OF LITHIUM SALT OF TAURINE

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The aim of this study was to investigate the cytotoxicity of the drug synthesized by us, a lithium salt of taurine. KCL-22 cells at a concentration of 0.5 * 10^6 cells/ml were cultured in 24-well plates for 24 hours, after which it was added to the test substance at different concentrations (1-1000 mg/mL). After 48 hours of incubation of 0.4% trypan blue dye and cell viability was determined.

To assess the cytotoxicity of the test drug elimination method using the vital dye trypan blue (Trypan Blue Exclusion Test Cell Viability) this method was used for counting the number of live/dead cells using an aqueous dye solution.

Results showed that a lithium salt of taurine is not cytotoxic towards human KCL-22 cells. The level of cell viability began to decrease significantly starting at a concentration of 10 mg/mL, but even at the maximum investigated concentration (1000 mg/mL), cell viability was 75%. Thus lithium salt of taurine is not cytotoxic towards human KCL-22 cells.

NOVEL BIVALENT INHIBITORS WITH SUB-NANOMOLAR AFFINITIES TOWARDS HUMAN GLYOXALASE I

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Human glyoxalase I (GlxI) is a 42 kDa dimeric Zn2+ metalloenzyme that detoxifies methylglyoxal in vivo by converting it into S-D-lactoylglutathione, which is then converted to D-lactate by glyoxalase II. Since high activities of GlxI are present in tumor tissues, inhibitors of GlxI increase the accumulation of cytotoxic methylglyoxal, which results in significant anti-tumor activity both in vitro and in vivo. In the present work, the bivalent inhibitors polyBHG2-62 and polyBHG2-54 exhibit much tighter binding ability than BHG itself, with Ki values of 1.0 nM and 0.3 nM, respectively. Compounds polyBHG2-62 and polyBHG2-54 have similar solubilities (26 mg/mL and 32 mg/mL, respectively). In addition, poly BHG2-62 and poly BHG2-54 are almost 50-fold more active than CHG, respectively. CHG binds 78-fold less tightly to GlxI than to hGlxI. Thus, cross-linking increases the inhibitor selectivity by approximately 158-fold, as CHG binds 78-fold more tightly to hGlxI than to yGlx, while poly BHG2-54 binds about 12,300-fold more tightly. A comparison of the inhibition constants of CHG and poly BHG2-54 for hGlxI versus bGlxII shows that cross-linking increases binding selectivity 8.6-fold, from 37-fold to 320-fold.

Keywords: Glyoxalase I, Methylglyoxal, Bivalent inhibitor, Cross-linking, Inhibition constant.
LIVISIN: A NOVEL AMPHIBIAN BOWMAN-BIRK PROTEASE INHIBITOR FROM THE SKIN SECRETION OF THE GREEN CASCADE FROG, ODORRANA LIVIDA: MOLECULAR CLONING, ISOLATION/IDENTIFICATION AND EVALUATION OF MODIFIED ANALOGUES IN FUNCTIONAL ASSAYS

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The Bowman-Birk (BBI) family of protease inhibitors is a prototype group found mainly in plants, particularly grasses and legumes, which have been subjected to decades of study. However, the discovery of attenuated peptides containing the canonical Bowman-Birk protease inhibitory motif, has recently been reported from amphibian skin secretions, mostly from members of the family Ranidae. Their roles in amphibian defence have been proposed as working cooperatively with antimicrobial peptides and reducing peptide degradation. A novel trypsin inhibitory peptide, named livisin, was found in the skin secretion of the green cascade frog, Odorrana livida. Its biosynthetic precursor-encoding cDNA was cloned using a RACE strategy and the predicted mature peptide was characterized by HPLC and MS/MS sequencing. The amino acid sequence of livisin was confirmed as: GFLRGCWTKSFPPKCL, with a disulfide bridge between Cys6 and Cys16, forming the typical inhibitory loop of a BBI. A comparative activity study between the native peptide and its inhibitory loop fragment found that both processed a similar inhibition efficacy against trypsin, consistent with the predefined activity motif. However, a modification by amidation of the C-terminus of both peptides increased their inhibition potency by 10-fold. Replacement and substitution of Lys9 by Phe, altered the proteolytic inhibitory activity of livisin to that of a chymotrypsin inhibitor. These data demonstrate that amphibian skin secretion is a remarkable source for discovery of novel protease inhibitors which can act as leads for potential drug discovery/development purposes.

Keywords: Amphibian skin secretion, molecular cloning, host defence, BBI, trypsin inhibitor.
Welcome Note

The “Global Biotechnology Congress 2016” would provide eminent scientists the opportunity to present their cutting edge researches in the field of biotechnology and its applications in medicine. Four Nobel Laureates and leading researchers will participate in this important conference.

It is our pleasure to welcome the participants to GBC 2016. We expect that they will enjoy the lectures delivered by leading authorities in their respective fields. A large number of students will also be participating to make the most from this scientifically enthralling venture.
PLENARY LECTURES
**NOVEL DRUG DESIGN**

**Sidney Altman**

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Drug resistance of bacteria and other microbes is a world-wide medical problem in the human population. A new technology is needed to provide drugs that can easily attack several targets in bacteria and other microbes and will be stable for longer periods of time in humans than currently available drugs. Such a technology can be provided immediately and potential therapeutic compounds are very active in laboratory cultures against several bacteria and the malaria parasite, *Plasmodium falciparum*. The molecular structure of the new compounds contains a RNA-like molecule and is much larger than traditional drugs.

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**BIOCATALYSIS AND DRUG REPOSITIONING- A WAY FORWARD FOR COST EFFECTIVE LEAD DISCOVERY**

**M. Iqbal Choudhary and Atta-ur-Rahman, FRS**

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Microbial transformation is an effective tool for structural derivatizations that are difficult to achieve by conventional chemical methods. Microbial systems are also extensively employed in the study of drug metabolism and bioremediation. The process is the best tool in medicinal chemistry for the introduction or modification of specific functionalities at the positions difficult to access by conventional chemical methods. In last two decades, this methodology has become an indispensable tool for asymmetric synthesis, not only in academic research but also at the industrial scale. There is a need to fully exploit the potential of biotransformation in creating new and novel chemical space for the discovery of lead molecules against prevalent diseases.

During our studies we structurally modified a number of existing drugs into their structural analogues by microbial and plant cell suspension cultures. The resulting metabolites have exhibited interesting biological activities, different from their precursor drugs. Medrysone (11β-hydroxy-6α-methylpregn-4-ene-3,20-dione) is an anti-inflammatory agent used in ophthalmic treatments. The microbial transformation of medrysone with the filamentous fungi, *C. blakesleeanum* (ATCC 8688a), *N. crassa* (ATCC 18419) and *R. stolonifer* (TSY 0471). Fermentation of medrysone with these fungi yielded seven new metabolites. Various cellular assays, such as phagocyte oxidative burst, T-cell proliferation, and cytokines analysis, were performed on the drugs and metabolites to evaluate their anti-inflammatory potential. Oxyxetholone which is marketed as anadrol, a synthetic anabolic steroid developed in 1960 by Zoltan `Anadrol Z` F. It has been approved by the US Food and Drug Administration for the treatment of anemias caused by deficient red cell production. Its biotransformation was carried out with various fungi resulted in the production of various new and a known metabolites. Oxyxetholone and some of its metabolites showed anti-inflammatory activity. Similarly, Exemestane (trade name aromasin) is a steroidal aromatase inhibitor, used for the treatment of breast cancer. Aromatase inhibitors block the synthesis of estrogen. This lowers the estrogen level, and slows the growth of cancers. Exemestane was invented and synthesized by the Italian company using commercially available boldenone (androsta-1,4-diene-17β-ol-3-one) FDA approved it in October 2005. After biotransformation cytotoxicity was checked, which showed that new metabolite of exemestane showed activity against HeLa and PC3 cancer cell lines. Similarly melengestrol acetate is used as a feed additive for feedlot heifers, was found to be a potent anti-inflammatory agent along with its new transformed product. Tibolone is a synthetic steroid hormone drug, used for the treatment of endometriosis and hormone replacement therapy in post menopausal women, we have successfully biotranformed the drug into its new derivatives and find our
their potent activity as alpha glucosidase inhibitors. These results showed that resulted new and known compounds can fasten the process of drug development.

During this presentation, underlying philosophy and approach of our research on cost-effective discovery of lead molecules by using drug repositioning and biotransformation strategies will be discussed.

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**PL-2**

**THYMOSINS: FROM DISCOVERY TO CLINICAL APPLICATION**

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The Thymosins are a family of small peptides with hormonal-like properties first isolated from calf thymus glands. They are biological response modifiers (BRMs) and belong to a large class of molecules that modulate the immune system and are important to the repair and regeneration of tissue following injury. The first account of the isolation and partial characterization of the active peptide components of the thymus, collectively called "Thymosins" was reported in 1966. Over the next several years, a partially purified and standardized heat stable preparation termed Thymosin fraction 5 (TF5) was developed which was amenable for scale-up and suitable for clinical trials. In April 1974, the first clinical trial with TF5 began under the clinical direction of Arthur Amman, the Director of Pediatric Immunology at the University of California San Francisco Medical School. His first patient treated with TF5 was a 5 year old girl with DiGeorge Syndrome, presenting with a body weight of 26 lbs. She had extremely low numbers of T-cells and was critically ill with overwhelming infections. In a landmark paper published in 1975 in the New England Journal of Medicine, the results of the use of TF5 to treat children with a variety of primary immune deficiencies were published.

Since the early pre-clinical and clinical studies with TF5, in patients with PIDs, cancer, infectious diseases and autoimmune diseases, the major research interests of our laboratory has been in purifying and characterizing the biologically active components in TF5 and translating these studies from the lab bench to the clinic. Two of these molecules, Thymosin A1 (Ta1) and Thymosin B4 (Tb4) have been synthesized and have reached the clinic.

Ta1, the acetylated N-terminal 28 amino acid fragment of prothymosin a (113 amino acids), is now approved in 35 countries for the treatment of hepatitis B and C, and as an immune stimulant and adjuvant under the commercial name of Zadaxin. In addition to its recognized efficacy in the broad areas of infectious diseases, immune deficiency diseases and cancer, the most event reports of clinical trials with Ta1, are pointing to important, hitherto unrecognized, applications in a number of other diseases and disorders, including septic shock, acute respiratory distress syndrome, peritonitis, acute cytomegalovirus infections, TB and lung infections in critically ill patients. It is also emerging as a promising chemo-protective agent in patients undergoing chemotherapy.

Tb4 is also acetylated at the N-terminal serine position. It is a peptide of 43 amino acids and is the first of the synthesized beta-Thymosins to reach the clinic. Many of its activities directly affect the repair and regeneration cascade following injury. Tb4's pleiotropic biological activities centered around accelerating wound healing and repair have provided the scientific foundation for ongoing and projected Phase 2/3 human trials. Indications for treatment include dermal wounds, eye injuries, including severe dry eye and neurotrophic keratitis, and repair of the heart following a heart attack. Recently reported animal studies indicate that Tb4 may also be useful in treating brain injuries follow stroke, trauma or neurological diseases such as multiple sclerosis as well as a number of peripheral neuropathies. The ability of Tb4 to reduce scarring and to down-regulate NFkB and a large number of inflammatory chemokines and cytokines point to a number of additional activities in treating other autoimmune diseases, fibrosis and diseases associated with the aging process. Now, 50 years after the original discovery of the Thymosins, advances in genomics, proteomics, and gene therapy are rapidly amplifying our understanding of the important role of these thymus-derived peptides in both health and disease and their future potential. From these studies has come the real promise that synthetic versions of several of the Thymosin peptides isolated from TF5 will be useful in the treatment of a number of difficult to treat life threatening acute and chronic diseases and to promote the healing and remodeling of wounds following injury and trauma.
**PL-118**

**Track:** CNS Drug Discovery & Therapy

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**EPIGENETICS OF ALZHEIMER'S DISEASE AND DEMENTIA: POTENTIAL DRUG TARGETS**

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Epigenetic mechanisms contribute to several neurodegenerative diseases, including Alzheimer’s disease (AD). Over time, environmentally induced epigenomic changes can result in an increased risk of dementia, yet individually these changes are essentially latent. Should sufficient alterations to the epigenome accrue, gene regulation becomes sufficiently perturbed, resulting in dementia. Such disruption is biochemical (epigenomic tags). AD and other idiopathic dementias are associated with epigenetic transformations. These transformations connect the environment and genes to pathogenesis and have led to the investigation of epigenetic-based targets. The epigenome-based latent early-life associated regulation (LEARn) hypothesis states that accumulated environmental ‘hits’ produce latent epigenetic changes. This process can occur across generations via transgenerational LEARn (tLEARn). In the case of tLEARn, each person is a ‘unit’ accumulating preclinical or subclinical ‘hits’ as in the original model. These changes can then be epigenomically passed along to offspring.

These hits can alter biochemical pathways until a pathological threshold is reached, which appears clinically as the onset of dementia. This leads to a novel remedial possibility: Since epigenetic changes occur over time in response to environmental effects, impending dementia of a high-risk individual could be averted through environmental changes, including explicit pharmaceutical intervention, healthy lifestyle choices, and other environmental adjustments. We posit that LEARn-based drug design could lead to effective treatments by identifying potential epigenetic marker-based therapeutic strategies. In short, the epigenetic evidence suggests that dementia is not an abruptly occurring and harshly delineated state, but rather a gradual change in critical biochemical and cellular pathways that transforms an otherwise healthy individual to a dysfunctional one, following neurodegeneration. Thus, evidence from epigenetics could lead to ways to detect and reverse such processes before clinical dementia ensues.

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**PL-73**

**APPLICATION OF NITRIC OXIDE RESEARCH TO DRUG DEVELOPMENT**

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The role of nitric oxide in cellular signaling in the past three decades has become one of the most rapidly growing areas in biology. Nitric oxide (NO) is a gas and a free radical with an unshared electron that can regulate an ever-growing list of biological processes. Nitric oxide is formed from L-arginine by a family of enzymes called nitric oxide synthases. These enzymes have a complex requirement for a number of co-factors and regulators including NADPH, tetrahydrobiopterin, flavins, calmodulin and heme. The enzymes are present in most cells and tissues. In many instances, nitric oxide mediates its biological effects by activating the soluble isoform of guanylyl cyclase (SGC) and increasing cyclic GMP synthesis from GTP Cyclic GMP, in turn, can activate cyclic GMP-dependent protein kinase (PKG) and can cause smooth muscles and blood vessels to relax, decrease platelet aggregation, alter neuron function, etc. These effects can decrease blood pressure, increase blood flow to tissues, alter memory and behavior, decrease blood clotting, etc. The list of effects of nitric oxide that are independent of cyclic GMP formation is also growing at a rapid rate. For example, nitric oxide can interact with transition metals such as iron, thiol groups, other free radicals, oxygen, superoxide anion, unsaturated fatty
acids, and other molecules. Some of these reactions result in the oxidation of nitric oxide to nitrite and nitrate to terminate the effect and perhaps act as NO reservoir for future NO formations; while other reactions can lead to altered protein structure function and/or catalytic capacity. These effects of (NO) probably regulate bacterial infections, inflammation of tissues, tumor growth, and other disorders. These diverse effects of nitric oxide that are cyclic GMP dependent or independent can alter and regulate numerous important physiological events in cell regulation and function. Nitric oxide can function as an intracellular messenger, an autacoid, a paracrine substance, a neurotransmitter, or as a hormone that can be carried to distant sites for effects. Thus, it is a unique molecule with an array of signaling functions. However, with any messenger molecule, there can be too little or too much of the substance, resulting in pathological events. Some of the methods to regulate either nitric oxide formation, metabolism, or function have been in clinical use for more than a century with the use of organic nitrates and nitroglycerin in angina pectoris that was initiated in the 1870’s. Inhalation of low concentrations of nitric oxide can be beneficial in premature infants with pulmonary hypertension and increase survival rates. Ongoing clinical trials with nitric oxide synthase inhibitors and nitric oxide scavengers are examining the effects of these agents in septic shock, hypotension with dialysis, inflammatory disorders, cancer therapy, etc. Recognition of additional molecular targets in the areas of nitric oxide and cyclic GMP research will continue to promote drug discovery and development programs in this field. Current and future research will undoubtedly expand the clinician's therapeutic armamentarium to manage a number of important diseases by perturbing nitric oxide formation and metabolism. Such promise and expectations have obviously fueled the interests in nitric oxide research for a growing list of potential therapeutic applications. There have been and will continue to be many opportunities from nitric oxide and cyclic GMP research to develop novel and important therapeutic agents. There are presently more than 150,000 publications in the areas of nitric oxide research. The lecture will discuss our discovery of the first biological effects of nitric oxide and how the field has evolved since our original reports in 1977. The possible utility of this signaling pathway to facilitate novel drug development and the creation of numerous projects in the Pharmaceutical and Biotechnology industries will also be discussed.

REFERENCES


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**PL-117**

**TRANSITION METAL CATALYSIS FOR A SUSTAINABLE AND PROSPEROUS WORLD**

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Until recently, most of the 24 d-block transition metals had been used primarily as useful materials for (i) construction and also as tools and containers, etc., (Ti, Zr, Fe and their alloys with V, Cr, Mn, Co, Ni, etc.), (ii) precious and ornamental items (Au, Pt, Ir, Os, Ag, etc.), and (iii) electromagnetic applications (Cu, Nb, Ta, W, Re, etc.). Over the past several decades, their superb properties as chemically useful substances, especially as catalysts for chemical reactions, have been increasingly recognized. “Why are they so useful as catalysts?”

In most cases, their superb catalytic properties may be attributed to one or both of the following two: (1) ability to provide simultaneously both filled nonbonding valence-shell orbitals (one or more) and empty valence-shell orbitals (one or more) within thermally stable species and (2) ability to undergo simultaneously both reduction and oxidation under one set of reaction conditions in one reaction vessel.

A combination of these two properties can be exploited in devising a wide variety of useful catalytic reactions for formation and cleavage of C–C, C–H, C–O and other bonds.

For critically important C–C bond formation, a) reductive elimination, b) carbometalation, and c) migratory insertion may be exploited. As representative examples of reductive elimination and carbometalation, the Pd-catalyzed cross-
coupling proceeding via reductive elimination and Zr-catalyzed asymmetric carboalumination of alkenes (ZACA) proceeding via carbometalation will be discussed.

PL-1

ELUCIDATION OF NOVEL MEDIATORS IN RESOLUTION OF INFECTIOUS INFLAMMATION

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Uncontrolled inflammation is now known to be a component of many widely occurring chronic diseases such as arthritis, periodontal disease, asthma, cardiovascular diseases and neurodegenerative diseases. Using a systems approach with self-limited inflammatory infectious exudates to map tissue events, cell traffic and identification of protein and chemical mediators, we identified 3 structurally separate families of potent n-3 essential fatty acid-derived (EPA, DPA, DHA) novel mediators, termed resolvins, protectins and maresins. Complete structural elucidation and total organic synthesis of these new molecules demonstrated their functions in vivo in the resolution of acute inflammation in many animal models. Each family member is chemically distinct and functions as a pro-resolving local mediator that controls the duration and magnitude of acute inflammatory responses with actions in pico- to nanogram concentration range in vivo in animal disease models. The biosynthetic pathways and potent mediators from the resolvin, protectin and maresin bioactive metabolites are coined specialized pro-resolving mediators (SPM). Mapping of these resolution circuits provides new avenues to probe the molecular basis of many widely occurring diseases (CN Serhan Nature 2014) [1]. This presentation focuses on our recent advances on the biosynthesis and functions of specialized pro-resolving mediators (SPM), stereochemical assignments, total organic synthesis of new resolvin D4 and their actions in counter-regulation of pro-inflammatory cytokines (TNF, IL-6) and pro-inflammatory eicosanoids. SPM possess potent multi-pronged anti-inflammatory, pro-resolving, and anti-microbial actions in animal models. We use LC-MS-MS mediator-metabololipidomic to profile SPM in human tissues (serum, plasma [2], breast milk [3], adipose and brain) which uncovered new pathways that stimulate tissue regeneration and bacterial clearance [4, 5]. Several SPM are in clinical development and in ongoing clinical trials in humans. Identification of SPM during inflammation-resolution indicates that resolution is an active programmed process challenging the old concept that resolution is a passive process where chemotactic molecules dilute and simply wane to resolve the local leukocyte exudates. Together these findings indicate that endogenous resolution pathways may underlie prevalent diseases associated with uncontrolled inflammation and open the potential for resolution-based pharmacology. The author acknowledges support of NIH grant P01 GM095467.

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**PI-170**

*Track: Genomics*

ENTPRISE: AN ALGORITHM FOR PREDICTING HUMAN DISEASE-ASSOCIATED AMINO ACID SUBSTITUTIONS FROM SEQUENCE ENTROPY AND PREDICTED PROTEIN STRUCTURES

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The advance of next-generation sequencing technologies has made exome sequencing rapid and relatively inexpensive. A major application of exome sequencing is in the identification of genetic variations likely to cause a Mendelian diseases. This requires processing large amounts of sequence information. Therefore computational approaches that can accurately and efficiently identify the subset of disease-associated variations are needed. The accuracy and high false positive rates of existing computational tools leave much room for improvement. Here, we develop a boosted tree regression machine-learning approach to predict human disease-associated amino acid variations by utilizing a comprehensive combination of protein sequence and structure features. On comparing our method, ENTRPRISE, to the state-of-the-art methods SIFT, PolyPhen-2, MUTATIONASSESSOR, MUTATIONTASTER, FATHMM, ENTRPRISE exhibits significant improvement. In particular, on a testing dataset consisting of only proteins with balanced disease-associated and neutral variations, the Mathews Correlation Coefficient by ENTRPRISE is 0.493 as compared to 0.432 by PPH2-HumVar, 0.406 by SIFT, 0.403 by MUTATIONASSESSOR, 0.402 by PPH2-HumDiv, 0.305 by MUTATIONTASTER, and 0.181 by FATHMM. ENTRPRISE is then applied to nucleic acid binding proteins in the human proteome. Disease-associated predictions are shown to be highly correlated with the number of protein-protein interactions. Both these predictions and the ENTRPRISE server are freely available for academic users as a web service at http://cssb.biology.gatech.edu/entprise/.

**PI-116**

*Track: Pharmaceutical Biotechnology*

DISCOVERY OF HIGHLY MODIFIED MACROCYCLIC PEPTIDES THROUGH mRNA-DISPLAY

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The mRNA-display method results in the covalent attachment of a nascent protein or peptide to its own mRNA. In this way extremely large libraries of random sequence peptides can be generated, and subjected to cycles of selection and amplification. We have used this approach to generate very high affinity ligands to protein and small molecule targets. We have extended this approach to the *in vitro* selection of highly modified cyclic peptides, a promising class of therapeutic agents.
PI-74

Track: Hot Topics in Medicinal Chemistry

CELL-PENETRATING MINI-PROTEINS

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One of the most vexing problems in life science is that of “undruggability,” the difficulty of targeting certain biological macromolecules in vivo using existing drug or ligand discovery technologies. It has been estimated that as many as 80-90% of all potential targets, including many that have been extensively validated in humans and in animal models, are undruggable. The Verdine laboratory is developing powerful new chemistry-based platform technologies to address these undruggable targets. Specifically, the lab is developing cell-penetrating mini-proteins, molecules that, like protein therapeutics, possess the ability to target large flat surfaces, but that, like small molecules, are fully synthetic and hence can be modified at will. Progress on the development of one class of cell-penetrating mini-proteins – hydrocarbon-stapled alpha-helical peptides – will be reviewed in this talk.

REFERENCES

KEYNOTE LECTURES
DNA sequencing has enabled the widespread construction of phylogenetic trees, revealing that multicellular organisms evolved independently from unicellular ancestors about 25 times among prokaryotes and eukaryotes. Multicellular organisms can be classified as simple, in which all of the cells are in direct contact with the surrounding milieu, or complex, in which some cells are completely surrounded by other cells. Current phylogenetic trees indicate that complex multicellular organisms evolved independently from unicellular ancestors about 10 times, and only among the eukaryotes, including once for animals, twice each for green, red, and brown algae, and thrice for fungi.

Given these multiple independent evolutionary lineages, we asked two questions: 1. Which molecular functions underpinned the evolution of multicellular organisms?; and, 2. Which of these molecular functions depend on intrinsically disordered proteins (IDPs, reviewed in [1])? The former requires the advent of molecules for cellular adhesion, for cell-cell communication and for developmental programs. In addition, the developmental programs need to be regulated over space and time. Finally, each multicellular organism has cell-specific biochemistry. To answer the second question we used Key-words in Swiss Protein ranked for associations with predictions of protein structure or disorder. With a Z-score of 18.8 compared to random-function proteins, “differentiation” was the biological process most strongly associated with IDPs. As expected from this result, large numbers of individual proteins associated with differentiation exhibit substantial regions of predicted disorder [2]. All five of the underpinning molecular functions for multicellularity were found to depend critically on IDP-based mechanisms [3].

These new findings necessitate a rethinking of the gene regulatory network models currently used to explain cellular differentiation and the evolution of complex multicellular organisms [4].

REFERENCES


SALICYLIC ACID AND ITS BINDING PROTEINS AT THE CROSSROADS OF PLANT AND HUMAN HEALTH

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Since our discovery in 1990 that SA regulates plant immunity, we have attempted to determine its mechanisms of action in plant immunity and other biological processes using genetic, molecular, and biochemical approaches. Over two dozen plant SA-binding proteins (SABPs) have been identified primarily through biochemical methods, including three high-throughput screens (Manohar et al., 2015; also see http://bioinfo.bti.cornell.edu/SA2010/). SA binding alters the biochemical and/or biological activities of these proteins, generally by inhibit them. We have extended this work to humans, since the most widely used medicine aspirin (acetyl SA) is rapidly converted to SA after ingestion and SA has most of the same pharmacological activities of aspirin. Two novel targets of SA/ aspirin have been identified across the animal and plant kingdoms. Together the two human SABPs are associated with most of the major human diseases, including atherosclerosis, stroke, sepsis, rheumatoid arthritis, lupus, inflammatory bowel disease, inflammation-associated cancers, hepatitis, and neurodegenerative diseases. One of the identified human SABPs is High Mobility Group Box1 (HMGB1). In addition to its nuclear role in condensing DNA and regulating gene expression, extracellular HMGB1 is a damage-associated molecular pattern (DAMP), which activates immune and inflammatory responses. Low μM levels of SA suppress both the chemo-attractant activity of HMGB1 and the increased expression of pro-inflammatory cytokine and COX-2 genes induced by HMGB1 (Choi et al., 2015a). An HMGB1 protein mutated in one of the SA-binding sites identified in the HMGB-box domain by NMR analyses retained its chemo-attractant activity, but lost binding of and inhibition by SA, thereby firmly establishing that SA binding to HMGB1 directly suppresses its pro-inflammatory activities. A synthetic SA derivative acetyl 3-aminoethyl SA and natural derivative from the Chinese medicinal herb Glycyrrhiza foetida (licorice) amorfrutin B1 have been identified, which are 40-70 times more potent inhibitors than SA of the pro-inflammatory activities of HMGB1. Interestingly, our parallel study of the plant ortholog AtHMGB3 revealed that it also functions as a DAMP to activate plant immunity. Moreover, it binds SA and mutations in its corresponding HMGB box domain are associated with Alzheimer’s, Parkinson’s, and Huntington’s diseases. We discovered that SA, like the anti-inflammatory drug deprenyl, suppresses nuclear translocation of GAPDH, an early step in cell death associated with Alzheimer’s, Parkinson’s, and Huntington’s diseases. We discovered that SA, like the anti-Parkinson’s drug deprenyl, suppresses nuclear translocation of GAPDH, an early step in cell death, as well as cell death induced by the DNA alkylating agent N-methyl-N-nitroso-N2-nitroguanidine (Choi et al., 2015b). Acetyl 3-aminoethyl SA and amorfrutin B1 not only more tightly bind to GAPDH, but also more effectively suppress nuclear translocation of GAPDH and cell death than SA. In addition to GAPDH’s role in neuronal cell death, some animal and plant viruses, such as human Hepatitis A, B, C Viruses and Tomato Bushy Stunt Virus (TBSV), usurp this host protein for their replication. We discovered that SA binding to GAPDH inhibits its interaction with the TBSV minus RNA strand, thereby suppressing viral replication. This finding reveals a novel mechanism of SA action in defense against viral pathogens (Tian et al., 2015).

In summary, these studies demonstrate that SA can modulate both plant and human health via shared SABPs. Furthermore, the identification of human HMGB1 and GAPDH as pharmacological targets of SA/aspirin provides new insights into the mechanisms of action of one of the world’s longest and most used natural and synthetic drug. It may also provide an explanation for the protective effects of low-dose aspirin usage. Moreover, the identification of natural and synthetic SA derivatives with greater potency for inhibition of HMGB1 and GAPDH provides proof-of-concept that new SA-based compounds with high efficacy are attainable (Klessig, 2016; Klessig et al., 2016).

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INVITED LECTURES
**IL-130**

**Track:** Nanobiotechnology

**NANOTECHNOLOGY IN DRUG DELIVERY: FROM DISCOVERY TO APPLICATIONS**

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Liposomes can increase the therapeutic effectiveness of the encapsulated drugs and decrease their toxicity. They are widely accepted as drug delivery systems. Particularly, nanoliposomes are considered as promising carriers, especially in the case of bioactive agents, cosmetics and nutraceuticals. Long-chain polyunsaturated n-3 fatty acids, namely eicosapentaenoic acid and docosahexaenoic acid are well established in the prevention of a number of diseases, neural development, prevention of cerebral apoplexy, and Alzheimer disease. Lecithin extracted from marine products avoiding organic solvent by using enzymatic tools, is a natural source enriched of DHA. We formed the nanoliposome from these natural lecithin and various hydrophilic and hydrophobic active molecules were encapsulated. We measured the different physico-chemical properties like as the size and the charge of nanoliposome, the morphological and nanomechanical properties before and after active molecule encapsulation. In order to study the effect of nanoliposomes from natural marine source extracted by green process, *in vitro*, primary cortical neurons were treated with different concentrations. Our data demonstrate an increase in viability and decrease in apoptosis. Furthermore, administration of our nanoliposomes promotes formation of neuronal networks.

**Keywords:** Neurons, Apoptosis, Nanoliposomes, Alzheimer, Liposomes.

**IL-139**

**Track:** Regenerative Medicine

**STEM CELL THERAPY FOR THE TREATMENT OF SEVERE TISSUE DAMAGE AFTER RADIATION EXPOSURE**

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Radiotherapy may induce irreversible damage on healthy tissues surrounding the tumour. It has been reported that the majority of patients receiving pelvic radiation therapy shows early or late tissue reactions of graded severity as radiotherapy affects not only the targeted tumor cells but also the surrounding healthy tissues. The late adverse effects of pelvic radiotherapy concern 5 to 10% of them, which could be life threatening. However, a clear medical consensus concerning the clinical management of such healthy tissue sequelae does not exist. Although no pharmacologic interventions have yet been proven to efficiently mitigate radiotherapy severe side effects, few preclinical researches show the potential of combined and sequential pharmacological treatments to prevent the onset of tissue damage. Our group has demonstrated in preclinical animal models that systemic MSC injection is a promise approach for the medical management of gastrointestinal disorder after irradiation. We have shown that MSC migrate to damaged tissues and restore gut functions after irradiation. We carefully studies side effects of stem cell injection for further application in patients. The clinical status of four first patients suffering from severe pelvic side effects resulting from an over-dosage was improved following MSC injection in a compassionate situation. Bone marrow-derived MSC from the patients’ children were injected to four patients. A quantity of 2 millions to 6 millions of MSC/kg were infused intravenously to the patients. Pain, hemorrhage, frequency of diarrheas and fistulisation as well as the lymphocyte subsets in peripheral blood were evaluated before MSC therapy and during the follow-up. Two patients revealed a substantiated clinical response for pain and hemorrhage after MSC therapy. In one patient pain reappeared after 6 months and again substantially responded on a second MSC infusion. A
beginning fistulisation process could be stopped in one patient resulting in a stable remission for more than 3 years of follow-up. The frequency of painful diarrhea diminished from an average of 6/d to 3/d after the first and 2/d after the 2nd MSC injection in one patient. A decline of CD4+ and CD8+ T lymphocytes and an increase of potentially regulatory CD25+ T cells accompanied the clinical response in this patient after the MSC injections. In all patients, prostate cancer remained in stable complete remission. A modulation of the lymphocyte subsets towards a regulatory pattern and diminution of activated T cells accompanies the clinical response in refractory irradiation-induced colitis. No toxicity occurred. MSC therapy was safe and effective on pain, diarrhea, haemorrhage, inflammation, fibrosis and limited fistulisation. For patients with refractory chronic inflammatory and fistulising bowel diseases, systemic MSC injections represent a safe option for salvage therapy. A clinical phase II trial will start in 2016.

**H-40**

*Track: Pharmaceutical Biotechnology*

**11BETA-DICHLORO INHIBITS CYST PROGRESSION IN AN ADULT ADPKD MODEL**

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**Background:** ADPKD is the most common monogenic disorder for which no effective therapy exists. We have previously shown that the novel antitumor agent 11β-dichloro is a specific inducer of apoptosis of Pkd1 null cells. Administration of 11β-dichloro resulted in amelioration of cystic disease in the Pkd1fl/fl; Pkhdl-Cre neonatal murine ADPKD model. In the current work we explored the pathways involved in the pro-apoptotic effect of 11β-dichloro and investigated whether the beneficial effect seen in the early model is also present in an adult inducible Pax8rtTA; TetO-cre; Pkd1fl/fl model which is more akin to the human disease.

**Results:** 11β-dichloro treated adult mice resulted in a decrease in KW/BW ratio as compared to vehicle injected controls (2.6±0.1 vs. 6.1±0.4). These changes were accompanied by a decrease in the cystic index (29%±1.5 vs. 49%±1.4), BUN (41±2.4 vs. 83±2.7), and creatinine (0.18±0.007 vs. 0.37±0.02). 11β-dichloro specifically increased apoptosis in cyst-lining cells but not in wild-type. UPR and ROS have been implicated as potential drivers of the 11β-dichloro-dependent pro-apoptotic phenotype. We found that upregulation of the UPR marker XBP1s and its transcriptional targets BiP and Erdj4 was specific to the Pkd1 null cells compared with wild-type, *in vitro* and *in vivo*. Treatment with 11β-dichloro increased mRNA levels of the antioxidant genes catalase and SOD1 specifically in the Pkd1 cystic kidneys and not in vehicle-treated kidneys.

**Conclusions:** 11β-dichloro specifically induces UPR, ROS, and apoptosis in cystic vs. wild-type kidneys. In an adult inducible cystic model, the compound ameliorates polycystic disease progression and improves kidney function.
**H-173**

**Track: Industrial and Manufacturing**

**MEMBRANE-ASSISTED PROCESSES FOR PRODUCTION AND SEPARATION IN BIOTECHNOLOGY**

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The down-stream bioprocess production and separation of macromolecules of biological origin is a key feature in industrial production. The rational use and recycle of bioactive molecules is also an important aspect in order to obtain sustainable production systems. Biomolecules are in general quite labile and need mild operating conditions during separation in order to preserve their biological functions. Membrane operations are unique systems able to operate physical separation with high performance at low temperature and pressure. Membrane-assisted separation is obtained based on molecular size exclusion, electrostatic repulsion, biomolecular recognition, physic-chemical affinity.

The separation of proteins with similar molecular weight can be obtained. For example, proteins such as α-lactoalbumin (14000 Da) and β-lactoglobulin (18000 Da) could be separated in one step with 100% purity and recovery higher than 90% using charged membranes. The combined effect of pore size and electrical repulsion was used as basic mechanism to achieve the challenging result. Membrane properties suitable for protein recovery and purification will be highlighted.

Hybrid systems such as bioreactors combined with membrane operations are also suitable for the production and simultaneous separation of biomolecules of interest. So called continuous membrane fermenters, have proven to be suitable for mass production.

The use of membranes as support for enzymes in the development of biocatalytic reactors will be also presented. Besides separations, membranes can also work as contactors, emulsifier and crystallizer. Their potentiality in industrial biotechnology will be discussed.

**H-126**

**Track: Nanobiotechnology**

**PATCHY NANOPARTICLES: PROPERTIES AND CHARACTERIZATION**

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Patchy nanoparticles are nanoparticles whose surface is composed by several chemical entities arranged in domains. These surface domains provide unique properties to the particles, ranging from a different solubility due to their structural interfacial energy to cell membrane penetration [1], enhanced catalytic activity, or selective molecular recognition.

One remarkable way to obtain patchy nanoparticles is with the use of binary self-assembled monolayers (SAMs) where mixtures of ligand molecules can self-assemble at the surface of metallic nanoparticles giving rise to different nanodomains. Scanning Tunnelling Microscopy (STM) [2], is the gold standard to evaluate the arrangement of these ligand molecules, and has already shown different kind of arrangements that go from “striped” to “Janus”. Despite the high versatility of STM, this microscopy technique is restricted to measure only a few nanoparticles and with short ligands, and it requires very good scanning conditions to observe features that are at the limit of resolution. Here novel characterization methods are reported allowing macroscopic measurements and giving information about not only the patchiness arrangement but also the surface activity of these nanoparticles. This includes among others neutron...
reflectivity [3] at the air-water interface and co-precipitation of oppositely charged nanoparticles [4]. These novel techniques provide complementary techniques to STM that help at the evaluation of patchiness arrangements and open new possibilities to the characterization of these promising nanoparticles.

**Keywords:** Nanodomains, ligands, Nanoparticles, surface, solubility.

**REFERENCES**


**II-94**

**Track:** Plant and Environment

**LIPID ENHANCEMENT IN POTATO TUBER THROUGH AN INTEGRATED METABOLIC ENGINEERING APPROACH**

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The increasing food and biodiesel fuel demands as the result of the growing world population and environmental requirement will need substantial growth in future global vegetable oil supply. Potato tuber is a high yielding food crop known for its high levels of starch accumulation but only negligible levels of triacylglycerol (TAG). The potential for lipid production in potato tubers was evaluated by simultaneously introducing three transgenes, including *WRINKLED 1 (WRI1), DIACYLGLYCEROL ACYLTRANSFERASE 1 (DGAT1)* and *OLEOSIN* under the transcriptional control of tuber-specific (patatin) and constitutive (CaMV-35S) promoters. This coordinated metabolic engineering approach resulted in over 100-fold increase of TAG accumulation to levels up to 3.3% in tuber dry weight (DW). Phospholipids and galactolipids were also found to be significantly increased in the potato tuber. The increase of lipids in these transgenic tubers was accompanied by a significant reduction in starch content and an increase in soluble sugars. Increases in TAG and polar lipids were also observed in the leaf tissues of transgenic potato. This study represents an important proof-of-concept demonstration of oil increase in tubers and provides a model system to further study carbon reallocation during development of non-photosynthetic underground storage organs.

**Keywords:** Phospholipids, biodiesel, lipids, tubers, approach.

**II-77**

**Track:** Pharmaceutical Biotechnology

**BIOTECHNICAL POTENTIAL OF ENGINEERED ENZYMES FROM THE GSTOMES**

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Glutathione transferases (GSTs) are ubiquitous and abundant enzymes in eukaryotes. The GSTome encompasses several classes and the majority of the GSTs are soluble dimeric proteins. In several organisms longevity is associated with GST overexpression, possibly by countering oxidative stress. In *Drosophila* a GST transgene increased the life-span of flies under chemical stress. In *Arabidopsis* GST overexpression protected plantlets against the explosive TNT and showed potential for phytoremediation. GSTs are multipurpose catalysts and can be engineered to high stereoselectivity and catalytic efficiency in reactions of pharmaceutical significance. A human GST featuring 170-fold enhanced activity with azathioprine was obtained by directed evolution.
Engineered GSTs combined with prodrugs could be useful in ADEPT. GST proteins and catalytically incapacitated variants enter cells by endocytosis and influence cellular functions, suggesting their usefulness as therapeutic agents.

II-162

Track: Pharmaceutical Biotechnology

ACHIEVING WELLNESS THROUGH BIOTECHNOLOGY SOLUTIONS: THE BALANCE OF EFFICACY AND PALATABILITY

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Market drivers and technical challenges in the healthcare and well-being sectors necessitate innovation and immediate technology transfer. Biotechnology enables the transformation of raw materials into high value chemicals or medical diagnostic tools, and is the key to long-term sustainability of the pharmaceutical industry. Biotechnology solutions allow reliable processing, efficient delivery and accurate measurements through tailored enzymatic approaches, fermentation processes, encapsulation technologies or nanobiosensing devices. The development of pharmaceutical products enriched with active macro-/micro-molecules is an important wellness strategy to tackle metabolic disorders caused by nutrient deficiency, physical stress, hormonal imbalance and/or detrimental metabolic inhibitors. Further, modern biotechnologies coupled with improved ecology and biology knowledge demonstrate advantages over traditional biotechnologies especially in the utilization of biowastes for sustainable production of pharmaceutical products with desired efficacy and dietary or digestive attributes. This lecture highlights recent research that synergistically combines biotechnology and pharmaceutical science to create novel generation pharmaceutical ingredients targeting well-being. Case studies are provided to showcase key concepts of novel bioprocesses, smart delivery systems and real-time detectors for dietary adulterants, contaminants and metabolites. The importance of improved hazard monitoring and communication with consumers for successful biotechnology uptake is highlighted.

II-172

Track: Nanobiotechnology

3-DIMENSIONALLY ORDERED MACROPOROUS THIN FILMS FOR FOOD ADULTERANT DETECTION, AMPEROMETRIC GLUCOSE BIOSENSING AND CONTROLLED DRUG DELIVERY

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Global concerns about food safety and human health motivate the development of new and improved technologies for the detection of food adulterants, point of care diagnostics (POCD) and controlled drug delivery. This talk describes the successful application of nanotechnology, and in particular nanostructured 3-dimensionally ordered macroporous (3DOM) thin films, in these three key areas.

3DOM thin films comprise a face-centred cubic array of macropores (typical diameters 200-400 nm) within a host matrix. Due to the periodically modulated refractive index with exists in 3DOM materials, the 3DOM films behave as photonic crystals and selectively diffract and reflect certain wavelengths of visible light. The inherent optical and structural properties of 3DOM thin films allows the development of a wide range of sensing platforms and novel medical devices. By decoration of 3DOM TiO₂ thin films with gold nanoparticles, we created novel 3D Surface Enhanced Raman Spectroscopy (SERS) substrates that could detect aqueous melamine at concentrations as low as 0.1 ppm [1]. By immobilization of glucose oxidase on the surface of a 4 wt.% Pt/3DOM carbon thin film, a very sensitive
amperometric glucose biosensor was obtained (response time < 2 min; sensitivity 1.9 mA M⁻¹ and a linear response with glucose concentration up to 10 mM) [2]. Finally, by synthesizing 3DOM polypyrrole (Ppy) thin films, we were able to successfully construct an ocular implant for the electrically triggered release of dexamethasone [3]. These studies highlight the wider potential of 3DOM thin films in the biotechnology sector.

**Keywords:** 3DOM thin films, photonic crystal, nanotechnology, sensing, drug delivery.

**REFERENCES**


SESSION LECTURES
OPTIMIZATION OF SACCHARIFICATION POTENTIAL FOR PLANT BIOMASS OF RECOMBINANT HEMICELLULASES FROM BACILLUS LICHENIFORMIS ATCC 14580

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The evaluation of saccharification potential of hemicellulases (xylanase and β-xylosidase) cloned from Bacillus licheniformis ATCC 14580 into E. coli BL21 (DE3) for the production of bioethanol from plant biomass was studied. The expression of cloned genes was optimized for various parameters in a fermenter. Xylanase production was maximum (fermenter volume; 70%, agitation rate; 200 rpm, air supply; 2.0 vvm, dissolved oxygen; 20%, inoculum concentration; 3%, temperature; 37°C and pH; 7.0) while for β-xylosidase production (aeration rate; 2.5 vvm, inoculum size; 2%, agitation rate; 200 rpm, dissolved oxygen; 25%, temperature; 37°C, pH; 7.5). Both of these enzymes were able to produce xylene by using birchwood xylan and p-nitrophenyl-D-xylopyranoside as substrates and also possess the ability of bioconversion of plant biomass like wheat straw, rice straw and sugarcane bagasse. Saccharification potentials of both enzymes were optimized individually as well as collectively by optimizing various parameters. Highest saccharification percentage was observed when both hemicellulases were used with 1% sugarcane bagasse after 72 hours of incubation at 50°C with 20 units of each enzyme. The results suggested that recombinant hemicellulases could be used in bioconversion of natural biomasses into simple sugars that could be later used for the production of biofuel.

GENETIC DIVERSITY OF RHANTERIUM EPAPPOSUM AND HALOXYLON SALICORNICUM, THE NATIVE PLANTS OF KUWAIT

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Kuwait is an arid country with dry, hot summer and cool winter. Due to these extremities in weather, the species diversity in the region is very limited. However, the native species which are well adapted to the environment can be an excellent source of gene pool consisting of stress tolerant genes. Rhantierium epapposum and Haloxylon salicornicum are two important perennial shrub species that possess good drought and salt tolerance nature. Due to various reasons, these species are highly threatened and are on the verge of extinction. Documentation of genetic diversity of these species would greatly help in conservation of this species in the region. The presentation will cover the importance of native plants and data from our group on the genetic analysis of two important native plants. Diversity analysis of Rhantierium epapposum was performed using twenty-four Random Amplified Polymorphic DNA (RAPD) and 23 Sequence Related Amplified Polymorphism (SRAP) markers from 18 different samples collected from five major locations in Kuwait. Results indicated that there were 64 alleles produced by RAPD, while 129 alleles were produced by SRAP. For studying the diversity of Haloxylon salicornicum, diversity analysis was performed using RAPD and ISSR technique. Twenty five RAPD and 24 ISSR primers produced 946 and 1016 bands respectively. RAPD produced a relatively higher proportion of polymorphic bands (49.4%) compared with ISSR (47%). This study indicated that the DNA-based markers could be used to obtain efficient, accurate, and high throughput fingerprinting, revealing significant variation among the existing locations that can be explored in order to preserve the native species. Genotyping by sequencing (GBS) is being performed now for detailed genetic analysis of these two species.

Keywords: Diversity, weather, species, variation, analysis.
SL-142
Track: Nanobiotechnology

NANOCOATINGS ON NANOIBERS FOR STRAIN SPECIFIC ANTIBACTERIAL ACTIVITY

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Silver (Ag) nanoparticles are well established for its antibacterial activity. In study we demonstrate the antibacterial activity of the electrospun nanofiher mats coated with various ratios of Ag and ZnO nanoparticles and relate it with the hydrophilicity of the membrane imparted due to Ag nanoparticles. Electrospun nanofibers were prepared from a 1:1 blend of two polymers: PCL and PMMA that was sputter coated with inorganic nanoparticles (Ag and ZnO) at three ratios thus adding another layer of nanocomposition to the resulting polymer nanocomposite nanofiber scaffold. The PF-QNM characterization results showed different shapes, sizes and DMT modulus of the inorganic nanoparticles (Ag and ZnO), appearing at the surface of the nanofibers. Ag and ZnO nanoparticles were observed heterogeneously distributed on the nano fiber mesh and varied at different locations along the nanofibers lengths based on their ratios used in sputtering. Increasing ZnO content increased both the hardness and water contact angle (almost double as compared to Ag for the same increase in content) of the nanofiber mesh. The antibacterial activity of scaffolds coated with different ratios of Ag and ZnO was tested against MRSA ATCC®. The visible bacteria were monitored by counting the number of colony forming units (CFUs/ml). The results revealed a significant reduction (p < 0.05) in the number of CFUs/ml after only 15 min of exposure to the scaffolds coated with Ag:ZnO (1:1) and Ag:ZnO (3:1) respectively. Nevertheless, the scaffold coated with Ag:ZnO (1:3) required longer time (30 min) to show reduction in the number of CFUs/ml. There was a significant difference between the number of CFUs/ml after 0 min exposure to scaffolds coated with different ratios of Ag and ZnO and the number of CFUs/ml after 30 min exposure. Taken together these results show superior antibacterial activity for scaffolds coated with different ratios of Ag and ZnO against pathogenic bacteria MRSA, which demonstrates potential applications of these scaffolds in medical and biomedical fields.

Keywords: Nanofibers, nanomechanical properties, antibacterial properties, electrospinning.

SL-64
Track: Pharmaceutical Biotechnology

SPONTANEOUS INACTIVATION OF THE SWELLING-STIMULATED POTASSIUM FLUX IN RABBIT AND HUMAN SS RED CELLS

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In this study, the characteristics of swelling – stimulated potassium transport in rabbit and human ss red cells were described. Both kinds of cells display an anion–dependent potassium (\(^{86}\)Rb) transport process that is stimulated either by cell swelling or by treatment with N-ethyl - maleimide. The data in this study described a time–dependent inactivation of the swelling – stimulated \(^{86}\)Rb flux. Incubation of cells in hypotonic low potassium medium causes the anion–dependent potassium transport to decrease over time such that there is essentially no swelling–stimulated flux even in a very hypotonic medium after three hours. The inactivation of the transport requires the loss of potassium, because incubation in hypotonic high potassium media caused only slight inactivation of the swelling–stimulated Rb influx. The inactivation is not related to ATP depletion during the incubation: the cells were fed (the medium contained 10mM glucose in phosphate buffer), and the NEM – stimulated transport, which is inhibited by ATP depletion, is not affected by the hypotonic pre incubation.

The possibility was considered that the transient nature of the swelling – activated transport is related to only a small fraction of the cells which may lose a disproportionate amount of potassium during the reincubation. However, the inactivation was observed even in cells that had been separated according to density to select a
relatively homogeneous “young” cell population. Osmotic fragility measurements on the cells before and after the incubation showed that the entire population had lost potassium during the pre-incubation. Therefore, the inactivation of the swelling–stimulated transport represents a true time – dependent desensitization.

**SL-157**

**Track:** Others - Food Biotechnology

**DISSIPATION, HALF-LIVES, AND MASS SPECTROMETRIC IDENTIFICATION OF CHLORPYRIFOS AND ITS TWO METABOLITES ON FIELD-GROWN COLLARD AND KALE**

**George F. Antonious**

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Chlorpyrifos (O,O-diethyl O-3,5,6-trichloropyridin-2-yl phosphorothioate) also known as Dursban or Lorsban is a non-systemic organophosphorus insecticide that remains one of the most widely used insecticides in the agricultural field. The persistence and fate of chlorpyrifos and its two metabolites, chlorpyrifos-oxon and the 3, 5, 6-trichloro-2-pyridinol (TCP) break-down product were investigated on kale and collard greens under field conditions. A simultaneous extraction and quantification procedure was developed for chlorpyrifos and its two main metabolites. Residues of chlorpyrifos, chlorpyrifos oxon, and TCP were determined using a gas chromatograph (GC) equipped with an electron capture detector (GC/ECD). Chlorpyrifos metabolites were detectable 23 days following spraying. Residues were confirmed using a GC equipped with a mass selective detector (GC/MSD) in total ion mode. Initial residues of chlorpyrifos were greater on collard (14.5 μg g⁻¹) than kale (8.2 μg g⁻¹) corresponding to half-lives (T1/2) values of 7.4 and 2.2 days, respectively. TCP, the hydrolysis product, was more persistent on collards with estimated T1/2 of 6.5 days than kale (T1/2 of 1.9 days).

**Keywords:** GC-MSD, Half-life, Metabolites, Chlorpyrifos oxon, 3, 5, 6-trichloro-2-pyridinol.

**SL-179**

**Track:** Industrial and Manufacturing

**FORMULATION OF INDUSTRIAL RELEVANT ENZYMES**

**Grit Baier, Sonja Kübelbeck, Sebastian Schoof and Frank Runge**

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Industrial enzymes are an attractive market with high annual growth. They are key performance enablers for food & feed applications and for detergent formulations in the laundry area. New methods and appropriate enzyme formulation approaches are of crucial importance to protect enzymes against environmental influences. In addition to the established phytases and proteases, BASF will focus in future on the formulation of different enzyme classes as well. Fundamental knowledge is necessary to formulate enzymes without any loss of enzyme activity which is directly connected to the performance and subsequently to the margin of the product.

We will present different strategies (e.g. polyelectrolyte complexes, coacervates, hydrogels, encapsulation processes) to formulate enzymes. These approaches enable the design of both liquid and solid formulations for stabilizing and delivering enzymes. The aim is to provide stabilization and activity in applications using enzymes with activities greater than average. Afterwards, the colloidal and physico-chemical stability was characterized in terms of size, size distribution, electro-kinetic potential, and morphology. The thermodynamic parameters of interactions in solution were analyzed by calorimetry. Enzyme shelf life was checked by specific enzyme test assays and showed promising results with regard to their potential in stabilizing enzymes.
**SL-176**

*Track: Industrial and Manufacturing*

**APPLICATION OF ELECTROMEMBRANE SEPARATION PROCESSES IN BIOTECH MANUFACTURING**

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As the biotechnologies are increasingly utilized for production of various substances, electrodialysis (ED) and other electromembrane processes find their place in downstream purification of the products. Electromembrane separation processes like ED are effective in separation of the dissociated ionic compounds from the neutral molecules and often offer more effective alternative to the conventional separation systems. The objective of the contribution is to present possibilities and performance of the ED especially in production of the prebiotics and food ingredients.

One of the important application is the manufacturing of the galacto-oligosaccharides, Purification of the biomolecules is usually the combination of pressure-driven membrane processes (MF, UF, NF), adsorption, ion exchange, chromatography, evaporation and drying. ED could be the alternative process for ion exchange. It was verified that ED can decrease the ash concentration in the product to 0.5 wt% (on dry matter). It was also found that ED does not cause the product dilution and could be beneficial in the cases where there is no need for separation of individual (oligo) saccharides.

Another application of ED is for the desalination and purification of L-Carnitine. The solution after fermentation contains water, L-Carnitine, NaCl, NaOH, Ethanol, 4-Hydroxycrotonic acid. ED successfully removed inorganic salts as well as organic acids.

**Keywords:** Electrodialysis, ion-exchange membrane, GOS, L-Carnitine.

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**SL-88**

*Track: Pharmaceutical Biotechnology*

**MANIPULATIONS OF A HUMAN VIRUS WITH PRECISELY INCORPORATED BIOORTHOIONAL CHEMISTRY**

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Co-translational, site-specific incorporation of unnatural amino acids (UAAs) into proteins in living cells has emerged as a valuable tool for studying and engineering protein structure and function. We have established a platform enabling the generation of adeno-associated virus (AAV) incorporating UAAs into specific sites of its capsid. AAV is a promising vector for gene therapy and a well-established model system for parvovirus assembly, infection, and genome release. Using our UAA-incorporation platform, a variety of small biophysical and biochemical probes can be installed into distinct sites on AAV capsid, facilitating a detailed investigation of its cell-invasion process. Our technology also provides precisely-positioned attachment sites for targeting agents to generate target-specific viral vectors for gene-therapy applications, overcoming limitations of current strategies; genetic fusion, which is limited to protein, based targeting agents and often perturbs virus packaging and infectivity; or non-specific chemical attachment, which randomly coats the virus surface, compromising functionally important sites.
PRECISION GENOMICS AT THE SINGLE MOLECULE LEVEL

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DNA (and chromosomes) exists as single molecules in individual cells. A human genome has six billion bases in 46 different chromosomes in a human cell, each undergoing stochastic genomic variations that cannot be synchronized among individual cells. This necessitates single cell and single molecule measurements in order to study genome instability, which causes many diseases. We have been developing single-cell whole genome sequencing methods, reaching the highest accuracy for single nucleotide variation and micro deletion/duplication. This opens opportunities to study genome instability with an unprecedented precision, making it possible to avoid genetic disorders in newborns and prevent passage of these disorders to future generations.

PROTEIN ENGINEERING FOR FUNCTIONAL NANOSTRUCTURES AND BIOMATERIALS

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Self-assembly of biological molecules into defined functional structures has a tremendous potential in nanopatterning, and the design of novel biomaterials and functional devices. Molecular self-assembly is a process by which complex three-dimensional structures with specified functions are constructed from simple molecular building blocks. We present the assembly properties of modular repeat proteins, in particular designed consensus tetratricopeptide repeats (CTPRs), and their application as building blocks in order to generate functional nanostructures and biomaterials. CTPR proteins can be assembled into self-standing thin films [1], and thin nanometer fibers in solution [2]. In Fig. (1), we show the use of CTPRs as scaffolds to template: (1) Photoactive organic molecules. In particular, CTPR proteins are used as scaffold for ordering organic chromophores, while preserving their structure. The unique self assembly properties of CTPR scaffolds have been exploited to generate ordered conductive films of the protein-porphyrin conjugates. (2) Fluorescent nanoclusters. We show the ability of CTPR to encapsulate and stabilize fluorescent gold nanoclusters. Since the structural and functional integrity of the protein template is critical for applications, protocols that retain the protein structure and function have been developed. Finally, a CTPR module with specific binding capabilities has been successfully used to stabilize nanoclusters and tested as a sensor [3].

Fig. (1). Repeat proteins as scaffolds for functional nanostructures and materials. 1. CTPR proteins have been used to order photo and electroactive molecules and to form solid ordered thin films with anisotropic conductivity [4]. 2. In addition, the same modular
scaffolds have been applied for the synthesis of metal nanoclusters (AuNCs). CTPR-AuNCs conjugates combine specific recognition functions and fluorescent properties and can be used as sensors [3].

ACKNOWLEDGEMENTS

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Keywords: Nanopatterning, nanostructures, scaffold, chromophores, sensor.

REFERENCES


SL-150

Track: Nanobiotechnology

PLASMON ENHANCED BIOSENSING

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Novel class of bio-sensing platforms have been developed based on plasmon coupling phenomena on (Fig. 1a) wavelength-scaled gratings at dielectric-metal interfaces, (Fig. 1b) periodic arrays of nanoparticle aggregates, (Fig. 1c) complex periodic patterns composed of different mini-arrays, and (Fig. 1d) nanoparticles made of noble metal alloys. It was proven that the optical responses and the near-field distribution can be tailored by varying the structure of various architectures supporting plasmonic modes and by tuning the illumination direction. On bimetal films covered by wavelength-scaled periodic polymer gratings enhanced sensitivity was achieved during streptavidin, amyloid and lysozime detection, due to the overlap between enhanced near-field and attached bio-molecules in the valleys of periodic structures [1, 2]. On arrays of bio-functionalized noble metal nanoparticles the existence of resonator modes accompanied by large near-field enhancement makes it possible to increase sensitivity in aggregates-based bio-sensing [3, 4]. Fano-shaped spectral lines originating from coupling of localized and propagating modes ensure enhanced sensitivity and specificity in detection of bio-layers and fluorescent molecules accumulating in complex nano-object patterns, which can be fabricated by integrated lithography [5, 6]. It was shown that the sensitivity of hemoglobin and ferritin detection can be improved by alloy nanoparticles due to the fluorescence enhancement occurring in their proximity.

Keywords: Plasmon, patterns, optical, sensitivity, hemoglobin.
REFERENCES


SL-6
Track: Pharmaceutical Biotechnology

BISPECIFIC ANTIBODIES FINALLY COME OF AGE

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Bispecific antibodies were first designed in the early 1980’s, but due to a variety of design and manufacturing limitations, they did not advance as therapeutics for 20 years. Starting with a series of innovative approaches published about 10 years ago, the discovery of new bispecific platforms and the development of manufacturable therapeutic bispecific antibodies have now exploded, with two bispecific antibodies approved in major markets and over 40 bispecific antibodies now in clinical trials. These clinical stage bispecific antibodies are built using a variety of platforms, including BiTE, DVD-Ig, DART-Fc, TandAb, Duobody, antibody-peptide fusions and other platforms. Additionally, many more bispecific antibodies are in preclinical development and are expected to reach the clinic within the next few years. One of the key therapeutic approaches that depends on the use of bispecific antibodies is T cell redirection to kill cancer or other undesired cells. A number of bispecific platforms and their characteristics as well as therapeutic mechanisms of action will be explored and detailed for these immuno-oncology approaches. The development of manufacturable bispecific antibodies will forever change the landscape of antibody therapeutics, and will provide exciting new therapeutic approaches for patients with cancer, immune disorders, metabolic disease and more.

SL-93
Track: Industrial and Manufacturing

A NEW TECHNIQUE TO FABRICATE HIGH-PERFORMANCE BIOLOGICALLY INSPIRED MEMBRANES FOR WATER TREATMENT

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Aquaporin, a highly selective water channel protein, has received worldwide attention because of its potential to form biomimetic membranes with high flux and rejection for water reuse and desalination. In this study, purified aquaporins were incorporated into the active layer of the polybenzimidazole (PBI) nanofiltration membrane. Aquaporins were dispersed in gum arabic and embedded in amphiphilic polyvinyl alcohol with alkyl side chains (PVA-alkyl). PVA-alkyl embedded with treated aquaporins was then attached to flat sheet PBI membranes using carbodiimide chemistry. PVA-alkyl acted as support for
quororlons to prevent their chemical alteration and also gave the membranes mechanical strength. It was found that membranes modified with PVA-alkyl-AqpZ displayed lower flux declines and higher flux recoveries as compared to unmodified PBI membranes. Higher protein and salt rejections were also observed using PVA-alkyl-AqpZ modified membranes as compared to unmodified PBI membranes.

**SL-32**

**Track:** Pharmaceutical Biotechnology

**EVOLUTION OF ANTIOXIDANTS IN CAPULIN FRUITS (PRUNUS SEROTINA EHRH) DURING PRE-HARVEST AND HARVEST AND THE DEVELOPMENT OF ANTIOXIDANT MICROCAPSULES**

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Extracts of capulín fruit have showed antioxidant activity. The objective of this work was to evaluate the influence that harvest time has on the antioxidant content in the fruit and to develop a process for antioxidant microcapsule production. Phenolic content, flavonoids, anthocyanins along ripening process of this fruit were evaluated during pre-harvest and harvest. Total phenols, flavonoids and antioxidant activity showed a similar behavior; higher content was present in early ripening stages; meanwhile in the end of ripening these parameters showed lower content. The anthocyanin content incremented when the ripening process started. The process for microcapsule production was developed using the aqueous acidified extract from capulín fruits, rich in phenolic compounds mainly anthocyanins, with maltodextrin as a matrix. The process included a series of purification steps, as micro- and ultra-filtration followed by adsorption/desorption. The microcapsules were produced by spray drying.

**SL-161**

**Track:** Food Biotechnology

**THE EFFECTS OF FAT SUBSTITUTION USING PALM STEARIN ON THE COLORIMETRIC AND SENSORIAL CHARACTERISTICS OF CAKE**

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Fats used in baking contain trans fatty acid that has been proven to contribute towards various health problems. Palm stearin is used to substitute shortening in different ratios to observe the effects on the sensorial and colorimetric properties of cake. Formulations A, B, C, D, and E each have palm stearin substitution of 0%, 25%, 50%, 75%, and 100% respectively. All formulations were analysed for its colour analysis and sensory analysis. At 25 % level of substitution (formula B), overall liking in sensory analysis (5.5 ± 1.10) are found to be similar with formula A. Formula B for colour analysis 80.84 ± 0.20 (L*), 2.79 ± 0.40 (a*), and 30.30 ± 0.64 (b*) are however significantly different with formula A. It is found that a different substitution ratio does affect the sensorial and colorimetric characteristics of the cakes. Substitution up to 25 % shows that it is best in producing cakes most similar to formula A. Further studies need to be carried out in order to find a method that may incorporate higher palm stearin substitution as well as palm stearin functionality in a cake system.

**Keywords:** Baking, palm stearin, cakes, sensory evaluation, fat substitution.
SL-195
Track: Industrial and Manufacturing

CHARACTERIZATION OF GEOBACILLUS STEAROTHERMOPHILUS PROTEASE GENE SUITABLE FOR DETERGENT INDUSTRY

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Thermophilic proteases have been exploited for industrial use. Protease from thermophilic strain of Geobacillus stearothermophilus B-1172 was successfully cloned and expressed in E. coli BL 21. For its maximal production, influence of various parameters such as pH, temperature and different inducers were optimized. After production, the protease was purified by ammonium sulfate precipitation following affinity chromatography. A 16.9-fold purification, with specific activity 120 U mg\(^{-1}\) protein and a total recovery of 55.68% was achieved. The purified enzyme was stable at elevated temperature 90°C in a range of pH 6-9. The effect of EDTA, different metal ions, inhibitors, surfactants and detergents was also studied. EDTA effect on the protease activity was non-significant, confirming its nonmetal-enzyme nature. Further, stability of the enzyme was unaffected by an addition of metal ions such as Ca\(^{2+}\), Mg\(^{2+}\), Ni\(^{2+}\), Cd\(^{2+}\), Cu\(^{2+}\), Zn\(^{2+}\). Among various inhibitors, PMSF was found to be a strong inhibitor for the enzyme. Washing performance of the protease was assessed with detergent solution supplemented with protease enzyme and compared with detergent without protease enzyme. Compared with control, washing results were superior with washing powder supplemented with the protease. Its stability at high temperature and wide pH range make it good candidate for industrial exploitation.

SL-191
Track: Industrial and Manufacturing

MULTI-OBJECTIVE ANALYSIS FOR CLOSED-LOOP SUPPLY CHAIN OF ENVIRONMENTAL CONSIDERATION TYPE PRODUCT

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In recent years, new materials with few influence on the environment at the time of disposal are developed by the evolution of biotechnology. However, if reuse of these materials is performed, influences on environment are further reducible. Therefore, development of the new materials considered for the environment should be performed by the design of a recyclable product. On the other hand, the design of the closed loop supply chain in those products supports social responsibility and competitive superiority. However, in order to establish supply chains for sustainability, it is necessary to consider into not only the environment but also economic efficiency and various quality of the materials.

The aim of this study is to perform multiple-purpose evaluation about the influence on economic efficiency and an environmental impact for a closed loop supply chain. Many research on the closed-loop supply chain in consideration of economic efficiency and environmental impact is performed from various viewpoints. However, there are few studies which have focused on disposal materials. In this study, the quality of the material influences the quantity and recycling possible quantity of a return. We evaluate system economy and an environmental impact using some scenarios about various qualities of the materials.

Keywords: Supply chain management, Reusable returns, End-of-life returns, Demand fluctuation, Dynamic return data.
**DEVELOPMENTALLY INSPIRED APPROACH TO TISSUE REGENERATION OF ARTICULAR CARTILAGE**

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There is a need for engineered grafts for treating full-thickness articular cartilage defects in advanced osteoarthritis. Structural organization of articular cartilage is rooted in the arrangement of mesenchymal stem cells (MSCs) into morphologically distinct zones during embryogenesis as a result of spatiotemporal gradients in biochemical, mechanical, and cellular factors which is central to the function of cartilage as an articulating tissue. Strategies that mimic zonal organization of articular cartilage are more likely to create an engineered tissue with more effective clinical outcome. The objective of this work was to determine the effect of physiomechanical, biochemical, and cellular factors on zone-specific chondrogenic differentiation of MSCs encapsulated in engineered matrices simulating the superficial, middle, and calcified zones of articular cartilage. Human MSCs with zone-specific cell densities were encapsulated in engineered hydrogels and cultured with or without zone-specific growth factor, optimum matrix modulus, and fiber addition and cultured in basic chondrogenic medium. Analysis of the results indicated that the optimum or zone-specific matrix modulus had a dominating effect on differentiation of MSCs to the superficial and calcified zone phenotype. The addition of aligned nanofibers parallel to the direction of matrix surface significantly enhanced expression of collagen type II in the superficial zone chondrogenic differentiation of encapsulated MSCs. Conversely, biomolecular factor insulin growth factor-1 in combination with transforming growth factor-β1 had a dominating effect on the middle zone chondrogenic differentiation of encapsulated MSCs. These findings could potentially lead to the development of multilayer grafts for regeneration of full-thickness articular cartilage defects.

**ACKNOWLEDGEMENTS**

This work was supported by grants from the National Science Foundation under Award Numbers CBET1403545 and IIP150024 by the National Institutes of Health under Award Number AR063745.

**Keywords:** Articular cartilage, chondrogenesis, zonal cell differentiation, human colony-forming stem cells.

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**SL-10**

*Track: Pharmaceutical Biotechnology*

**THE RESEARCH MECHANISM OF ANTI-AGING BIOACTIVE PEPTIDES WITH FOOD SOURCE**

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Infinitus (China) Company Ltd., a member of Lee KumKeehealth products group, are now carrying out cutting-edge research on bioactive peptides with food source to discover and confirm the efficacy of functional components currently used in aging and aging-related health products to the prevention and treatment of “senile diseases” and try to interpret the action mechanism with the information of multiple omics, which will lead Infinitus' core technical development with international cooperative research.

The procedures and methods include: high-throughput screening, preparation, efficacy validation, and mechanism research from the points of different levels which are listed as below:
Organismal Level: Reveal the mechanism of the bioactive peptide on the neurodegenerative animal models by means of omics (genomics, transcriptomics, metabolomics and proteomics) to detect the multiple network changes in the gene, RNA, protein and metabolite molecule which are caused by bioactive peptide.

Tissue and Organ Level: Identify and utilize the experimental data of the anti-aging mechanism of bioactive peptides on the areas of proteostasis, neural biological activity and antioxidant on different levels to interpret the mechanism of absorption, distribution and metabolism of the bioactive peptide in blood, tissue and organ respectively.

Cellular Level: Validate the improvement effect of the bioactive peptide on the activity and function of neuron and other target cell models and on the membrane lipid destruction and mitochondrial dysfunction, and clarify the cellular and sub-cellular localization of efficacy factor of the bioactive peptide.

Molecular Level: Explore the molecular mechanism of neurodegenerative improvement of the bioactive peptide, including the inhibition on the toxic protein aggregation (Aβ42, Tau), the promotion of autophagy (mTOR) and the effect on anti-oxidative stress pathway and related signal-regulating networks.

Most important, Infinitus will aim to reveal the visualized mechanism of bioactive peptides with the high resolution imaging technology in living system, and make a renovation to present the mechanism visually with “beautiful” and “fascinating” video and pictures to satisfy promotional requirement of growing market.

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**MOLECULAR MARKER ASSISTED BREEDING OF THREE LINES HYBRID IN CYTOPLASMIC MALE STERILITY UPLAND COTTON**

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Utilization of heterosis is an important approach to improve cotton yield. Now, most cotton hybrids are produced by artificial emasculation and pollination, it is time and labor consuming. With the gradually increase of labor cost in China, it is need to find a convenient way for cotton hybrid seeds production. The cytoplasmic male sterility (CMS) system has been widely employed to facilitate the utilization of heterosis in major crops. Compared with artificial emasculation and pollination, the labor saving up to 40%. For better understanding the molecular mechanism of CMS in *Gossypium harknessii* cytoplasm (CMS-D2) in upland cotton and developing molecular markers can be used for three lines hybrids production. Southern blot analysis was performed using 10 mitochondrial gene-specific probes, the results demonstrated that three probes (cox3, atpA, and nad6) revealed restriction fragment length polymorphisms (RFLP) between the CMS-D2 and its isogenic maintainer line. Genome walking and rapid amplification of cDNA ends (RACE) further confirmed that about 500 bp significantly different fragment was existed downstream of the atpA gene between the two materials. Then a CMS-D2 specific sequence characterized amplified region (SCAR) marker was developed and used to identify the cytoplasmic types of individual plants at the seedling stage. On the other hand, SSR, SLAF-seq and re-sequencing were performed for molecular mapping of restorer gene *Rf1*. Some SSR, CAPS, SNP and indel markers tightly linked to the restorer gene were identified. Further study confirmed that these markers can be used to track the restorer gene and identify the homozygous state of restorer gene locus, and this will greatly speed up the process of breeding of restorer lines. With the CMS-D2 specific SCAR marker and markers tightly linked to the restorer gene, it is easily to distinguish the three lines hybrids, male sterile lines, restorer lines and artificial emasculation and pollination hybrids. So, this research provides a platform for further studies of mitochondria-nuclear interactions in upland cotton and enhances the role of three lines in cotton heterosis utilization.

**Keywords:** Heterosis, pollination, polymorphisms, emasculation, marker.
**SL-62**

*Track: Medical Biotechnology*

**HIGHLIGHTS OF MEDICAL BIOTECHNOLOGY PROGRAM AT THE UNIVERSITY OF WINDSOR, CANADA**

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The Master of Medical Biotechnology (MMB) program is a professionally designed unique 16 months program, which is a unique fusion of biotechnology and business-related curricula. Through science and business courses, the program equips graduate students for working in the highly dynamic field of the biotechnology industry. Information on various courses offered by the Master of Medical Biotechnology (MMB) program at the University of Windsor will be shared. The presentation will also walk through various initiatives and experiences in preparing our students more market ready leading to Program’s success. In MMB Program, students’ get hands on experience in an extensive biotechnology lab with state of the art equipment and gain skills about cutting edge techniques including recombinant protein expression and purification using affinity chromatography, cell culture techniques, side-directed mutagenesis, gene silencing and FACS for cancer biology. The skills and knowledge taught in this program allows one to develop a successful career in biotech entrepreneurship, medical and pharmaceutical materials characterization, medical diagnostics or biotechnology product development/monitoring. In addition, the Master of Medical Biotechnology program can be a route for career advancement if one is currently employed in biotechnology and/or related medical and pharmaceutical industries.

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**SL-106**

*Track: Plant and Environment*

**A TRAIT STACKING SYSTEM IN PLANTS VIA INTRA GENOMIC HOMOLOGOUS RECOMBINATION AND NUCLEASE-MEDIATED CASSETTE EXCHANGE**

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To meet the need for durable, broad-spectrum control of weed and insect pests in different geographies, modern agriculture requires the use of multiple transgenes and the flexibility of combining them with new traits as they are developed. We recently developed a gene targeting platform for creating linked, multigene stacks [1]. The method utilized a unique intron sequence inserted directly downstream of a promoter controlling the expression of a selectable marker in a donor sequence and its use in homology-directed repair for Nuclease-Mediated Cassette Exchange (NMCE) between target and donor. We now further extend this gene targeting method to convert a transgene stack containing two unlinked trait loci into a single locus stack. The method utilizes intra-genomic homologous recombination [2, 3] (IGHR) between stably integrated target and donor loci, which share sequence homology and nuclease cleavage sites whereby the donor contains a promoterless herbicide resistance transgene. Upon crossing with a zinc finger nuclease (ZFN)-expressing plant, double strand breaks (DSB) are created in both the stably integrated target and donor loci. DSBs flanking the donor locus result in intra-genomic mobilization of an excised, selectable marker-containing donor sequence, which can be utilized as a template for homology-directed repair of a concomitant DSB at the target locus. The method was successfully demonstrated in maize and up to 3.3% of the resulting progeny embryos cultured on selection medium regenerated plants with the donor sequence integrated into the target locus. The method could be extended to multiple cycles of trait stacking by virtue of a unique intron sequence homology for NMCE between the target and donor loci. This is the first report that describes NMCE via IGHR thereby enabling trait stacking using conventional crossing.

**Keywords:** Agriculture, target, donor, expression, cleavage.
REFERENCES

SL-112
Track: Plant and Environment

TRANSGENIC PLANTS FOR REMEDIATING OIL CONTAMINATED SOIL

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Plants and microbes have been successfully used for remediating contaminated environment. Microbes are capable of degrading complex toxic pollutants into simpler forms and therefore used in cleanup of environment polluted with various organic and inorganic chemicals. Few plant species possess ability to uptake toxic compounds into harvestable biomass and thus, facilitate in removal of pollutants from soil in an environment friendly and cost effective manner. Contamination of soil with petroleum hydrocarbons is a major cause of concern in oil producing countries. Genetic engineering can play a crucial role in improving the ability of the plants to remediate contaminated soil. The presentation will focus on latest developments in the field of application of genetic engineering for improved phytoremediation. In our ongoing research, alfalfa, Indian mustard, barley and Atriplex have been screened for remediation of oil contaminated soil and data on degradation of crude oil and heavy metal uptake efficacy is presented. Arabidopsis plants were exposed to nickel and vanadium, two major heavy metals associated with crude oil contaminated soil. Next generation sequencing of the transcriptome revealed several differentially expressed genes and pathways in response to exposure to heavy metals in Arabidopsis. In continuation of this work, ATP sulfurylase gene from Arabidopsis thaliana has been cloned and being used to engineer alfalfa plants to improve heavy metal tolerance and uptake into harvestable biomass. The transgenic lines are now being tested under controlled conditions to determine their phytoremediation efficiency.

Keywords: Efficacy, microbes, removal, phytoremediation, contamination.

SL-182
Track: Industrial and Manufacturing

PRODUCTION OF 1,3-PROPANEDIOL FROM GLYCEROL BY MUTANT KLEBSIELLA PNEUMONIAE J2B DEVOID OF 2,3-BUTANEDIOL FORMATION

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The 2,3-butanediol (BDO) is produced as a byproduct during the production of 1,3-propanediol (PDO) from glycerol under limited aeration conditions by Klebsiella pneumoniae. In the present study, The PDO pathway genes, budA, budB, budC and budO (whole-bud operon), were deleted from K. pneumoniae J2B ΔldhA and the mutants were studied for glycerol metabolism and alcohols (PDO, BDO) production. Only the budO deletion mutant could completely abolish BDO production but it exhibited serious reduction in cell growth and PDO production. By modifying culture medium such as increasing buffering capacity (from 29 mM phosphate to 100 mM phosphate) and adding bicarbonate (50 mM), the performance of the budO deletion mutant could be recovered to a similar level of the base strain (91.1 mM PDO under microaerobic condition) on flask scale. However, in fed-batch bioreactor experiment, the budO deletion mutant produced significantly less PDO (502 mM) than the base strain (753 mM). In addition, the budO deletion mutant produced significant amount of pyruvate (>73 mM) and lactate (>38 mM). The low PDO
production in *K. pneumoniae* J2B ΔldhAΔbudO was attributed to the accumulation of glycolytic intermediates such as dihydroxyacetone and glyceraldehyde-3-phosphate, which are highly inhibitory to glycerol dehydratase.

**Keywords:** *Klebsiella pneumoniae* J2B, 1,3-Propanediol, 2,3-Butanediol, *Klebsiella pneumoniae* J2B ΔldhA, *Klebsiella pneumoniae* J2B ΔldhAΔbudO.

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**SL-48**

*Track:* Pharmaceutical Biotechnology

**PRODUCTION AND APPLICATION OF PHAGELYSATES AS NEW GENERATION OF IMMUNOMODULATORS**

**Besarion Lasareishvili, Jaiani Eka and Tediaishvili Marina**

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In the last decades, deterioration of the ecological and social environments led to the increase of various pathologies associated with disfunction of immune system. Adequate stimulation of immune system is especially important in the treatment of oncological pathologies, recurrent indolent infections and infections caused by multi drug resistant (MDR) bacteria. Therefore, development of cost effective, potent immunostimulators with minimal side effects are of a great practical value.

We have developed technology for the production of the new type immunostimulatory preparation – bacterial phagelysates. The preparation consists of 3 important components: 1) Pathogen associated molecular patterns (PAMPs), which are capable to rapidly stimulate innate immunity; 2) Highly immunogenic antigens participating in activation of adaptive immunity and formation of immunological memory; 3) Viruses of bacteria, which selectively lyse pathogenic hosts and act as as nonspecific stimulators of the immune cells. Hence, these types of immunobiological preparations combine properties of vaccine, adjuvant, immunostimulator and phage as an antimicrobial agent.

Three bacterial strains *E. coli, E. carotovora* and *P. aeruginosa* and their specific phages, Un, № 9 and PNM were used to obtain phagelysates. The bacteria were grown in liquid culture and the phages were added at the exponential growth phase with the multiplicity of infection 1:10. After this point, cultivation was continued under decreased temperature. The phage growth period ranged from 5-9 h depending on the bacterial and phage growth rate as well as phage burst size. At maximum lysis point the phage titer ranged between 2×1010-1×1011 pfu/ml, while bacterial concentration was 2×103-2×105 cfu/ml. After lysis completion the preparation was purified from bacterial cells and aggregates. The potency of bacterial phagelysates in formation of fast, nonspecific, anti-infective immunity as well as in induction of specific humoral responses has been studied. Also the immunotherapeutic effects of the preparation were tested on the laboratory models of intracellular chronic infections (Salmonellosis) and Ehrlich Carcinoma.

Our results strongly indicate that phagelysates can be used for express prevention of acute infections and immunostimulatory therapy of chronic infections and cancers. Besides, phagelysate preparation technology may have wide application in production of microbial lysates. In the end, the bacterial phagelysates can be applied in immunotherapy of recurrent indolent infections and fight against bioterrorism.
AN OUTLOOK ON BIODIESEL PRODUCTION FROM MICROALGAE BY BIO-MEMBRANE TECHNOLOGY: OPPORTUNITIES AND CHALLENGES

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In recent years, biodiesel has being receiving a great attention as a potential energy source due to its biodegradability, renewability, and better quality of exhaust gas emissions [1].

Currently, the major feedstock for biodiesel production is represented by microalgae, which show several advantages such as efficient biosynthesis of lipids, high productivity potential, and less competition with food production [2].

Conventional biodiesel processes are usually energy intensive and lead to an increasing of GHG emission. However, the use of membrane technology, in which biodiesel production and its separation take place in the same tool, can be considered as a promising alternative to the conventional processes. As a result, higher purity and quality biodiesel fuel are provided as well as an enhancement of the biodiesel yields is obtained.

In this contest, membranes play an important role and their several properties are the key for making them as potential candidates for biodiesel production. In this regards, this study reviews the current state of the art of biodiesel production by membrane technology. In particular, different membranes as well as the effects of operating conditions are examined, while opportunities and challenges of both biodiesel as renewable sources and membrane technology as alternative process are discussed.

REFERENCES


DEVELOPMENT OF CHROMOSOME-SPECIFIC MARKERS FOR ALLOTETRAPLOID COTTON

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Tetraploid cotton contains two sets of homologous chromosomes, the At- and Dt-subgenomes. Consequently, many markers in cotton were mapped to multiple positions during linkage genetic map construction, posing a challenge to anchoring linkage groups and mapping economically-important genes to particular chromosomes. Chromosome-specific markers could solve this problem and they were developed by comparing SSR flanking sequences from each chromosome with those from the other 25 chromosomes. The chromosome-specific SSRs and previously-reported chromosome markers were grouped together, and no marker mapped to another homologous chromosome, proving that the chromosome-specific SSRs were unique and could distinguish homologous chromosomes in tetraploid cotton. The SSRs reported here will facilitate a number of genetic and genomic studies in cotton, including construction of high-density genetic maps, positional gene cloning, fingerprinting, and genetic diversity and comparative evolutionary analyses among Gossypium species.

Keywords: Chromosomes, marker, genetic, cotton.
SL-158
Track: Medical Biotechnology

BUILDING ON EXPERTISE
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A new strategy combining availability, disponibility and privileged practices using an “in situ” simulation laboratory near work, Thiel’s cadavers and distant cameras for debriefing is used in combination, to establish continuity in teaching, reflection in action and working on metacognition during debriefing. The ultimate goal is to work on retention of learning and autonomy towards self-learning program.

SL-154
Track: Medical Biotechnology

CLINICAL CHARACTERIZATION AND FREQUENCY OF OBSERVATION OF HEREDITARY RETINAL DISEASES. MULTICENTRIC STUDY IN PANAMA. 2012-2013
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Introduction: Hereditary retinal dystrophies is a group of diseases genetically determined, implying the loss of function of the outer retina. There is a wide phenotypic and genotypic variability among them, what makes difficult to establish a potential standard treatment as they have different mechanisms of pathogenicity, despite their similar clinical presentations.

One of the research lines for these diseases is centered in the determination of the most commonly affected genes, and their most frequent clinical presentations in different populations.

There is very little phenotypic, genotypic and epidemiologic data on retinal dystrophies, in Panama, and in Latin America in general. The current research was targeted to describe the most common clinical presentations of retinal dystrophies in Panama, to orient ophthalmologist to perform specific genetic testings that explain the most frequent phenotypes. This information might guide the future of diagnosis and genetic therapeutic research to treat these patients in the area.

Objective: To describe the epidemiologic and clinical characteristics in patients with hereditary retinal and choroidal diseases, along with their family members; and to perform an incidence study and a frequency of observation estimate of these diseases in the base of the hospital retinal clinics in Panama.

Methods: We performed a descriptive study, over two years, in which we collected contact information of all consecutive patients with retinal dystrophies seen in the main retinal consults in the Republic of Panama. All detected patients were given a free appointment to gather their phenotypic characteristics and give them the most probable diagnosis. A pedigree was elaborated for each family.

Results: In the two years period, from January the 2nd of 2012 to December the 31st of 2013, 18,684 patients attended to the retina clinics of the public hospitals for adults in Panama. Among them, 10 patients were diagnosed of retinal dystrophies for the first time, which implied an incidence of 5 new diagnoses per year and an accumulated incidence of 5.35 patients per 10,000 patients attended along the two years of the study. A total of 22,104 patients attended the main retinal clinics in Panama City, including the 18,684 patients attended in the public hospitals and 3,420 attended in retina private consult at Consultorios America. From those, 60 patients (49 families) had inherited retinal dystrophies, giving a frequency of observation of 2.7 cases per 1,000 patients. Fourty-two patients (34 families) agreed to be included in the
phenotypic study. From those, 29 rod-cone dystrophies (69%), 6 cone-rod dystrophies (14.3%), 3 Stargardt disease (7.1%), 2 Stargardt-like (4.8%), 1 Central areolar choroidal dystrophy, and 1 Congenital stationary night blindness were diagnosed. The median age of all patients was of 26.3 +/- 18.9 years. The main family antecedent found in the series was blindness, [18 out of 42 patients (42.8%)]. Retinal pigment was present only in 21 out of 29 patients with rod-cone dystrophies, and in 2 out of 6 patients with cone-rod dystrophies (54% of the total studied). Pelli-Robson median in rod-cones dystrophies was 1.75. Most of the patients with cone-rod dystrophies became first symptomatic when nictalopia appeared. Besides 13.8% of rod-cone dystrophies and 50% of cone-rod dystrophies showed strabismus. Most of them presented also vascular thinning. Autosomal recessive inheritance pattern was the most frequently found.

Conclusions: Incidence and frequency of observation of inherited retinal diseases was calculated for the hospital population, which gives an idea about this data in a Hispanic population. This study gives the first phenotypic data of retinal dystrophies in Panama. The information collected might be used to orient the clinical approach and start a DNA bank, which could permit a better diagnosis and phenotyping-genotiping correlation for retinal dystrophies in Central America.

SL-66

Track: Medical Biotechnology

BIOTECHNOLOGICAL/MOLECULAR METHODS FOR GENOTYPING OF CLINICAL BRUCELLA ISOLATES INFECTING HUMANS IN KUWAIT

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Biotechnological/Molecular methods are important tools for characterization and genotyping of human pathogens. The aim of this study was to evaluate three methods viz.; the Real-time PCR (RT-PCR) based HRM (High resolution melting curve analysis), MicroSeq® 500 Bacterial 16s rDNA gene sequencing and ERIC-PCR (Enterobacterial Repetitive Intergenic Consensus) for Brucella species identification and genotyping. A total of 76 clinical isolates of Brucella were included in the study. All of the isolates were identified as Brucella melitensis by RT-PCR HRM analysis and 16s rRNA gene sequencing. ERIC-PCR-based fingerprinting in combination with advanced chip-based electrophoresis (Agilent Bioanalyzer 2100) and bioinformatics data analysis (BioNumerics v7.5) proved to be highly discriminatory for genotype analysis of B. melitensis. It generated 75 genotypes out of the 76 isolates with a discriminatory index (DI) of 0.997. Cluster classification of ERIC dendograms discovered the occurrence of eight clusters diverging at ~80%. The maximum number of genotypes were 33 classified as C, followed by 24 classified as D. The minimal spanning tree (MST) of ERIC fingerprints of B. melitensis appeared profusely branched, suggesting it to be a polymorphic species sharing some common variants amongst individual strains. Supported by Kuwait University Research Sector grants MI04/15 and SRUL02/13.
HIGH ACCURACY IN TRANSLATION AT THE DECODING SITE OF RIBOSOME

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The author has presented a mechanism of high accuracy in translation at the decoding site of small and large subunits of ribosome [1]. The 3D arrangement of elongation factor Tu and pre-A site tRNA as well as the relative arrangement of A and P site tRNAs were very well fitted to the finding of those on the Escherichia coli 50S subunit based on a cryo-EM reconstruction at 7.5 angstrom resolution [2]. On the other hand, a universal rule was found by the author about nucleotide sequence complementarities between the regions 2653-2666 in the GTPase binding site of 23S rRNA ans 1064-1077 of 16S rRNA as well as the region 1103-1107 of 16S rRNA and GUUCG (or GUUCA) in the T-loop of all tRNAs [3]. Based on this finding, a transition-state conformation of three tRNAs was constructed for explaining the mechanism of the negative cooperativity between A and E site tRNAs [4]. Under a physiological condition of Mg ion concentration about 1 mMol, RNA structures of the whole ribosome are supposed to be more dynamic than that of X-ray structure of the ribosome such as [5]. It is known that U33 in the anticodon loop of tRNA is highly conserved for almost all tRNAs. Conformational transition between U33-folded and U33-extended forms of anticodon loops of tRNAs and G-C pair formation and disruption between C1399 and G1504 of 16S rRNA, etc. play the central role in explaining why E-site tRNA can automatically be expelled when an aminoacyl-tRNA at the A site turns out to be cognate. Besides, the mechanisms of hybrid-state formation and why spectinomycin inhibits elongation factor-G dependent translocation can reasonably be explained by this approach that is based on the highly conserved nucleotide sequences of rRNAs at the decoding site and tRNAs.

REFERENCES


IMMOBILIZATION OF BIOFILMS OF PSEUDOMONAS AERUGINOSA NY3 AND THEIR APPLICATION IN THE REMOVAL OF HYDROCARBONS FROM HIGHLY CONCENTRATED OIL-CONTAINING WASTEWATER ON THE LABORATORY SCALE

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To explore the potential of Pseudomonas aeruginosa NY3 for the treatment of highly concentrated crude oil-contaminated water, the immobilization of strain NY3 on the surface of polyurethane foam (PUF), the conditions for using these biofilms and the possibility of recovering the used biofilms were studied. The results demonstrated that the biofilm formation process for strain NY3 was quick and easy. Under optimum conditions, the biomass immobilized on the PUF surface could reach 488.32 mg dry cell/g dry PUF. The results demonstrated that when the degradation time was 12 h, the average oil removal rate in 2 g crude oil/L contaminated water was approximately 90% for 40d. Meanwhile, the biofilms could be recovered for reuse. The recovery ability and the high and steady oil removal rate facilitated the application of the biofilms for the removal of concentrated oil from wastewater.
Keywords: *Pseudomonas aeruginosa* NY3, Immobilization, Polyurethane foam, Hydrocarbon, Oil-contaminated water.

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**SL-83**

*Track*: Pharmaceutical Biotechnology

**CHEMOPROTEOMIC EVALUATION OF TARGET ENGAGEMENT BY KINASE INHIBITORS PREDICTS CANCER CELL RESPONSE**

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Kinases are an important class of targets for a number of therapeutic indications, particularly cancer. Herein we apply a chemoproteomics platform utilizing an ATP or ADP acyl phosphate desthiobiotin probe (KiNativ™) to profile kinase inhibitor target engagement in live cells. We demonstrate that for a particular inhibitor, the direct targets are qualitatively similar in both inhibitor sensitive and resistant cell lines. In sensitive cell lines, secondary effects that result from the inhibition of the direct targets are also observed, and these are not observed in resistant cell lines. Significantly, this general approach can be applied to assess target engagement in human clinical studies.

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**SL-22**

*Track*: Pharmaceutical Biotechnology

**IMPACT OF BIOLOGICAL GRAIN ATTRIBUTES ON IN VITRO DIGESTIBILITY OF COOKED RICE**

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Different from wheat and maize, rice (*Oryza sativa* L.) is usually consumed as cooked grain of which structure is almost maintained during cooking process. Therefore, the biological grain attributes like tissue structures influence on the cooked rice properties, *e.g.* its textural characteristics during chewing. Although it is usually thought that the grain structures are destructed by mastication, the structure in microscale such as cell structures are mostly maintained through mastication and peristaltic motion. Thus, the grain attributes must be related to its digestibility. To examine the impact of biological grain attributes on a cooked rice digestibility, a simulated gastro-intestinal *in vitro* digestion technique focused on changes in starch hydrolysis and antioxidant activity was applied to various cooked rice samples in this study. As a result, the grain aleurone layers inhibited the penetration of digestive fluid into the grain core that influenced the starch hydrolysis rate during simulated *in vitro* digestion. This result indicated that the grain structural attributes would relate to the degree of rise in blood sugar in the actual human body. The structural attributes also influenced on the change of antioxidant activities during *in vitro* digestion.
SL-100

Track: Plant and Environment

PROTEIN LYSINE ACETYLATION AND ITS ROLE IN STORAGE NUTRIENT REGULATION IN RICE (ORYZA SATIVA)

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Lysine acetylation is a highly conserved post-translational modification of proteins. However, only a limited number of acetylation sites has been reported in plants and its role in nutrition quality regulation is still largely unknown. In this report, we found that rice endosperm is an organ with the highest level of lysine acetylation among all tested rice tissues. Using affinity enrichment followed by mass spectrometry analysis, we identified 1003 lysine acetylation sites in 692 proteins. Following the motif analysis, eight distinguished acetylation motifs were found in the acetylation sites. While five of them are common in both eukaryotes and prokaryotes, at least one specific motif is reported in this study for the first time. Biological process analysis showed that 437 of the 692 acetylated proteins are related to metabolism. Further pathway-based enrichment analysis showed that carbon metabolism enzymes, amino acid biosynthesis enzymes, and storage proteins are significantly enriched in lysine acetylation. Our results suggest that lysine acetylation controls starch synthesis via modifying the key enzymes in the starch synthesis pathway and regulate storage protein nutrition quality by modifying lysine - the number one limiting essential amino acid in cereals.

Keywords: Lysine Acetylation, nutrition quality, Rice (Oryza sativa).

SL-185

Track: Industrial and Manufacturing

EFFECT OF PRESENCE OF DIVALENT IONS, PH ON FOULING OF NF MEMBRANES IN CORELATION WITH DEMINERALIZATION AND LACTOSE LOSS IN DAIRY WASTE SAMPLES

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Valorisation of lactose from dairy waste samples is a challenge due to high concentration of mineral ions. The aim of the current study is to find the correlation between operating parameters (pH, cross flow velocity and TMP) and membrane fouling of commercial nanofiltration membranes using dairy waste in presence of mineral ions. High calcium and phosphates in the dairy waste samples were found to be influencing the membrane fouling and significant loss of lactose (20-30%) was noticed. Lowering of pH-4 does help in preventing the fouling of the membrane but demineralisation pattern seems to be not much altered by changing the pH. Presence of monovalent and divalent ions were influencing membrane fouling and lead to lactose loss during NF operation. Experimental data has been validated on pilot scale operation (50L scale) and removal of calcium, phosphate metal ions prior to nanofiltration with higher cross flow velocity, TMP and large membrane area were minimising the lactose loses. Present study will helps in choosing best operating conditions in purifying the dairy waste streams containing high minerals content with minimum loss of lactose for valorisation.

Keywords: Membrane fouling, pH, divalent ions, transmembrane pressure (TMP), product loss.
NOVEL RADIOMITIGATOR FOR RADIATION-INDUCED BONE LOSS


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Radiation-induced bone loss may occur following radiotherapy of cancer patients, accidental radiation exposure and long-term spaceflight. Bone loss due to ionizing radiation (IR) is likely due to an early increase in oxidative stress, inflammation and bone resorption, resulting in imbalanced bone remodelling. Furthermore, exposure to radiation can damage the bone-forming progenitors and reduce bone formation. Current treatments for osteoporosis inhibit bone resorption but do not protect both bone formation and skeletal progenitors cells. We recently found that Dried Plum (DP) diet prevents bone loss in mice exposed to IR with low-energy ion species (low-LET) and with the more damaging heavy ions (High-LET) (Schreurs et al. Sci Rep 2016). DP prevented both an early IR-induced rise in several markers of bone resorption, and protected bone-forming osteoblast progenitors from high-LET radiation. DP also modulated both oxidative stress and inflammatory pathways in skeletal cells and tissues. Furthermore, DP diminished the IR-induced rise in a serum marker of oxidative damage (malondialdehyde), indicating that dietary DP may be an effective radiomitigant for multiple tissues. Thus, dietary DP appeared to improve the balance of bone remodelling by reducing resorption and protecting the capacity of progenitors to form bone via reduced oxidative stress.

Keywords: Bone, Bone marrow, radiation, bone loss, diet intervention.

REFERENCE


NEW OPPORTUNITIES FOR MEMBRANE MICROFILTRATION BY EFFECTIVE PARTICLE MIGRATION, MEMBRANE AND MODULE DESIGN

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Membrane microfiltration is used within different industries as part of e.g. waste water treatment, processing of fermentations and raw materials for food, chemical and pharmaceutical products. The microfiltration process is used to separate particles on size or to remove unwanted particles completely; examples from the biotechnology field would be the fractionation of raw materials, of emulsions (oil droplets), and the removal of bacteria from fermentation liquids. In these processes, pore size determines retention of the particles; when pores are small, suspended particles will be retained to some extent, and accumulate on the membrane and possibly adsorb there and inside the pores. As a result flux and retention behaviour change in time. Any process that would be able to operate at constant flux and retention, would be of great interest, and for this we have developed a new concepts based on particle behaviour. Particles can be kept away from the membrane, based on their size, and the process conditions, and here we describe the window of operation for such process.

Surprisingly, we found that with nickel sieves that had uniform pores that were even five to seven times larger than the largest particles, significant retention coefficients could be obtained for dilute and concentrated suspensions, with smaller particles permeating the membrane and larger ones being (mostly) retained. For dilute suspensions, based on a characteristic time analysis, the particle size, membrane pore geometry, and process conditions could be linked to the retention behaviour. Retention in concentrated suspensions was mainly determined by process conditions, ratio between
large and small particles as well as total concentration of the suspension. The actual fluxes were high for both diluted and concentrated suspensions, in the order of 0.2-2.2 m²/m²/h, while the retention was constant as function of time, and no effects of fouling were noted on the flux. In our experiments, different particle migration mechanism played a role and optimal process conditions changed accordingly. An overview of each of the mechanisms involved will be presented and illustrated with experimental results based on specific requirements for membrane and membrane module layout.

In summary, the different particle migration mechanisms all resulted in relevant separation characteristics using processes in which separation is not (much) determined by pore size, but by suspension characteristics, process conditions, membrane and module design. This novel approach allows us to rethink current processes, and improve them in what may seem surprising directions at first glance, but that are actually part of a hardly explored niche within the membrane field.

**Keywords:** Microfiltration, separation, fractionation, particle migration.

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**SL-193**

*Track: Industrial and Manufacturing*

**IMPROVEMENT IN BIOLOGICAL PHARMACEUTICAL PROCESSES THROUGH THE IMPLEMENTATION OF AN INTEGRATED PROCESS EXCELLENCE DRIVEN LEAN STRATEGY**

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Modern Biological processes are very complex and require various levels of skill to operate efficiently and profitably. In relation to modern pharmaceutical/biopharmaceutical processes where there are quality compliance/regulatory issues, the complexity is even more enhanced.

Without proper business process structures and an integrated approach to these operations it is almost impossible to make products without incurring additional costs which may damage profitability. This may become a potential process tipping factor in the case of biosimilars or certain vaccine products for example, where margins are reduced over innovator product situations.

This paper will outline an integrated Lean approach where the use of process excellence principles is used to drive quality and process operations functions to reduce in-process waste (TIMWOOD), streamline business processes such as: Supply Chain, Manufacturing, Quality Control and Quality Assurance, and to enhance business process efficiency to positively improve overall profitability.

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**SL-153**

*Track: Plant and Environment*

**GENOME SEQUENCING OF COTTON AND PRIMARY FUNCTIONAL ANALYSIS OF GLAND RELATED GENES**

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Cotton (*Gossypium* spp.) is one of the most important economic crops in the world. We have sequenced and assembled the genome of *G. raimondii* (DD), *G. arboreum* (AA) and *G. hirsutum* (AADD). Evidence of the hexaploidization event shared by the eudicots as well as of a cotton-specific whole-genome duplication was observed the genome of *G. raimondii* and *G. arboreum*. Insertions of long terminal repeats in the past 5 million years are responsible for the two-fold difference in the sizes of
these genomes. Transposable elements originating from Dt seem more active than from At. Reduction in the AtDt genome size occurred after allopolyploidization. There cotton genomes will facilitate the screening for new target genes for important agronomic traits. We located the Gl2 gene which could inhibit the formation of the pigment glands within a 15-kb genomic interval using the genome sequences. Only one gene was identified which encodes a MYC transcription factor. Function analysis showed that this gene control the formation of pigment gland. The Gl2 gene will facilitate the research on glandless trait and low-gossypol cotton breeding.

Keywords: Genome, pigment, allopolyploidization, elements, traits.

**SL-97**

**Track:** Plant and Environment

**FUNCTIONAL GENOMICS AND TRANSGENIC IMPROVEMENT OF ENVIRONMENTAL STRESS TOLERANCE IN RICE**

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Various environmental stresses including high salinity, drought and cold seriously damage rice production every year. Global climate change has accelerated the severity of these stresses. Scientists and crop breeders have been facing these challenges and are seeking for feasible solutions. We have developed an efficient two-element maize Ac/Ds gene trap system and generated around 20,000 Ds insertion rice lines. We subjected these lines to drought, high salinity and cold stress screens and evaluated these lines with respect to their tolerance to these stresses. Based on this evaluation, we observed that random Ds insertions into the rice genome have led to various variations in response to these stress conditions. Subsequent to these screens, over 800 lines responsive to drought, salinity or cold stress were obtained. Some of these lines and their tagged genes were further characterized in their biological functions. Our data suggest that rice has the genetic potential to survive under environmental stresses when appropriate endogenous genes were suppressed. The mutant lines that display higher tolerance to these environmental stresses may be used for rice breeding by conventional backcrossing combining with molecular marker-assisted selection. In addition, by exploiting the behavior of Ds to leave footprints upon remobilization, we have shown an alternative strategy to develop new rice varieties by knocking down a gene without insertion of foreign DNA sequences in their genome. On the other hand, we have genome-widely identified genes with differential expression under drought and high salinity stresses. We have identified total of 735 and 723 genes with up-regulated expression signal under drought and high salinity stress treatments, respectively. These genes encode various proteins functioning as transcription factor, kinase, phosphatase as well as in detoxification, iron homeostasis, and hormone biosynthesis and so on. We have generated several transgenic plants by over-expressing these genes in the rice genome. Further investigation showed that these transgenic plants exhibited significantly higher tolerance to these environmental stresses. Thus, our studies provide an alternative way to reduce the damage due to these environmental stresses under continuously changed global climate.
SL-86

Track: Pharmaceutical Biotechnology

REDOX REGULATION WITHIN THE ER INFLUENCES THE BONE MARROW NICHE AND DRUG RESPONSE

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Cysteine is a malleable amino acid susceptible to many types of post-translational modifications. S-glutathionylation, occurs through the reversible addition of a proximal donor of glutathione (GSH) to thiolate anions of cysteines in target proteins - where the modification alters molecular mass and charge, structure/function and/or prevents degradation from sulfhydryl over-oxidation and proteolysis. Catalysis of both the forward (glutathione S-transferase P; GSTP) and reverse (glutaredoxin; sulfiredoxin; GST omega) reactions creates a cycle that can regulate certain functional protein clusters including those involved in redox-dependent cell signaling events and protein folding. Pertinent to the latter, GSTP can exist as an endoplasmic reticulum (ER)-resident protein where it demonstrates both chaperone and catalytic functions. Redox based proteomic analyses identified a number of proteins cooperatively involved in regulation of ER stress (immunoglobulin heavy chain-binding protein [Bip], protein disulfide isomerase [PDI], calnexin, calreticulin, endoplasmic, sarco/endoplasmic reticulum Ca2+-ATPase [SERCA]) that both co-immunoprecipitate with GSTP (implying protein complex formation) and are subject to S-glutathionylation following treatment with drugs such as disulfiram. S-glutathionylation of these proteins was attenuated in cells (liver, embryo fibroblasts or bone marrow dendritic) from mice lacking GSTP compared to wild type. Knockout cells were also significantly more sensitive to the cytotoxic effects of the ER-stress inducing drugs, thapsigargin (7-fold) and tunicamycin (3-fold). Contextually, these results provide mechanistic evidence that GSTP can exert redox regulation in the oxidative ER environment and indicate that, within the ER, GSTP influences the lethality of the unfolded protein response (UPR) through S-glutathionylation of a series of key interrelated proteins that control UPR pathways.

To interrogate why GSTP is important in regulating bone marrow cell differentiation and proliferation, we isolated crude bone marrow (BM), lineage negative (Lin (-)) and bone marrow derived-dendritic cells (BMDCs) from both WT and knockout mice. Comparison of the two strains showed distinct thiol expression patterns. WT had higher baseline and reactive oxygen species (ROS)-induced levels of S-glutathionylated proteins, some of which (SERCA, IP3R) regulate Ca2+ fluxes and subsequently influence proliferation and migration. Redox status is also a crucial determinant in the regulation of the chemokine system. CXCL12 chemotactic response was stronger in WT cells, with commensurate alterations in plasma membrane polarization/permeability and intracellular calcium fluxes; activities of the downstream kinases, ERK and Akt were also higher in WT. In addition, expression levels of the chemokine receptor CXCR4 and its associated phosphatase, SHP-2, were higher in WT. Inhibition of SHP2 decreased the extent of CXCL12-induced chemotaxis in WT BMDCs. The differential surface densities of CXCR4, SHP-2 and IP3R in WT and KO cells correlated with the differential CXCR4 functional activities (chemokine-induced directional migration and differences in intracellular signaling). These observed differences contribute to our understanding of how genetic ablation of GSTP causes higher levels of myeloproliferation and differentiation.

In clinical applications, quantitative and qualitative levels of S-glutathionylated serum proteins (e.g. serine proteinase inhibitors [serpins] A1 and A3) have been shown to be useful biomarkers in predicting exposure of individuals (who may also have polymorphic expression of GSTP) exposed to agents that cause oxidative or nitrosative stress (ROS/RNS). In individuals exposed to hydrogen peroxide mouthwash, human buccal cells are found to have increased levels of S-glutathionylated proteins suggesting that these cells are useful surrogates for predicting exposure to ROS in the oral cavity. These biomarkers are useful in clinical trials as extrapolated pharmacodynamic indicators for assessing the impact of drugs or radiation that cause ROS and impact redox homeostasis.
**SL-52**

*Track: Pharmaceutical Biotechnology*

**N-ACETYL-SEROTONIN AND MELATONIN OFFER NEUROPROTECTION IN EXPERIMENTAL MODELS OF NEUROLOGICAL DISEASE**

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The identification of neuroprotective agents for neurological diseases including stroke, Amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD) remain elusive. We test whether melatonin receptor 1A agonists N-acetyl-serotonin (NAS) and melatonin are neuroprotective in experimental models of stroke, ALS, and HD.

We demonstrate that NAS and melatonin inhibit cell death induced by oxygen-glucose deprivation or H2O2 in primary cerebrocortical neurons, primary hippocampal neurons, NSC34 motoneurons, mutant-huntingtin ST14A striatal cells *in vitro*. We further found that NAS and/or melatonin reduce hypoxia/ischemia injury in the middle cerebral artery occlusion mouse model of cerebral ischemia, and delay disease onset and extend mortality in mSOD1G93A transgenic ALS mice and R62 transgenic huntington's disease mice *in vivo*. Our data show that NAS and melatonin are neuroprotective by inhibiting the mitochondrial cell death pathway including the inhibition of the release of apoptogenic factors cytochrome c, Smac, and apoptosis-inducing factor from mitochondria to cytoplasm, and activation of caspase-3, -9. Furthermore, pro-IL-1β processing, and activation of caspase-1 are evaluated in melatonin-mediated neuroprotection. Moreover, we demonstrate that the neuroprotective effects of NAS may result from the suppression of the autophagic cell death pathway under stress conditions by increasing LC3-II and Beclin-1 levels and decreasing p62 level. Taken together, we conclude that melatonin receptor 1A agonists NAS and melatonin have the potential as the novel therapies for ischemic injury, ALS and HD.

**SL-14**

*Track: Pharmaceutical Biotechnology*

**PRODUCTION AND FUNCTION OF NOVEL BIOACTIVE LIPIDS - DIACYLGLYCEROLS**

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Oil and fats have profound physiological effects on human health. They not only provide people with energy and essential nutrients, but are also associated with chronic diseases such as obesity, cardiovascular disease, diabetes etc. Structured lipids, including diacylglycerols (DAGs) and lipids with omega-3 polyunsaturated fatty acids, have been shown to exhibit desirable metabolic properties. Among them, DAGs are recognized as functional oils for prevention of obesity (a major social problem worldwide). Although DAGs have market potential, industrial production technologies for DAGs are currently limited. By comparison with chemical methods, enzymatic methods are an efficient and safe way to make structured lipids because enzymes have high substrate specificities and good reaction efficiency, while requiring mild reaction conditions. Partial glycerol lipases have demonstrated activity only towards monoacylglycerol (MAG) and DAG, and thus are a good choice for DAG production compared with triacylglycerol lipases. This presentation will review novel partial glycerol lipase discovery, its activation, mechanism of substrate selectivity and application to produce DAGs.
THE VALUE OF GM2: EXPLORING CONSUMER WILLINGNESS TO PAY FOR GM2 FOOD

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Despite the lack of scientific evidence to suggest genetically modified (GM) foods are less safe than traditional foods, the presence of GM foods for human consumption is a highly contentious issue. Prior studies seem to have suggested that consumers, in general, have a somewhat negative attitude towards GM foods. Accordingly, effective marketing strategies are of paramount importance for the future of GM products, in order to overcome negative consumer perceptions.

Previously, GM crops have been typically producer-oriented - designed to increase yield by introducing traits such as insect resistant and herbicide tolerant. Some scholars are now describing these as the first generation of GM crops. First generation GM crops are faced with much opposition world-wide, as they were deemed only profit-focused and showed little direct benefits to the consumers. The second generation of GM crops is posited to create tangible consumer benefits such as increased nutrition and health, better taste, and environmental sustainability. There is hope that the second generation of GM crops will change consumer perception of biotechnology for the better, as well as increase production yield to satisfy the anticipated population growth.

The purpose of the study is to explore consumers’ attitudes toward such second generation GM foods and their willingness to pay for such enhanced attributes derived from GM. This study employed on-line survey questionnaire method using Qualtrics program. Seven hundred and fifty (750) Canadian individuals over the age of 18, and resides in one of the western Canadian provinces (British Columbia, Alberta, Saskatchewan, and Manitoba) participated in our study. The survey was quasi-experimental in nature. Participants were randomly assigned to one of three groups. The participants were presented with different types of fictitious ads of new novel food items containing GM food ingredients, such as gourmet bread (GM wheat), Canola oil, and tofu (GM soy beans).

In the first condition, the descriptions of these three food items emphasize on their healthy attributes. The gourmet bread offers abundant fiber and protein, the Canola oil has zero cholesterol, and Tofu offers high concentration of easy-to-digest vegetable protein. In the second condition, the descriptions of these three food items emphasize on the fact that they are made with genetically modified ingredients - GM wheat, GM Canola, and GM soy beans, respectively. In the third condition, the descriptions of these three food items emphasize on the relationship that the enhanced nutritional value is achieved through genetic modification.

Preliminary results indicate that consumers respond positively to the additional functional benefits they derive from the novel foods. The GM attribute, and particularly the perceived risks of GM, resulted in a negative willingness to pay (WTP). When the consumers were presented with a novel food with ingredients that were genetically modified to create personal value, the WTP turns positive.

Keywords: GM, GM2, Functional food, Marketing.

PROSPECT OF ENGINEERED GRAPHENE-BASED THERAGNOSTIC NANOFORMULATION FOR CANCER PRECISE TREATMENT

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Theragnostic nanomedicine shows great promise for cancer precise treatment. Myriads of multifunctional nanoformulations have been investigated and even some had been in preclinical trials. Among of those, graphene and its derivatives have been seen a promising applications in the area of nanomedicine due to their unique characteristics, such as water solubility, abundant hydrophilic groups, large specific surface area,
photoluminance and biocompatibility. In this contribution, we will review data regarding graphene-based nanomedicine for high efficient cancer treatment and imaging. Case studies of our group demonstrating the synergistic anticancer efficiency of chemotherapy, photodynamic, photothermal therapy and immunotherapy will be presented. Also, we will focus on the imaging function of graphene-based probes, such as photothermal imaging, photoacoustic imaging, fluorescent imaging and MR imaging. How manipulation of the physicochemical properties of the nanoformulations influences their anticancer and imaging functions will be analyzed. Finally, the challenge and promise of graphene-based engineered platform for cancer precise therapy will be commented on.

Keywords: Graphene, nanomedicine, theranostics.

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**SL-188**

**Track:** Industrial and Manufacturing

**INTEGRATION OF CLOSED-LOOP AND LAW-CARBON SUPPLY CHAINS: MODELING, SATISFICING AND POTENTIAL BIOTECHNOLOGY FOR SUSTAINABILITY**

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For environmental issues by industries such as global warming, material starvation and biodiversity, manufacturing should be more environmentally conscious for sustainability. In order to bring us products every day, supply chains (SC) by manufacturing inevitably consume natural resources for materials and energy, and emit Greenhouse Gases (GHG) and wastes throughout the whole product lifecycle. To promote GHG reduction and material circulation simultaneously, closed-loop for recycling and low-carbon for CO₂ reduction should be environmentally and economically integrated by modeling for visualization and satisficing for optimization since they are interrelated and interactive each other. Additionally, biotechnology such as biomass energy/plastics and biodegradable plastic must have affected SC design.

This study identifies the environmental issues in manufacturing, proposes an integration of the closed-loop and law-carbon supply chains by modeling and satisficing, and discusses potential impacts by biotechnology for the supply chain design. First, the environmental issues in the SC are identified, and the relationships between the closed-loop and low-carbon SC are stated. Next, the modeling and satisficing of the closed-loop and the low-carbon SC for disassembly/assembly are developed along with our research projects between the US and Japan. Finally, the potential impacts by biotechnology are discussed for designing the closed-loop and low-carbon SC.

Keywords: Environmentally conscious manufacturing, Disassembly, Recycling, Life cycle assessment, Biomass.

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**SL-91**

**Track:** Pharmaceutical Biotechnology

**HYDROGEN SULFIDE STIMULATES ADIPOGENESIS IN 3T3-L1 PREADIPOCYTES**

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Hydrogen sulfide (H₂S) has been recognized as one important gasotransmitter analogous to nitric oxide. Cystathionine-gamma-lyase (CSE)-derived H₂S is implicated in the regulation of insulin resistance and glucose metabolism. The involvement of CSE/H₂S system lipid metabolism and adipogenesis has not been explored. Here we showed that CSE expression and H₂S production are increased during adipocyte differentiation in mouse 3T3-L1 cells, and the mRNA expression pattern
of CSE was similar to that of C/EBPβ and C/EBPδ, two key regulators for adipogenesis. Promoter-reporter analysis and chromatin immunoprecipitation assay demonstrated that both C/EBPβ and C/EBPδ bind to the CAAT box in CSE promoter and stimulate CSE gene transcription. We further found that exogenously applied H₂S induces PPARγ transcriptional activity and stimulates adipocyte differentiation in a hormone-dependent manner. Down-regulation of CSE gene suppressed but up-regulation of CSE gene stimulated adipocyte-specific gene expression and adipogenesis. Ablation of CSE in mouse embryonic fibroblasts resulted in impairment of adipocyte differentiation. In vivo, high-fat diet induced fat mass and insulin resistance was lost in CSE-deficient mice in comparison with wild-type mice. Taken together, our results suggest that CSE/H₂S system acts a novel regulatory circuit for adipogenesis through improvement of PPARγ function in adipocytes (Supported by NSERC discovery grant).

**SL-103**

*Track: Plant and Environment*

**HAIRPIN RNA TARGETING MULTIPLE VIRAL GENES CONFERS STRONG RESISTANCE TO RICE BLACK-STREAKED DWARF VIRUS**

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Rice black-streaked dwarf virus (RBSDV) belongs to the genus *Fijivirus* in the family of *Reoviridae* and causes severe yield loss in rice producing areas in Asia. RNA silencing, as a natural defense mechanism against plant viruses, has been successfully exploited for engineering virus resistance in plants including rice. In this study, we generated transgenic rice lines harboring an hairpin RNA (hpRNA) construct targeting four RBSDV genes *S1*, *S2*, *S6* and *S10*, encoding the RNA-dependent RNA polymerase, the putative core protein, the RNA silencing suppressor and the outer capsid protein, respectively. Both field nursery and artificial inoculation assays of three generations of the transgenic lines showed that they had strong resistance to RBSDV infection. The RBSDV resistance in the segregating transgenic populations correlated perfectly with the presence of the hpRNA transgene. Furthermore, the hpRNA transgene was expressed in the highly resistant transgenic lines, giving rise to abundant levels of 21-24 nt small interfering RNA (siRNA). Small RNA deep sequencing analysis of the RBSDV-resistant transgenic lines detected siRNAs from all four viral gene sequences in the hpRNA transgene, indicating that the whole chimeric fusion sequence can be efficiently processed by Dicer into siRNAs. Taken together, our results suggest that long hpRNA targeting multiple viral genes can be used to generate stable and durable virus resistance in rice as well as other plant species.

**Keywords:** Silencing, resistance, assays, virus, sequence.

**SL-56**

*Track: Pharmaceutical Biotechnology*

**FUNCTION OF TGF-β REGULATED MIRNAS IN THE MAINTENANCE OF CARDIAC HOMEOSTASIS**

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Cardiac hypertrophy is an adaptive enlargement of the myocardium in response to physiological or pathological stimuli. The cellular responses of cardiomyocytes to various signaling pathways should be tightly and delicately regulated to maintain cardiac homeostasis. The role of TGF-β signaling in cardiac hypertrophy has been being debated. We have previously shown that the function of endogenous TGF-
β/Smad signaling in maintaining cardiac homeostasis involves the downregulation of miRNAs inducing cardiac hypertrophy. Very recently, we found that miR-199a acts as a key regulator of cardiac autophagy and cardiac hypertrophy. We generated cardiac-specific miR-199a transgenic mice and demonstrated that overexpression of miR-199a was sufficient to inhibit cardiomyocyte autophagy and induced cardiac hypertrophy in vivo. Mechanistically, miR-199a impaired cardiomyocyte autophagy in a cell- autonomous manner by targeting glycogen synthase kinase 3β (GSK3β)/mammalian target of rapamycin (mTOR) complex signaling. Activation of autophagy using rapamycin was sufficient to restore cardiac autophagy and decrease cardiac hypertrophy in miR-199a transgenic mice. Interestingly, inhibition of endogenous miR-199 led to physiological cardiac hypertrophy, uncovering a surprising role for endogenous miR-199 in the maintenance of cardiac hemostasis. These results suggest that targeting miRNAs regulated by TGF-β is a potential therapeutic strategy for cardiac disease.

**SL-149**

*Track: Plant and Environment*

**PAGODA1 IMPACTS PLANT ARCHITECTURE BY REGULATING BR**

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Cotton is an important crop as a source of fiber and oil. Optimal plant architecture can increase cotton yield and quality. We identified a T-DNA tagged cotton mutant from an activation-tagging genetic pool, which was designated as *pagoda1*. *pagoda1* exhibited extreme dwarfism and shortened petioles. Histological analysis revealed that cell elongation and expansion were largely reduced in *pagoda1* compared to wild-type, which explained the dwarfed and compact phenotype. *pagoda1* showed a de-etiolated phenotype in the dark, and exogenous application of brassinolide (BL) can rescue the growth of *pagoda1*, suggesting that the mutant is likely caused by BR deficiency. And tissue specific BL treatment only promoted the growth of local branches of *pagoda1*. *PAGODA1* gene was isolated from the *pagoda1* mutant by T-DNA tagging technique, and encodes a cytochrome P450 protein. Sequence analysis showed that *PAGODA1* was a homolog of Arabidopsis P450 that inactivated BRs via C-26 hydroxylation. Over-expression of *PAGODA1* in Arabidopsis recapitulated the dwarfed phenotype seen in the cotton mutant. Interestingly, the expression level was negatively correlated with the height of the transgenic Arabidopsis plants. Together, PAGODA1 can impact plant architecture through regulating BR homeostasis in cotton. Therefore, *PAGODA1* is a good candidate for future plant architecture manipulation via genetic engineering.

**Keywords:** Phenotype, dwarfism, elongation, mutant, petioles.

**SL-80**

*Track: Pharmaceutical Biotechnology*

**AGONIST ANTIBODY THAT INDUCES HUMAN MALIGNANT CELLS TO KILL ONE ANOTHER**

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An attractive, but as yet generally unrealized, approach to cancer therapy concerns discovering agents that change the state of differentiation of the cancer cells. Recently, we discovered a phenomenon that we call “receptor pleiotropism” in which agonist antibodies against known receptors induce cell fates that are very different from those induced by the natural agonist to the same receptor. Here, we show that one can take advantage of this phenomenon to convert acute myeloblastic leukemic cells into natural killer
cells. Upon induction with the antibody, these leukemic cells enter into a differentiation cascade in which as many as 80% of the starting leukemic cells can be differentiated. The antibody-induced killer cells make large amounts of perforin, IFN-γ, and granzyme B and attack and kill other members of the leukemic cell population. Importantly, induction of killer cells is confined to transformed cells, in that normal bone marrow cells are not induced to form killer cells. Thus, it seems possible to use agonist antibodies to change the differentiation state of cancer cells into those that attack and kill other members of the malignant clone from which they originate.

**Keyword:** Pleiotropism, leukemic cells and granzyme B.

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**SL-36**

*Track: Pharmaceutical Biotechnology*

**THE ROLE OF MICRORNAS IN BRAIN FUNCTION**

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Despite a number of discovered proteins and signal structures associated with brain function, how the brain forms memory and consciousness is still poorly understood. On the other hand, it has recently been revealed that microRNA (miRNA), a member of small non-coding RNA (ncRNA) which is evolutionally conserved between species, plays important roles in various biological processes including brain functions such as production of brain chemical, control of neural cells, nervous diseases, and memory modification by regulating target gene expression.

Here, reports about miRNA dynamics in regulation of neuronal or brain functions were collected and then neural specific miRNA targets were searched by TargetScan and miRTarBase. The high scored miRNA/mRNA interactions were picked up furthermore, their miRNA quantum values (DNS) were computed.

We found that the bio-informed miRNA/miRNA dynamics in the brain were simplified according to the miRNA memory package under the RNA wave 2000 model, a theory that each miRNA has different quantum potentials, rather than ready-made computing analyses.

Thus, the miRNA/miRNA quantum interaction in silico would be deeply implicated in the brain memory formation and the DNS analysis of functional miRNAs is useful for the enigmatic mechanisms of brain system such as plasticity and preservation and transfer of memories.

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**SL-146**

*Track: Nanobiotechnology*

**REAL TIME MONITORING OF DRUG RELEASE OF CARBON NANOMATERIALS**

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Silver (Ag) nanoparticles are well established for its antibacterial activity. In study we demonstrate the antibacterial activity of the electrospun nanofiber mats coated with various ratios of Ag and ZnO nanoparticles and relate it with the hydrophilicity of the membrane imparted due to Ag nanoparticles. Electrospun nanofibers were prepared from a 1:1 blend of two polymers: PCL and PMMA that was sputter coated with inorganic nanoparticles (Ag and ZnO) at three ratios thus adding another layer of nanocomposition to
the resulting polymer nanocomposite nanofiber scaffold. The PF-QNM characterization results showed different shapes, sizes and DMT modulus of the inorganic nanoparticles (Ag and ZnO), appearing at the surface of the nanofibers. Ag and ZnO nanoparticles were observed heterogeneously distributed on the nano fiber mesh and varied at different locations along the nanofibers lengths based on their ratios used in sputtering. Increasing ZnO content increased both the hardness and water contact angle (almost double as compared to Ag for the same increase in content) of the nanofiber mesh. The antibacterial activity of scaffolds coated with different ratios of Ag and ZnO was tested against MRSA ATCC®. The viable bacteria were monitored by counting the number of colony forming units (CFUs/ml). The results revealed a significant reduction (p < 0.05) in the number of CFUs/ml after only 15 min of exposure to the scaffolds coated with Ag:ZnO (1:1) and Ag:ZnO (3:1) respectively. Nevertheless, scaffold coated with Ag:ZnO (1:3) required longer time (30 min) to show reduction in the number of CFUs/ml. There was a significant difference between the number of CFUs/ml after 0 min exposure to scaffolds coated with different ratios of Ag and ZnO and the number of CFUs/ml after 30 min exposure. Taken together these results show superior antibacterial activity for scaffolds coated with different ratios of Ag and ZnO against pathogenic bacteria MRSA, which demonstrates potential applications of these scaffolds in medical and biomedical fields.

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**SL-24**

**Track:** Marine Biotechnology

**A COMPARATIVE TRANSCRIPTOMICS ANALYSIS OF EYESTALK IN BOTH GENDER OF GREEN MUD CRAB (SCYLLA PARAMAMOSAIN)**

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**Background:** Green mud crab, *Scylla paramamosain*, is an important commercial species, because its characters like big size, high meat yield and delicate flavor make it a high sought-after quality food. With the continuous expansion of *S. paramamosain* cultivation, fry and fingerling shortage has been a bottleneck of green crab aquaculture. Therefore, we performed a large-scale transcriptome study from eyestalk, which controls several metabolites, reproduction and immune function, to open an avenue of research on the mechanism of reproductive and immune regulation in *S. paramamosain*.

**Results:** In this study, a total of 45,215 unique sequences were obtained from two cDNA libraries, which were constructed from female and male eyestalk respectively. Among the unique transcripts, 741(F) and 1,351 (M) unique transcripts were matched against known genes in the NCBI non-redundant (nr) database (E-value≤10^{-5}). Gene ontology (GO) analysis revealed that 386 assembled ESTs were annotated in female and 686 in male. Further analysis revealed that there were 67 (F) and 137 (M) unique transcripts associated with 96 (F) and 136 (M) KEGG pathways respectively. An amount of sequences showed a dramatic transcript discrepancy between female and male tissues by preliminary quantification comparative expression analysis based on the depth of each unique sequence. A subset of specific or obvious discrepant express sequences was confirmed by quantitative real-time PCR. As the result, eleven unique transcripts were enriched in female eyestalk, and thirteen in male eyestalk. In addition, three specific expression unique transcripts were found in male and female eyestalk respectively. Several CHH family genes, ERK signaling pathway related genes, UPP and SUMO related genes, and immune related genes were obtained.

**Conclusion:** As a project on large-scale RNA sequencing of female and male eyestalk in *S. paramamosain*, this is a first report of an annotated overview of the transcriptome of *S. paramamosain* and an identification of sex differentially expressed genes. These data would enrich the knowledge of gonad development of crustacean and provide fundamental support for further studies in the molecular mechanisms of gonadal development regulation and immune regulation.
AN ASSOCIATION OF METABOLIC SYNDROME CONSTELLATION WITH CELLULAR MEMBRANE CAVEOLAE-A POSSIBLE MECHANISM

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Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that can predispose an individual to a greater risk of developing type-2 diabetes and cardiovascular diseases. The cluster includes abdominal obesity, dyslipidemia, hypertension, and hyperglycemia, all of which are risk factors to public health. While searching for a link between the aforementioned malaises, clues have been focused on the cell membrane domain caveolae, wherein the MetS-associated active molecules are colocalized and interacted with, to carry out designated biological activities. Caveola disarray could induce all of those individual metabolic abnormalities to be present in animal models and humans, providing a new target for therapeutic strategy in the management of MetS.

Active molecules involving in metabolic pathways are co-localized at cellular caveolae.

Stimulation of caveolae intra-cellular movement by external stimulators/potential therapeutical agents.

Using a cellular model of caveolae inter-cellular movement (with the eGFP-labelled-caveola), several potential herbal extracts and nutrients have shown their effects on externalization of caveolae, opening an initiative for the associated metabolic pathways. This is also supported by recent publications which have demonstrated that some clinically effective Chinese herbal or herbal extracts for the treatments of hypertension, hyperlipidemia and hyperglycemia can have a stimulating effect on cellular caveolae bioactivity. A new therapeutic target to effectively treat and prevent metabolic syndrome safely without significant side effects may become possible.
PHYTONUTRIENT AND BIOACTIVITY ANALYSIS OF TRADITIONALLY-USED NATIVE AMERICAN EDIBLE PLANTS

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Plant derived foods such as fruits and vegetables are rich sources of antioxidants, phenolics and other biologically active components shown to reduce the risk of chronic diseases. The association between the consumption of plant derived foods and a decreased risk of cardiovascular disease, cancer, and diabetes is supported by significant epidemiological evidence. Traditionally-used Native American edible plants are thought to be rich sources of phytonutrients, antioxidants, and biologically active components, however research reports providing data on content, processing and inflammation impacts are sparse. The objective of the study was to measure phytonutrients and other biologically active components of selected, Native American edible plants and plant parts from Southern California including prickly pear fruit pods (Opuntia ficus-indica), Yucca whipplei fruit pods and blossoms in fresh and thermally-processed samples. Sample analyses of pH, moisture, total soluble solids (TSS), total chlorophyll, total carotene, antioxidant activity, phenolic and flavonoid contents were conducted. HPLC chromatographic overlays were also made to illustrate the difference in antioxidant components in the fresh compared to processed plant samples. In addition, the plant extracts were investigated regarding the potential for novel preventive or therapeutic supplements for inflammation-related diseases. In summary, these plants were found to be rich sources of antioxidant activity and phenolic content, that processing significantly influenced activity in the plant samples.
POSTERS
SIMULTANEOUS GENETIC SCREENING OF THE COAGULATION PATHWAY GENES USING THE THROMBOSCAN TARGETED SEQUENCING PANEL

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Background: Thrombophilia is a condition where the blood has an increased tendency to clot. Blood clots can generate diseases such as deep vein thrombosis and pulmonary embolism. Thrombophilia can be acquired (due to autoimmune diseases, pregnancy, hormone therapy, malignancy, myeloproliferative disorders, postsurgical state and nephrotic syndrome) or inherited (due to genetics predisposition). Inherited thrombophilia is a result of DNA mutation in genes responsible for the production of blood clotting proteins (coagulation system). Antithrombin, protein S and protein C are the most important inhibitors of the blood coagulation system, as most of thrombotic patients have inherited deficiency of one of these proteins. While inherited thrombophilia can be caused by a number of mutations, the most common ones are factor V Leiden (FVL) and prothrombin (factor II). Factor V Leiden mutation is a single nucleotide point mutation (SNP) located at position number 506 and alters amino acid arginine to glutamine in FV gene. Prothrombin (factor II) is the precursor to thrombin, which is essential in the coagulation cascade and located on chromosome 11p11-q12. Prothrombin G20210A mutation (factor II mutation) is a SNP located at position 20210 and changes amino acid guanine to adenine in the prothrombin gene. This mutation is associated with high levels of prothrombin and was reported to increase the risk of thrombosis almost three fold. Patients with high levels of other procoagulants such as factors VIII, IX, XI, VII, fibrinogen, and Von Willebrand factor (VWF) are also at high risk of thrombosis.

Materials and Methods: Next Generation Sequencing allows high throughput DNA sequencing and mutation detection at a low cost and high turnover. This in turns has a major influence in both clinical care and understanding susceptibility to thrombophilia. Therefore, we have designed the Thromboscan panel which will allow the simultaneous screening of 23 coagulation genes using the AmpliseqT technology.

Results: In this study, a screening panel of 23 coagulation genes has been developed, optimized and tested for the early diagnosis of thrombophilia using the cutting edge technology of next generation sequencing. The results confirmed 99.26% coverage of the targeted genes with 430 amplicons with sizes ranges between 125-275 bp generating 81.56 kb of DNA sequence. We have demonstrated that this panel can be used on DNA extracted from peripheral blood or saliva.

Conclusion: The availability of this panel will help increase our understanding of genetic susceptibility to thrombophilia and other aberrant thrombotic events.

Keywords: Coagulation, genetic screening, thromboscan.

COMBINATION WARRANTY POLICY ANALYSIS FOR REMANUFACTURED PRODUCT

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Lately, the number of studies that address the issues at the end-of-life (EOL) stage of a product, has been an increasing. This is due, on one hand, to environmental factors, government regulations and public demands, and on the other hand, to potential economical profits that could be obtained by implementing reverse logistics and product recycling resolutions. Manufacturers try to cope with
consumer awareness towards environmental issues and stricter environmental legislation by setting up facilities which involve the minimization of the amount of waste sent to landfills by recovering materials and components from returned or EOL products.

This paper presents a non-renewable basic one-dimensional combination warranty policy analysis for an Advanced Remanufacturing-To-Order system for Sensor-Embedded Products (SEPs). The goal of the proposed approach is to predict a non-renewing one-dimensional Free Replacement and Pro-Rata combination warranty period for the disassembled components and remanufactured products using the sensor information about the age of each and every recovered EOL product on hand to meet remanufactured product and component demands while minimizing the cost associated with warranty and maximizing manufacturer’s profit. Different simulation scenarios are explained and a case example is presented for illustration of the model applicability.

**Keywords:** End-of-life, remanufacturing, sensor embedded products, simulation, one-dimensional, combination warranty.

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**PO-27**  
*Track: Pharmaceutical Biotechnology*

**HYPERSENSITIVITY DIALYSIS MEMBRANES**  

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**INTRODUCTION**

The development of a hemodialysis session involves some risks of adverse hypersensitivity reactions when in contact with a huge volume of blood with different synthetic materials

Described hypersensitivity reactions to non-biocompatible membranes as cuprophone, and recently even with synthetic membranes: polysulfone, Polyethersulfone Polyamide and PMMA [1]. Patients who presented these reactions to a synthetic membrane, normally they presented to all of these the problem only disappeared with only the use of a cellulose membrane [3].

**CASE REPORT**

The patient goes to the emergency department to present increased of normal dyspnoea until it became rest, with low diuresis of several days of evolution and moderate worsening renal function. After starting treatment with 1 gr. Furosemide, diuresis of 600 ml is achieved in 6 hours and is improved respiratory dynamics. Is decided hospital admission to treat and monitoring clinical picture compatible with cardiorenal syndrome is decided.

During hospitalization, heart failure partially improves after starting treatment with diuretics in high doses. However persists orthopnoea and dyspnoea at rest.

In addition, it has a chronic kidney graft failure, with clearance rates around 15 ml/min, that in the context of persistent heart failure restart indication represents renal replacement therapy by hemodialysis. Right jugular central venous catheter placed the hassle and hemodialysis begins with polyethersulfone filter (BLS 517) Getting Started decreasing doses of Tacrolimus.

At the beginning dialysis patient has a clinical picture that starts when is connected and with great general malaise, sudden hypotensin (60/20), loss of consciousness, desaturation (O₂ saturation of 65%), bronchospasm even stop respiratory which requires cardiopulmonary resuscitation. In principle we attribute the clinical picture to serious cardiovascular problems described above.

In the next dialysis the episode is repeated with the same features and in both cases, once the patient is revived and hand stable blood pressure, you can continue the dialysis session without complications.
Suspecting a hypersensitivity reaction to the dialysis membrane polyethersulfone we changed the dialyzer, a helixone (FX 60 Classix). The clinical picture is repeated with the same characteristics, we decided to change to a cellulose triacetate dialyzer (1.9 Sureflux Nipro). From that moment, the patient doesn’t to suffer any similar episode.

**DISCUSSION**

Patients with allergic diathesis and eosinophilie appear to be predisposed to such reactions, our patient had eosinophilie 8.5 % without leukocytosis (7,300/ mm3), once the synthetic dialyzer replaced by cellulose triacetate the patient had normal levels 4,5%.

Until recently it was thought that hypersensitivity reactions were rare four cases per 100.000 dialysis, but lately it has been found that the frequency It may be much higher [2].

Our patient has all the characteristics of a reaction type A for having presented at the very beginning of dialysis, after contact of blood with the dialyzer, and the symptoms, hypotension, desaturation, unconsciousness, respiratory arrest and could he has caused the death.

Suspecting hypersensitivity reaction we should stop the blood pump and totally discard the blood circuit, administer high-flow oxygen therapy, antihistamines and corticosteroids of short-acting and if is necessary artificial respiration. Our patient was recovered and hadn’t complications during hemodialysis.

The important fact is that just happens in other publications [1] the patient was not present other episode since the cellulose triacetate was used.

Cellulose triacetate dialyzer behaves as a high permeability, with reduced ability to activate complement and great biocompatibility.

**CONCLUSIONS**

1. We report this case to help us to learn and make us conscious that we must be aware of the possible occurrence of hypersensitivity to dialysis membranes.

2. The cellulose triacetate dialyzer induces less hypersensitivity reactions and should be the option to choose to a hypersensitivity reaction to the membrane.

**REFERENCES**


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**PO-42**

**Track: Biosafety and Bio-ethics**

**AN ANALYSIS IN TROPICAL REGION (INDIA) FOR THE PRESENCE OF ANTIMONY IN CONSUMER PRODUCTS PACKED IN PET BOTTLES**

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PET stands for Polyethylene terephthalate a type of plastic widely used in the world for packaging water, soft drinks, medicines, cooking oil etc. The transparency and light weight of these bottles make them highly suitable for packaging liquids especially. Polyethylene terephthalate is produced from ethylene glycol and dimethyl terephthalate (C6H4(CO2CH3)) or terephthalic acid. The reaction in which PET bottles are produced Antimony (Sb) is used as a catalyst. Antimony (Sb) is a metalloid element that is used as a catalyst in the form of compounds such as antimony trioxide (Sb2O3) or antimony triacetate in the production of PET. After manufacturing, a detectable amount of antimony can be found on the surface of the product. This residue can be removed with washing. Antimony also remains in the material itself and can, thus, migrate out into food and drinks. Exposing PET to boiling or microwaving can increase the levels of antimony significantly, possibly above USEPA maximum contamination levels. Fruit juice concentrates (for which no guidelines are established), however, that were produced and bottled in PET in the UK were found to contain up to 44.7 µg/L of antimony, well above the EU limits for tap water of 5 µg/L. The analysis of presence of antimony in water and liquids has been
performed so far in temperate regions such as USA and UK. In a tropical country like India where the temperature is way above than in temperate regions more analysis and authentic data are not available. Hence our team went on analysing liquids in PET bottles that are being transported in open hot sun, stored for many days and different samples that were exposed to different temperature conditions. Our results have concluded that an immediate awareness regarding handling of PET bottles should be made for preventing people from consuming high level of antimony without knowing.

**PO-19**

**Track:** Pharmaceutical Biotechnology

**A STUDY ON DUAL CONSUMMATION IN EATING UP OF PLASTICS**

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Plastics are non-biodegradable wastes serving as a major cause for environmental pollution. A group of Japanese scientists Yoshida *et al* discovered in 2016 a strain of bacteria that degraded PET in 6 weeks duration. Polyethylene terephthalate (PET) is commonly used in making plastic bottles which has high aromatic content and hence chemically inert. Dr. Yoshida and his team screened 250 PET debris-contaminated environmental samples. The team identified a distinct microbial consortium Ideonella sakaiensis 201-F6 once cultured, was able to grow on PET and degraded it at a rate of 0.13mg per square cm each day at 30°C and using the newly identified bacteria, the team almost completely degraded a PET film in just six weeks. They identified one gene, ISF6_4831 that encodes a protein that shares half of its amino acids with another enzyme that hydrolyses PET and the area of similarity includes the parts of the enzyme that is used for catalytic breakdown of PET. They named it PETase and it was certainly efficient than conventional degrading enzymes. As an addition to this new innovation my study is mainly on antimony which is used as a catalyst in PET manufacture. When exposed to boiling or microwaving PET gives away antimony which is highly toxic to living beings especially when people use these bottles with hot liquids and discard them. The non-degradable antimony containing bottles pose a serious threat to under privileged people who may use those discarded bottles again and also stray dogs and other organisms coming in contact with this Sb containing wastes. This can be degraded by Variovorax paradoxus strain IDSBO-4 to a less toxic form by collecting these bottles after they are discarded. Hence PET bottles exposed to boiling or microwaving containing toxic Sb can be converted to less toxic form and then degraded efficiently using Ideonella sakaiensis. In this way of incorporation of my idea of antimony poison prevention along with the degradation of PET by Ideonella will be a more environmentally safe way of degrading PET plastic.

**Keywords:** PET, Ideonella sakaiensis, antimony (Sb), Variovorax paradoxus strain IDSBO-4.

**PO-25**

**Track:** Business Development

**BUILDING COMMERCIAL VALUE IN CHANGING TIMES**

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For the biotechnology industry, patents have played important roles in protecting innovation, in garnering investment and in generating licensing and partnering revenues. Major changes in patent law are having an impact on the value of these patents. In the United States, the Leahy-Smith America Invents Act introduced numerous changes to U.S. patent law including the switch to a first to file patent system and new post-issuance proceedings to challenge the grant of issued patents. Recent U.S. Supreme Court decisions have changed the threshold determination of patentability under 35 U.S.C. § 101, altering the patentability standards for biotech/pharma inventions, as well as computer/business method inventions. In Europe, the framework for...
an emerging unitary patent system and Unified Patent Court, expected to be implemented in the next year or two, will add complexity to strategic patent planning for that region. The creation of these additional venues in the U.S. and Europe for challenging patents can be expected to affect the commercial value of the patents and potentially place downward pricing pressure on valuations and royalty rates. Strategies on how to build value during these turbulent times for cutting edge innovations will be presented.

**PO-14**  
**Track:** Pharmaceutical Biotechnology

**THE USE OF TWO MAMMALIAN EXPRESSION SYSTEMS FOR RAPID PRODUCTION AND SCREENING OF RECOMBINANT PROTEINS FOR VACCINE PRODUCTION**

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Genetic engineering can be used for the development of effective and safer vaccines for the control and eradication of zoonotic diseases, benefitting human and animal health. Brucellosis is a leading zoonotic disease, mainly in developing countries, with no vaccines yet available for humans. In this study, two recombinant proteins from *Brucella abortus* (Omp16 and Omp19) were produced either in bacteria (*E. coli*), using standard recombinant DNA procedures, or in two distinct mammalian expression systems: (a) *in vitro* expression in a bovine mammary gland cell line (Mac-T) using a lentiviral vector, with Omp16 and Omp19 successfully expressed, individually or in a bicistronic DNA construction under a single promoter, with both *orf* linked by self-processing 2A peptide; and (b) transient *in vivo* expression in the milk of non-transgenic goats using adenoviral system, with Omp16 produced for six days. Proteins were purified from the three systems and are currently in use for immunogenic and challenge assay tests in mice, separately and in combination, to assess their potential for vaccine development. If proven effective, transgenic cows will be produced for the production of the proteins in the milk for purification and development of a new low cost recombinant brucellosis vaccine.

**PO-13**  
**Track:** Plant and Environment

**NATURAL WOODWARDITE AND SYNTHETIC ANALOGUE FOR REE RECOVERY FROM WASTE MATERIALS**

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At the Libiola mine site, an abandoned Cu-Fe sulphide mine located near Sestri Levante (Genova-Italy), the formation of greenish-blue colloidal precipitates takes place as a consequence of Neutral Mine Drainage processes (NMD) (Fig. 1). This process involves the oxidation of sulphides to generate acidic, metal-rich solutions, then buffered by surrounding ophiolitic rocks and/or diluted by alkaline stream water to near neutral conditions (6.6-7.8 and Eh=230.5 mV). In woodwardite ([Cu₁₋ₓAlₓ](OH)₂(SO₄)ₓ·nH₂O] (structure in Fig. 1) occurring in the natural precipitates, a high concentration of REEs (up to 600 mg kg⁻¹ of Y and 200 mg kg⁻¹ of Ce and Nd) had been observed, making this mineral an interesting material to recover REEs from organic and inorganic wastes (e.g. electric and electronic waste, the red mud resulting from industrial aluminium production). The structure of woodwardite can host REEs in different ways, both in inorganic and organic compounds, affecting the method used to recover REEs. Just
for this purpose, the study of the relationships between REEs and woodwardite are of particular importance to use these minerals as REEs getter for both georemediation and georecovery exploitation (Fig. 2). In this work we describe the synthesis using a) $Y^{3+}$ and $Ce^{3+}$ doped woodwardite and b) different waste material containing REEs as reactants.

**Fig. (1).** Woodwardite crystal structure.

**Keywords:** REEs recovery, woodwardite.

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**PO-7**

**Track:** Pharmaceutical Biotechnology

**MICROBIAL BIOFILM BASED FIXED BED BIOREACTOR INVOLVED IN SIMULTANEOUS SEQUESTRATION OF NITRATE & PHOSPHATE FROM WASTEWATER**

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Fresh water is precious and its reserves are getting depleted at an alarming rate. 80% of the fresh water drained every day is used for non-potable application like agriculture. Along with it is used a lot of nitrate and phosphate containing fertilizers to enhance crop yield to meet the requirements of the ever increasing population considering the decreasing availability of cultivable land. Unfortunately only 12 to 30% of the applied fertilizer is used while the rest is lost in agricultural runoff. Nitrate production is an energy intense process while phosphate fertilizer is prepared using rock phosphate whose reserves are limited. Hence the need of the hour is to develop a strategy which would involve rapid sequestration of the plant growth nutrients from the waste water while treating the later to make it suitable for non-potable applications like agriculture and aquaculture. Microbial consortium have been developed for simultaneous sequestration of nitrate and phosphate from waste water. The consortium has been immobilized on a fixed bed.

Biofilm based fixed bed anoxic bioreactor maintained at ambient temperature was acclimatized in wastewater in presence of 0.05% citric acid as the carbon source for simultaneous sequestration of nitrate and phosphate using a combination of three Bacillus strains. The reactor operated for 212 days in batch mode with a maximum of 94% nitrate and 68% phosphate reduction with associated Chemical Oxygen Demand (COD), Biochemical Oxygen Demand (BOD) and Total Organic Carbon (TOC) reduction of 93%, 97% and 73% respectively at a retention time of 2 hours (h) where the initial concentration of nitrate was 345 ppm and that of phosphate was 42 ppm. The pH of the effluent was in the range of 6.8 ± 0.02. Analysis of the gaseous and liquid components of the system during operation revealed maximum accumulation of the nitrate within the biofilm which gets assimilated whereas the reduced phosphate accumulated within the biofilm in the form of polyphosphates. Response Surface Methodology (RSM) was employed to determine the optimal flow rate, nitrate and phosphate concentration which was found to be 1.97 L/h, 306.04 ppm and 19.62 ppm respectively (Fig. 1). The system was scaled up from 4.5 L to 75 L with a consistent performance. The treated
wastewater met criterion to be reused for non-potable applications like irrigation and aquaculture. Hence this is to the best of our knowledge the fastest waste water treatment system and the technology has been filed as an Indian patent, a Bangladesh patent and a PCT.

![Diagram a](image1)

![Diagram b](image2)

![Diagram c](image3)

![Diagram d](image4)

Fig. (1). Three dimensional response contour curves generated using Minitab 15 software for determining the optimum levels of the independent variables (initial nitrate and phosphate concentration; flow rate) and major interaction effects.

**PO-54**

**Track: Pharmaceutical Biotechnology**

**DIMETHOXYFLAVONE ISOLATED FROM THE STEM BARK OF STEREOBPERMUM KUNTHIANUM POSSESSES ANTIDIARRHOEAL ACTIVITY IN RODENTS**

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**Objectives:** This study was undertaken to evaluate the antidiarrhoeal activity of 3, 7, 4/-trihydroxy-3/-8/-acetoxy-7/-methyloctyl)-5, 6-dimethoxyflavone, a flavonoid isolated from the stem bark of Stereospermum kunthianum.

**Methods:** The antidiarrhoeal activity was evaluated using rodent models with diarrhoea. The normal intestinal transit, castor oil-induced intestinal transit and castor oil-induced diarrhoea tests in mice as well as castor oil-induced intestinal fluid accumulation in rats were employed in the study. The animals were pretreated with distilled water (10 ml/kg for
mice, 5 ml/kg for rats), dimethoxyflavone (25 mg/kg or 50 mg/kg), morphine (10 mg/kg), or indomethacin (10 mg/kg) before induction of diarrhoea with castor oil (0.2 ml for mice and 2 ml for rats).

**Results:** Dimethoxyflavone dose dependently and significantly reduced ($P<0.05$) castor oil-induced intestinal motility. Its antimotility effect at the dose of 50 mg/kg was higher compared to that of morphine (10 mg/kg). Dimethoxyflavone (25 mg/kg and 50 mg/kg) caused a delay in the onset of diarrhoea, reduction in the number and weight of wet stools and total stools in mice with castor oil-induced diarrhoea compared to the distilled water treated mice. Treatment with dimethoxyflavone (25 mg/kg or 50 mg/kg) did not produce any remarkable effect on castor oil-induced intestinal fluid accumulation in rats and normal intestinal transit in mice. The results indicate that dimethoxyflavone possesses antidiarrhoeal activity due to its intestinal antimotility effect and inhibition of other diarrhoeal pathophysiological processes.

**Conclusion:** Our results taken together indicate that dimethoxyflavone isolated from Stereospermum kunthianum stem bark reduced the frequency and severity of diarrhoea in the diarrhoeal models studied.

**PO-34**

**Track:** Pharmaceutical Biotechnology

**ANDROGRAPHOLIDE DERIVATIVE ADN-9 INHIBITS ANGIOGENESIS VIA ATTENUATING THE VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND ITS RECEPTOR (VEGFR2) SIGNALING PATHWAY**

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Tumor growth depends on angiogenesis and inducing angiogenesis is one of the most important hallmarks in the cancer development. The vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) have been shown to play major roles in cancer angiogenesis. Recently, andrographolide (AD), a major active diterpenoid lactone of Andrographis paniculata, has been reported to be an interesting pharmacophore with anti-cancer activity. In the present work, the anti-angiogenic effect of ADN-9, a novel andrographolide derivative designed and synthesized by our group, was explored by human umbilical vein endothelial cells (HUVEC) and the chick embryo chorioallantoic membrane (CAM) model. In HUVEC, ADN-9 dose-dependently inhibited the cell migration in two and three-dimensions, as well as the formation of three-dimensional tubular structure. While treated with ADN-9 at 5.0μmol/l, the cell migrations were inhibited 60.16% (two-dimensional migration) and 57.04% (three-dimensional migration), respectively, remarkably higher than those of AD. Similar to AD, ADN-9 significantly decreased the number of new blood vessel branches in the CAM, from 79.50± 21.05 (drug-untreated) to 36.30± 20.29 at 5.0μmol/l. Furthermore, we observed that the protein expression level of VEGF in HUVEC treated with ADN-9 at 5.0μmol/l was greatly lower than that of AD at the same concentration, and the activation of STAT3 and NF-κB, as well as the p-VEGFR2 and the p-AKT-1 in HUVEC induced by VEGF (10ng/mL) were significantly attenuated. Given those results, the better anti-angiogenesis effect, caused by ADN-9 than that of AD, probably associated with the inhibitions of VEGF expression, the attenuation of VEGF/VEGFR2 signaling pathway and inactivation of transcription factors STAT3 and NF-κB.

**Keywords:** Andrographolide; Angiogenesis; VEGF/VEGFR2.
PO-37

**Track:** Food Science

**FEED AN INDIVIDUAL, FEED A HOUSEHOLD AND FEED A COMMUNITY: THE USE OF SOY-EXTRUSION COOKING TO SOURCE THE DISADVANTAGED IN SOUTH AFRICA**

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The link to nutrition, well-being and health is food. However, this important source needed to sustain life is compromised due to food shortage, insecurity and inaccessibility. In South Africa, a substantial part of the population is rural and low-income households, thus poverty and insufficient income are major driving forces to securing food. In an attempt to address this issue the Centre of Sustainable Livelihoods (CSL) developed a Soy Research Laboratory. Soy is the choice of food as it packs a nutritional punch consisting of essential amino acids, fibre, vitamins and minerals. Additionally, soy has been linked to alleviating cholesterol and reducing the risk of cardiovascular diseases, cancer and osteoporosis. The prospective research by CSL involves soy-extrusion cooking. A twin-screw extruder machine, designed and manufactured by CFAM Technologies (Pty) Ltd. will serve as the pilot-scale plant for the experimenting of soy protein concentrates blended with commercial meat products to improve its nutritional profile. The work to be presented will include the plant commissioning and optimisation of the plant by testing nutritional quality of soy-meat blends under varied process control parameters. The overall goals of the research are: for CSL to be a production facility that continuously supplies food to local, disadvantaged communities; to create a desirable food product and a reliable production method; to enhance soy research; and to promote extrusion cooking in South Africa.

**Keywords:** Nutrition, soy, extrusion.

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PO-22

**Track:** Pharmaceutical Biotechnology

**ON THE MECHANISMS OF HORMONAL RESISTANCE AND LOSS OF RHYTHMIC ACTIVITY IN RAT AORTA UNDER THE DEVELOPMENT OF OBESITY AND TYPE 2 DIABETES**

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Endogenous rhythmic activity (RA), induced by hormones and neurotransmitters in non excitable cells (liver, pancreas, endothelial and smooth muscle cells, adipocytes, etc.), may be considered as a marker of dynamic activity and self-control of various signaling systems and functional state of corresponding organs and tissues. This RA is affected by the process: Obesity -Metabolic Syndrome (Insulin resistance, Hypertension) - Type 2 Diabetes (T2D). In comparative experiments performed on aorta rings from control (standard chow) and T2D rats (high-fat fed, 32-40 weeks) it was shown, that fast (sec) and slow (min) rhythmic contractions induced by phenylephrine and acetylcholine (Ach) and rings relaxation produced by Ach, are disappeared in T2D rats. Similar loss of RA (registered as Ca++ - oscillations), combined with the development of broad hormonal signaling resistance (HSR), was observed on cultured white adipocytes of T2D mice (Turovsky et al., 2012; Turovsky et al., in preparation). All this may indicate on universal background mechanisms. Preliminary results show, that in the liver and adipose tissue of T2D mice may be observed substantial and qualitatively similar changes in the profiles of RNA expressions of the proteins of two Ca++ -signaling systems (with positive feedback) involving: PLC/IP3/IP3R/ Ca++ and PI3K/PKB/eNOS/PKG/CD38/cADPribose/RyR/ Ca++ signaling loops. These changes in expression might account for observed loss of RA and development of HSR. Low intensity 6 week treadmill training of obese and T2D mice, combined with animals treatment by hepatoprotector «Helper-1» (Pat. RU № 2491062), may
diminish HSR, lower plasma glucose and insulin levels, improve lipids profile and reduce risk of single daily exercise bouts.

**PO-21**

*Track: Pharmaceutical Biotechnology*

**APPROACHES TO MODULATE THE HETEROPLASMY LEVEL OF PATHOGENIC MUTATIONS IN THE MITOCHONDRIAL DNA**

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Mitochondria are essential organelles of almost all eukaryotic cells and take part in several critical cellular processes; the most important one is providing the cell with energy in the form of ATP. Mitochondria contain their own genome (mtDNA) and import from the cytoplasm all the proteins required for its replication, transcription and translation, as well as several non-coding RNAs. It has been suggested that ncmtRNAs contribute to the crosstalk between the mitochondrial and nuclear genomes. For instance, cytosolic 5S ribosomal RNA is imported into mammalian mitochondria, but has not been detected in the mitochondrial ribosomes, indicating on its possible regulatory function.

MtDNA mutations are responsible for a broad variety of syndromes, such as mitochondrial encephalomyopathies. Most of the pathogenic mutations in human mitochondrial DNA are heteroplasmic and their phenotypic expression is intimately linked to the ratio between mutant mitochondrial DNA and wild-type one. Thus, modulating the heteroplasmy level appears as a potential therapeutic approach. Our team has developed an anti-replicative strategy, which consists in targeting mitochondria with recombinant RNA molecules containing sequences able to specifically anneal with the mutant mitochondrial DNA and interfere with its replication. We designed RNA vectors, containing the mitochondrial import determinants identified in human 5S rRNA structure, allowing us to address into the organelle the anti-replicative oligonucleotides. Applying our strategy to a large deletion in mtDNA, we created cybrid cell lines bearing recombinant 5S rRNA genes and demonstrated a stable decrease of the heteroplasmy level, dependent on the conditions of cells cultivation.

Another way to decrease the heteroplasmy level could be a selective degradation of mutant mtDNA molecules by a mitochondrially addressed CRISPR-Cas system. Using various import determinants, we succeeded to import into human mitochondria specific guide RNAs and nuclease Cas9. Moreover, we demonstrated that the recombinant CRISPR-Cas9 complex can specifically cleave the mutant mtDNA *in vitro*. Optimization of this system for *in vivo* application is now in progress.

The work was supported by Labex ANR-11-LABX-0057_MitoCross.

**PO-16**

*Track: Pharmaceutical Biotechnology*

**NIGERIAN PLANT RESOURCES; AN INCREDIBLE RESPONSIBILITY FOR ALLEVIATING FOOD INSECURITY AND MALNUTRITION**

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Food insecurity and malnutrition is a serious concern in Africa and other parts of the world impacting heavily on health, socio-economy and well-being of the population. Plant resources of a region represent heritable materials, which are of economic, scientific or societal value to humankind. They form an integral part of a huge inter-dependent system that encompasses the physical components and the biological community of life. Nigeria is a physically and climatically
diverse country that is endowed with substantial amount of plant resources. There are about 7, 895 indigenous plant species from over 338 families and 2, 215 genera that have been identified in the country with a number of them demonstrating potential in alleviating food security, hunger and malnutrition. Both the physical and the climatic diversity of Nigeria permit the growth of a wide variety of such plants. This paper discusses those plant resources in Nigeria as nature's incredible generosity with potential in alleviating food security, hunger and malnutrition. It also highlights the responsibility of harnessing them for future development and food security and safety.

**Keywords:** Plant resources, heritable materials, physical and climatic diversity, food security, hunger and malnutrition.

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**PO-48**

*Track: Pharmaceutical Biotechnology*

**PREPARATION AND CHARACTERIZATION OF A NANOCOMPOSITE MATERIAL THAT CAN BE USED FOR BONE REGENERATION PROCESS**

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In this study, a biopolymer-based nanocomposite was developed that can be used for bone regeneration process. This nanocomposite composed of two components that are; montmorillonite (MMT) as reinforcement and chitosan as matrix. Considering the positive effect of cations on bone regeneration, MMT was selected because of its quite high cation exchange capacity. MMT was saturated with different cations and different composites were prepared by solution intercalation method. Three groups of reinforcements were prepared by saturating MMT only with Al+3 for the first set of composite, with Sr+2 for the second set and by saturating Al+3 pillared MMT with Sr+2 for the third set of composite. After preparing the reinforcements, the suspensions of them with pure water were combined with chitosan solution that was prepared in dilute acetic acid. The characteristic properties of the biocomposite materials were investigated by using ATR spectrums, SEM images and XRD patterns. Nanomechanical properties were studied by using nanoindentation method. The ATR spectra of biocomposite materials have peaks that belong to the characteristic peaks of MMT, chitosan, Al+3 and Sr+2 cations. These peaks indicated that biocomposites composed of MMT and chitosan, and also showed that MMT was saturated with Al+3 and Sr+2. SEM images showed a well distribution of MMT in the chitosan matrix. The peaks of biocomposites at XRD patterns appeared at lower 2θ values according to the characteristic peak of MMT, this may be caused by the intercalation of chitosan in a monolayer disposition. The results of nanoindentation method indicated that the second set of biocomposites, which was prepared using MMT saturated with Sr+2, has the highest elastic modulus and hardness values.

**Keywords:** Biomaterial, biocomposite, bone regeneration, nanocomposite, montmorillonite, chitosan.
PO-6

Track: Pharmaceutical Biotechnology

DNA BASED IDENTIFICATION OF A VALUABLE MEDICINAL PLANT LAWSONIA INNERMIS BY DEVELOPMENT OF SCAR MARKERS

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Plants constitute an effective source of traditional and modern medicinal industry. The substitution or adulteration of a medicinal plant with low quality or a plant with different therapeutic properties is a burning issue in herbal industry. The DNA based identification of medicinal plants is a reliable tool for quality assurance and safety evaluation of herbal products before use in herbal industry and future research. In the present study Random Amplified Polymorphic DNA (RAPD) derived Sequence Characterized Amplified Region (SCAR) marker has been developed for a potent medicinal plant Lawsonia innermis and its common adulterant Marabilis jalapa. Both of these plants have medicinal value but have different therapeutic effects. Using the developed SCAR markers, Lawsonia innermis can be identified easily from its adulterant Marabilis jalapa. This DNA based approach is efficient and cheap for authenticate identification of medicinal plants.

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PO-5

Track: Plant and Environment

IMPROVING THE AGROBACTERIAL ATTACHMENT TO MONOCOT CELLS USING A CELLULOSE FIBROUS NETWORK

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Agrobacterium tumefaciens is an important biotechnological tool that has been used extensively as a vector for genetic transformation of plants. Cereal crops, such as barley, are not the natural hosts for the Rhizobiaceae family and therefore recalcitrant for Agrobacterium-mediated transformation. Modification of transformation procedures is still necessary due to difficulties in the inoculation step towards the high production of transgenic plants. In this study, we have transformed barley tissues with LBA4404 strain with pPZP201-GFP-PMI plasmid in the presence of fibrous cellulose in the inoculation medium. Addition of cellulose increased the T-DNA transfer efficiency based on the number of GFP-expressing clusters on calli counted after 10 days of transformation. Increased attachment to callus tissue was also confirmed by a binding assay which revealed that 2-5 fold more bacteria stayed bound on the tissue after a sonication treatment. Cellulose fibrils collected the free bacteria in the medium observed by phase-contrast microscopy. Bacterial cell attachment and proliferation on cellulose fibrils were assessed using scanning electron microscopy. Average 40-120 bacteria attached to cellulose fibrils with 50µm in size were observed. The fibrous cellulose network may be used for large-scale monocot transformations by eliminating the genotype-dependency.

Keywords: Agrobacterium, barley, SEM.
**PO-33**

**Track:** Plant and Environment

**ROLE OF CYTOKININS AND AUXINS DURING IN - VITRO REGENERATION OF INDIAN PENNYWORT (CENTELLA ASIATICA LINN)**

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To meet the fast growing need of novel and innovative therapeutic drugs to treat various life-threatening or chronic diseases, research scientists and many pharmaceutical companies now-a-days are concentrating on the development of herbal formulations. Indian Pennywort (Centella asiatica Linn.) is a slender and creeping herb widely used as a brain tonic, memory booster and antioxidant. It also has various medicinal and therapeutic uses in indigenous medicines. It is conventionally propagated by portion of nodes usually about 1-1.5 cm long and is a time consuming laborious methods. On the contrary, in vitro regeneration of elite clones through micropropagation offers a rapid, contamination free and controlled large-scale production of C. asiatica. In our research, the in-vitro propagation of Indian Pennywort has been carried out using known procedures of plant tissue culture under specific conditions of inoculation, and incubation in Murashige and Skoogs (MS) medium. In general, Cytokinins are employed only for shoot induction and multiplication, and Auxins are used only for root formation. In this present study, the influence of Cytokinins and Auxins during the regeneration of C. asiatica was investigated. It was found that the single nodal segments were to be the best for direct regeneration of shoots of the Indian Pennywor t plant. Therefore, the shoot multiplication is a function of Cytokinin activity and Auxins may inhibit the activity of Cytokinins. Cytokinins has been reported to overcome apical dominance, release lateral buds from dormancy and promote shoot formation. The pharmaceutical companies can benefit using this micropropagation technique for large-scale production of Centella asiatica. L which might be screened for various phytochemicals extraction. This micropropagation methods will also help to further conservation and may offer a means to improve genetic variability of this important endangered medicinal plant.

**PO-28**

**Track:** Pharmaceutical Biotechnology

**SYSTEMS BIOLOGY - NEGATIVE-FEEDBACK-LOOP BASED MODEL TO SIMULATE THE PROCESSES IN LIVING ORGANISMS**

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Recognition of the strategy employed in living organism is the main object of research and main goal for systems biology. The multidisciplinary approach is necessary to cover the exponential growth in the volume of biological knowledge. Five fundamental concepts: 1. Structure and Function, 2. Energy, 3. Information, 4. Regulation and 5. Interrelationship are the basic components ensuring the automatic control present in every structural unit of the organism. The only system ensuring the automatically regulated processes in thermodynamically open system to maintain its steady state is the negative feedback loop. One negative feedback loop is used as the fundamental unit for proteome construction. Each negative feedback loop is responsible for stabilization of special component, concentration of which is expected to be stable. The communication system between structural-functional units (negative feedback loop) is mediated through: 1. receptor and 2. effector as targets for extra-cellular signaling. These two molecules of high specificity are responsible first one for: "What?" is stabilized and the second for "How?" it is reached. The first one is sensitive to signal inducing allosteric properties of receptor. The second one (based usually on the concentration-dependent signal transmission) makes the effector to be active independently on receptor-originated signal. The feed-back loop system based examples may be shown. The presentation based on: Konieczny L, Roterman I, Spolnik P. Systems Biology - Functional Strategies of Living Organisms - Springer, New York, Heidelberg, Dordrecht, and London 2014.
Keywords: Multiple Myeloma, acute renal failure, dialysis High Cut Off filters.

PO-10
Track: Industrial and Manufacturing

A GOAL PROGRAMMING APPROACH FOR AN ADVANCED-REMANUFACTURING-TO-ORDER-DISASSEMBLY-TO-ORDER SYSTEM IN MULTIPLE PERIODS

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Electronic products with newer technologies are continuously being introduced in the market and in order to keep up with the technology, consumers constantly upgrade their products. This forces the products to reach their End-Of-Life (EOL) sooner. Therefore, even though a product is in good condition, its disposal is inevitable. Government has enforced strict rules and regulations in order to protect the environment from such hazardous waste. In order to comply with the rules Original Equipment Manufacturers (OEMs) implement product recovery techniques such as recycling and remanufacturing.

This paper considers an Advanced-Remanufacturing-To-Order-Disassembly-To-Order system which receives EOL products with design alternatives. The quality of the EOL products received is unknown which leads to inexact disassembly yields. The uncertainties about the quality of EOL products also make it difficult to identify the exact number of EOL products needed for disassembly in order to fulfill all the demands. The main objective is to determine the number of EOL products to be acquired such that it satisfies products, components and materials demands. A goal programming approach is considered to formulate and solve this multi-criteria decision making problem. An example is presented to illustrate the use of this methodology.

Keywords: Disassembly, goal programming, stochastic yields, remanufacturing.

PO-36
Track: Pharmaceutical Biotechnology

POTENTIAL OF CARVACROL AGAINST UROPATHOGENIC ESBL ESCHERICHIA COLI

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The antibiotic resistance among extended-spectrum β-lactamase (ESBL)-producing E. coli has increased drastically in recent years. ESBL E. coli belongs to Gram negative Enterobacteriaceae family, possessing enzymes which confer resistance to most of the β-lactam ring antibiotics. The ESBL are easy to transmit from mother to newborn baby, and difficult to treat as it is multi-drug resistant microbe. In our study, we have determined the mechanism of action of carvacrol against ESBL E. coli isolated from ascitic fluid of UTI patient. Carvacrol has MIC at 450 ug/ml and found to be reduced CFU counts in time-dependent manner. After treatment with carvacrol, E. coli killing time was found to be at 2 h. Furthermore, the carvacrol has potential to disrupt the cell membrane, release cellular contents 260 nm absorbing matter and proteins from E. coli. Moreover, carvacrol has ability to inhibit motility and exhibit invasion protection in HCT-116 cells. Carvacrol has ability to reduced oxidative stress (NO), in E. coli infected-macrophages. Therefore, carvacrol acts as a potential antimicrobial agent against ESBL E. coli.
MATERIAL ANALYSIS OF DISASSEMBLY PARTS SELECTION FOR CO₂ SAVING RATE AND RECYCLING COSTS BY GOAL PROGRAMMING

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Global warming and material starvation have been recognized as serious global issues, and they have been just addressed at G7 held in Ise-Shima in Japan. In order to reduce CO₂ emissions and to promote material circulation simultaneously, recycling for assembly products is one of effective ways to improve both of CO₂ saving and recycling rates. One of the reasons is that natural resources extracted from the earth can be saved for producing new materials. However, the recycling costs tend to be higher caused by higher labor costs due to complicated disassembly tasks. To establish a circular economy at recycling, a disassembly parts selection is often carried out. In there, each part should be disassembled manually for the recycling or destroyed for a disposal, while CO₂ volumes for each part depend on types of materials and weights.

This study focusses end-of-life products and presents bi-objective disassembly parts selection for the CO₂ saving rate and recycling costs by goal programming toward the circular economy. First, CO₂ saving rate for each part is estimated based on Life Cycle Inventory database. Next, the environmentally friendly and economical disassembly parts selections by goal programming are formulated. Finally, the results are discussed for materials types.

Keywords: Environmentally conscious manufacturing, circular economy, end-of-life assembly products, life cycle inventory database, recyclability evaluation method.

DEVELOPMENT OF ECO-FRIENDLY FUNCTIONAL COMPOST USING SPENT COFFEE GROUND, BIOCHAR AND BENEFICIAL MICROORGANISMS

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Spent coffee ground, chicken manure, and agricultural waste-derived biochar were used to manufacture a functional compost by bioaugmentation of beneficial microorganisms. Four pilot scale composting reactors were established to perform the composting for 45 days. NH₄⁺, NO₃⁻ and PO₄³⁻ significantly increased in the augmented composts passing the official compost quality standard. Moreover, germination indices for radish also increased by 14% and 34% for the augmented composts without (Tr-2) and with (Tr-3) amendment of biochar, respectively, indicating the composts are mature and biochar amendment could stimulate germination. Pepper growth tests have shown that the composts (Tr-2 and Tr-3) stimulated leaf length growth by 56% and 16%, respectively. Tr-2 also enhanced DPPH scavenging activity in leaves by 115% while Tr-2 and Tr-3 enhanced total phenolic content (TPC) by 43% and 40%, respectively. Moreover, the composts Tr-2 and Tr-3 boosted DPPH scavenging activity in leek by 41% and 17%, respectively, and Tr-3 increased TPC by 86%. This implies that composting facilitated by the microbial agent could shorten the composting time and produce a quality functional compost that could better compete with the commercially available fertilizers, and render an eco-friendly recycling of organic wastes such as spent coffee ground, chicken manure, and agricultural wastes.

Keywords: Spent coffee ground, biochar, beneficial microorganisms, composting, and antioxidant.
PO-31
Track: Pharmaceutical Biotechnology

FERMENTATION STRATEGIES FOR THE PRODUCTION OF HUMAN ENTEROKINASE IN PICHIA PASTORIS

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Enterokinase (EC 3.4.21.9) is a type II transmembrane serine protease composed of one disulfide-linked heavy-chain of 82-140 kDa that anchors enterokinase in the intestinal membrane and one light-chain of 35–62 kDa that contains the catalytic subunit. As physiological activator enterokinase recognizes the sequence DDDDK↓X of trypsinogen with high selectivity and turns it into active trypsin by removing N-terminal peptide following (Asp) 4Lys without any additional unwanted amino acids. Specifically light chain, which represents the catalytic domain, is widely utilized in biotechnology, in the cleavage of affinity tags or fusion protein from target recombinant protein with high efficiency to cut after recognition sequence and separate target protein from artificial fusion tags. Microgram quantities of enterokinase may enable the purification of sufficient amounts of target protein for functional studies and thus, enterokinase is regarded as an ideal enzyme to prepare target protein by sequence specific cleavage.

Recently, the constitutive promoter of glyceraldehyde-3-phosphate dehydrogenase gene, GAP, has become widely used as alternative promoter for constitutive expression of recombinant proteins, which do not inhibit or is not toxic for growth. In this works several fermentation strategies were assayed for production of human enterokinase in Pichia pastoris under just mentioned GAP promoter. Two of them with controlled specific growth rate during whole cultivation showed very low enterokinase activity of the fermentation medium. On the contrary, the combined fermentation with maximum specific growth rate at the initial phase of the fermentation and stationary-like phase during the rest of the fermentation showed significant accumulation of the enterokinase in the medium and notable higher activity compared to other strategies. Lower cultivation temperature had negative impact on enzyme accumulation during this fermentation strategy.

This research was supported by the Slovak Research and Development Agency under the contract no. APVV-0119-12.

Keywords: Pichia pastoris, human enterokinase, fermentation.

PO-20
Track: Pharmaceutical Biotechnology

INNOVATION IN THE USE OF AMITRIPTYLINE FOR PAIN TREATMENT BY COMBINATION WITH OMEGA-3 FATTY ACIDS

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Combination therapy is often used to increase the clinical utility of analgesic agents. The co-administration of two compounds may achieve analgesia at doses lower than those required for either compound alone, leading to enhanced pain relief and a reduction in adverse effects.

A tricyclic antidepressant, such as amitriptyline, is often used to treat many types of persistent pain, with their efficacy in this regard being well established. These conditions include diabetic neuropathy, postherpetic neuralgia, headache, arthritis, and chronic back pain.

The disadvantages of using amitriptyline include side effects such as cardiovascular problems (e.g., hypertension, postural hypotension and arrhythmias), drowsiness, dry mouth, nausea, changes in body weight and constipation.
The aim of this study was to examine in rats the antinociceptive effect of omega-3 fatty acids alone as well as in combined chronic treatments with amitriptyline (AMI) in the hot plate test.

We found that compared to control, omega-3 fatty acids dose-dependently increased the latency time, indicative of an antinociceptive effect, with the co-administration of AMI (20 mg/kg/day) and omega-3 fatty acids (0.72 g/kg/day) revealing a higher antinociceptive efficacy than the individual treatments.

The combination of omega-3 fatty acids with amitriptyline might produce better analgesia, thereby increasing the efficacy of pain management and reducing side effects through the use of a smaller dose of antidepressant.

PO-18
Track: Pharmaceutical Biotechnology

IN VIVO INHIBITION OF THE SIZE OF LUNG TUMOR OF NUDE MICE BY DC-CIK CELLS

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Objective: To study the dendritic cells with induced killer cells develop lung cancer stem cell inhibitory effect on a tumor-burdened nude mice, a preliminary study of the method of lung cancer.

Methods: From healthy human peripheral blood mononuclear cells successfully induce DC and CIK cells, CIK cells and DC cells 10:1 proportion mixing cultured 6 days for DC-CIK cells, flow cytometry instrument for measuring DC-CIK cells phenotypic changes, and lung cancer cell line A549 nude mouse model to observe the DC - CIK in vivo antitumor effect.

Result: Culturing 12 day DC-CIK cells compared with CIK cell culture group alone, proliferation rate (18.0±1.1) vs. (9.9±1.2) times, P< 0.05; The expression levels of CD3 + CD56 + increase obviously.

Conclusion: DC, CIK cells which can make the CIK cells to produce more proliferation activity and better role in tumor suppression.

Keywords: Co-culture, DC-CIK cells, tumor bearing mice, lung tumor.

PO-4
Track: Nanobiotechnology

DIAGNOSIS AND THERAPY OF LIVER CANCER CELLS BASED ON THE NEAR INFRARED NANOCARRIER TARGETED TO GPC-3

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Background: The expression of Glypican-3 (GPC-3) acts as the high specificity and sensitivity for the early diagnosis and treatment of hepatocellular carcinoma (HCC). As the ideal fluorescent probe, quantum dots (QDs) are widely studied in the field of detection and therapy for disease.

Methods: Novel core/shell CdSe/ZnS QDs is synthesized. Then the targeted nanocarrier coupled with the antibody GC33 and drug molecules celastrol on the surface of CdSe/ZnS QDs is prepared. The accurate therapy and dynamic labelling for liver cancer cells is studied based on the QDs marking and imaging targeted to GPC-3.
Results: This CdSe/ZnS QDs show the excellent and stable fluorescence in the visible and near infrared region, and have the low cytotoxicity (IC50 2.08 μM) in vitro with the dose-dependent and time-dependent manner. The targeted nanocarrier based on CdSe/ZnS QDs have the higher drug loading capacity with the loading efficiency 19.58±4.1% and encapsulation efficiency 78.51±4.6% in vitro, and show the pH sensitivity for celastrol release. These nanocarriers considerably enhance the cytotoxicity of CSL for liver cancer cells. Also liver cancer cells can be fluorescently labelled and imaged by this targeted nanocarrier.

Conclusion: This nanocarrier targeted to GPC-3 can be used for the early diagnosis and treatment of hepatocellular carcinoma.

PO-26

Track: Pharmaceutical Biotechnology

TWELVE PATIENTS TREATED WITH HCO FILTERS FOR ACUTE RENAL FAILURE SECONDARY TO MULTIPLE MYELOMA

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Introduction: Multiple Myeloma is a hematologic tumor that is characterized by uncontrolled proliferation of plasma cells and a significant amount of free chains in serum (FLCs), which can cause acute renal failure for intratubular precipitation of them, causing cast nephropathy.

Acute renal failure (ARF) is a complication that can happen in more than 20% of patients with multiple myeloma (MM) and one half of them require dialysis.

Treatments of Multiple Myeloma with high cut-off (HCO) filters were started in 2007

Methods: We report our experience with twelve patients (13 treatments) who were treated with dialysis using high cut off filter (HCO) during the period between July 2011 and February 2015.

Dialysis protocol: Dialysis treatments took place daily for six sessions, and later proceeded to happen every other day until levels of free light chains (FLCs) in blood were reduced to less than 500 mg/L or the recovery of renal functions allowed them to dispense with dialysis.

The duration of dialysis was six hours with a low blood flow between 250 and 300 ml/min, bath fluid flow 500 ml/min

Results: A total of 151 sessions were made, with an average of 11.6 sessions per patient (6-27 range).

The treatment proved to be effective in removing both Kappa and Lambda FLCs. At the end of the treatment, there was a FLCs decrease of 93.7 %. The average reduction was 57.7 % per dialysis session. In 10 out of 13 cases recovered sufficient renal function to become independent of dialysis.

There were no major changes in levels of albumin using a protocol infusion with 2 vials of 50 ml of 20% albumin at the end of dialysis session.

Discussion: The myeloma kidney treatment is oriented to reducing the exposure of the kidney to the FLCs. This is managed by acting on the Multiple Myeloma through chemotherapy treatment (dexamethasone, bortezomid, ciclophosphamide, etc.) to reduce its production, at the same time that are used as adjuvant treatment techniques of extracorporeal depuration to eliminate them.

The recovery of the renal function will depend not only on the reduction of the circulating FLCs, but also of the speed in which we can achieve this reduction, as Hutchison published.

In our opinion and once we have examined the bibliography, the treatment modality in which we get the best results is hemodialysis (HD) with dialysis membranes of very high permeability high-cut-off (HCO), these membranes have a pore size between 45 and 60 KDa, and are designed specifically for the kidney of the myeloma, but they present some disadvantages like the high loss of albumin and an elevated cost.
Conclusions: Combination treatment with chemotherapy and long dialysis HCO filters was effective in reducing the level of FLCs at 77% of cases. With HCO filters significant cost savings are achieved, contrary to what was previously believed.

Keywords: Multiple Myeloma, acute renal failure, dialysis High Cut Off filters.

**PO-32**

**Track:** Pharmaceutical Biotechnology

**DISRUPTION OF MALTASE GENE AS A KEY FOR EXPLANATION PLOIDY IN YEAST CANDIDA UTILIS**

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Yeast Candida utilis has been demonstrated as potential system for production of recombinant proteins with biopharmaceutical and biotechnology application. In this yeast we would like to produce human proteins that will be expressed into the media. In the secretome of C. utilis were not be detected extracellular protease. In spite of the industrial importance and benefits of this system, the use of C. utilis for the expression of recombinant proteins is limited, especially due to its polyploidy. The aim of this research was to determinate of ploidy. This knowledge would contribute to the basic understanding of the life cycle of Candida utilis and it will be necessary to determine the number integrations of the expression cassette in the future expression system. We prepared the series of deletion mutants for disruption of maltase gene and regulatory regions. We used plasmid pΔglc which includes mutagenesis cassette containing two homologous recombinant regions and selectable marker bordered by two loxP sites. When the copies of the maltase gene were disrupted, native allele still existed after the first disruption. The numbers of alleles of maltose gene we determined by multiplex PCR and qPCR. Deletion mutants and wild type strain were tested by activity of alpfa-glucosidase.

This research was supported by the Slovak Research and Development Agency under the contract No. APVV- 0119-12.

Keywords: Polyploidy, disruption of maltase gene, Candida utilis.

**PO-30**

**Track:** Plant and Environment

**CONTINUOUS MICROALGAE CULTIVATION IN TERTIARY WASTEWATER USING A MEMBRANE PHOTOBIOREACTOR**

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Microalgae account for over 60% of photosynthesis, and microalgal biomass is considered the most promising of sustainable feedstocks for biofuels production. Attempts to cultivate microalgae at large-scale have proved infructuous owing to high cost of cultivation and harvesting. One approach to reduce these costs is the use of urban wastewater and industrial flue gases as nutrient sources. This requires a photobioreactor system, which is able to cultivate microalgae under continuous operation at low hydraulic retention time (HRT).

In this research, a membrane photobioreactor (MPBR) has been designed and operated for microalgae cultivation in synthetic tertiary wastewater and flue gas. The strategy was to integrate a forward osmosis filtration unit with a conventional photobioreactor, such that the microalgae were completely retained in the MPBR under continuous
operation. The MPBR was operated for over two months wherein the effects of pH, HRT, nutrients concentrations and light/dark cycle on microalgae accumulation and nutrients removal were investigated. The MPBR exhibited nearly 100% nitrogen and phosphorus removal and accumulated large amount of biomass (> 2 g/L). Higher HRTs enhanced nutrients removal, whereas the performance deteriorated under light/dark cycle. These results indicate that the MPBR can be effective in high-throughput microalgae cultivation from wastewater and gases.

**PO-35**

**Track:** Pharmaceutical Biotechnology

**COMBINATION ANTIRETROVIRAL DRUG LOADED NANOPARTICLES: AN EFFICACIOUS NANO-DRUG DELIVERY SYSTEM FOR PREVENTION/TREATMENT OF HIV IN A HUMANIZED (HU-BLT) MOUSE MODEL**

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Combination Antiretroviral therapy (cART) has markedly improved the morbidity and mortality of Human Immunodeficiency Virus-1 (HIV-1) infected people. However, to enhance drug adherence once-daily dosing with a large drug dose (milligram) is been followed. This increases the risk of dose-limiting side effects. Even though effective, non-adherence can be a reason for accelerated HIV-1 resistance. Here nanotechnology can play a significant role to enhance combination antiretroviral drugs (cARVs) adherence.

The use of elvitegravir (EVG), tenofovir alafenamide fumurate (TAF) and emtricitabine (FTC) along with cobicistat is a new formulation that has recent been approved by FDA for oral therapy. To our knowledge, we are the first to report to formulate PLGA encapsulated cARV drugs (i.e. TAF+EVG+FTC) NPs for prevention/treatment of HIV in a humanized mouse model.

Nano-encapsulation of TAF+EVG and FTC resulted in nanoparticles (NPs) of <200 nm with entrapment efficiency ~40 and ~45% for each drug in the TAF+EVG NPs and ~62% entrapment for FTC NPs. Our study design was as follows, Hu-BLT mice (n=12) with functional human immune reconstitution were intra-vaginally infected with transmitted-founder viruses (WITO.c/2474 and SUMA.c/2821) at 2.5 x 10^5 TCID50 each. The treatment (Rx) mice (n=6) received 500 mg/kg cARV NPs (200 mg/kg each of TAF+EVG; 100 mg/kg FTC in 5% dextrose (D5W)) by subcutaneous (SubQ) injection starting 3 weeks after HIV-1 challenge. Four doses of cARV NPs were administrated over 6 weeks (dosed every alternate weeks). Control (Ctr) mice (n=6) received 2 mL D5W. From all mice blood was drawn for pVL analysis by qRT-PCR, every 2nd week (i.e. even week) for 10 weeks. However, every alternative week (i.e. odd week), blood was drawn for TAF+EVG+FTC trough drug levels and analyzed by LC-MS/MS.

The result shows, before the start of treatment with cARV, the baseline pVL averaged 1.2 x 10^4 + 5.3 x 10^4 copies/mL for Rx mice and 1.7 x 10^5 + 8.3 x 10^4 copies/mL for Ctr mice. At the end of the four doses, all Rx mice had non-detectable pVL (< 800 copies/mL) compared to Ctr mice 1.7 x 10^6 + 7.9 x 10^5 copies/mL, (p= 0.03). Till the end of the 10 week of study, a non-detectable viral load continued without re-dosing. Interestingly, all the three tested drug in the lymph node (known HIV reservoir) showed >90 ng/g tissue drug concentration even 3 weeks after last dosing.

In conclusion, it is evident that cARV NPs (SubQ injection) demonstrate sustained release efficacy in the humanized mice model of HIV-1. Our perception is that in near future nano-drug delivery system will reduce the drug adherence burden, cost and lengthen with dignity the life of HIV/Cancer patient.
**PO-3**

*Track: Pharmaceutical Biotechnology*

**SCREENING OF QUERCETIN CONTENT OF FRESH PINE BY USING RESPONSE SURFACE METHODOLOGY**

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Quercetin is one of the most studied types of flavonoids due to its anticancer, antiviral and antioxidant properties. It had been isolated from different type of plant materials; *e.g.* apples, berries, onions *etc.*. It was observed that all of the knowledge obtained from the literature based on the extraction of quercetin from nutrient-based plant materials. Thus, the aim of this study was chosen as quercetin extraction with methanol from a non-nutrient raw material, a fresh pine. To reach this aim, ultrasonic extraction parameters was optimized by using response surface methodology with Box- Behnken design. As a result of the reduced cubic model developed ($R^2=0.9999$), solid/liquid ratio was found as the most important parameter comparing to extraction time and temperature. It was found that from 20 mg quercetin could be extracted at the optimum conditions; *i.e.* extraction of 1g of pine at 35°C with 40 ml of methanol during 1 minute. As a conclusion, fresh pine might be a useful raw material for drug preparation of cancer since it has not any nutrient capacity.

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**PO-17**

*Track: Pharmaceutical Biotechnology*

**ANTIBACTERIAL EFFECT OF SYRIAN HONEYBEE (APIS MELLIFERA) VENOM ON DIFFERENT SPECIES OF BACTERIA**

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Venom collected from 12 Syrian honey bee hives (*Apis mellifera*) was examined for its inhibitory effect on different species of bacteria. Local bee venom in relatively lower concentrations showed nearly the same effect as purified venom purchased from Sigma. In this work, antibacterial activity of local bee venom proved to be concentration-dependent. It has an inhibitory bacteriostatic effect at low concentrations and exhibits a bactericidal activity at high concentrations. Our results revealed that gram positive bacteria, *e.g.* *Listeria monocytogenes*, and *Staphylococcus aureus*, were more sensitive to venom than the gram negative *e.g.* *E. coli*, *Salmonella enterica*, *Yersinia kristensenii*, *Klebsiella pneumoniae* and *Klebsiella oxytoca*. This antibacterial property of bee venom may be used for medical purposes and drug preparations, or by some modifications for food preservation.

**Keywords:** Antibacterial effect, bee venom.
PO-1
Track: Pharmaceutical Biotechnology

MICROFLUIDIC WET-DRY SPINNING OF WATER-SOLUBLE RECOMBINANT SPIDER SILK PROTEIN

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Spiders achieve superior silk fiber by controlling the molecular assembly of silk protein and the hierarchical structure of fiber. However, no recombinant spider silk fibers exhibit comparable mechanical properties as natural spider silks. On the one hand, it is difficult to keep recombinant spidroins soluble at high concentrations without the use of harsh solvents. On the other hand, the present wet-spinning process for recombinant spidroins has not sufficiently mimicked the natural spinning process. Here, water soluble recombinant spider dragline silk protein with low molecular weights (47 kDa) was synthesized by metabolically engineered Escherichia coli. Artificial spider silks were then continuously spun from the aqueous solutions of the spidroin by using microfluidic wet-dry spinning process. By mimicking the spinning apparatus of silkworm, we designed a microfluidic channel which is composed of shearing and elongational sections. The unique dry-spinning section after the wet-spinning section partially mimics the spinning process of natural spider silk and contributes greatly to the compact aggregation of microfibrils. The subsequent post-stretch further improves the crystalline orientation and mechanical properties of the fibers. The tensile strength and elongation of the post-treated fibers can reach up to 510 MPa and 15%.

Keywords: Recombinant spider protein, wet spinning, biomimetic, wide angle X-ray diffraction.

PO-41
Track: Medical Biotechnology

PRESERVATIVES USED IN EYE DROPS DOESN'T PRESERVE THE OCULAR SURFACE-A CLINICAL STUDY

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Medications are used to treat a disorder can we induce a disorder by using medications definitely not. My consumers the patients not only expects the treating doctor to be friendly but also prefers a user friendly gentle medications. Long term usage of topical eye drops results in deranged Ocular surface mechanism being allergic, toxic, or inflammatory, or interaction with the actual compound in ophthalmic solutions, is still being studied. Preservatives used in ophthalmic topical medications is of two categories: detergent and oxidizing preservatives and latest addition is ionic-buffered preservatives which acts similar to oxidizing preservative. Benzalkonium chloride a quaternary ammonium compound is most frequently used detergent preservative in concentration ranges from 0.004 to 0.02%. Stabilized oxychloro complex is an oxidizing preservative used at very low concentration of (0.005%), which has broad antimicrobial activity. Our study is to enlighten the toxic effects of BAK preserved eye drops with BAK free ophthalmic medications as a control group using SOC as a preservative. Clinically our study was based on 1) Patient history - burning sensation or stinging, grittiness 2) Schirmer's test to measure quantity of tear film 3) Tear film breakup time (TBUT) is the time required for the tear film to break up following a blink which is normally 15 to 20 seconds 4) Lissamine green stain helps in demonstrating disrupted ocular surface 5) Ocular surface disorder questionnaire.

Using these indices I justify using SOC preserved eye drops are definitively safe and ocular surface friendly which leads to good patient compliance and better visual quality.

Keywords: TBUT Tear break up time, BAK Benzly alkonium chloride.
**PO-8**

*Track: Pharmaceutical Biotechnology*

**MESENCHYMAL STEM CELLS FROM HUMAN DECIDUA REGULATE DECIDUAL NK CELLS FUNCTION**

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The aim of the present study was to identify the mesenchymal stem cells (MSCs) from human first-trimester decidua, here called decidual mesenchymal stem cells (DMSCs) and their regulation on decidual NK (dNK) cells through collagen. Decidual samples were collected from normal pregnancy undergoing elective vaginal surgical terminations of early pregnancy. DMSCs grew from human decidual tissues were cultured under differentiation conditions to detect their multipotent differentiation capacity and analyzed for specific markers. The coculture of dNK cells with DMSCs was established to determine the effect of DMSCs on the functions of dNK cells. The expression of cell surface molecule (NKP30 and KIR2DL1) and the secretion of cytokines (IFN-γ, TNF-α, IL-10, IL-4 and perforin) were examined by Flow cytometry (FCM). For demonstrating DMSCs’ regulation on dNK cells by collagen, pretreatment with human recombinant LAIR-2 and transfection of DMSCs with pScoR-GFP-hP4H were used to block the interaction of LAIR-1 with collagen.

In conclusion, we demonstrate that DMSCs can grow in vitro for prolonged periods with the ability to differentiate into different cell lineages. What’s more, DMSCs are proved to modulate the function of dNK cells through the collagen and LAIR-1 interaction.

**Keywords:** Mesenchymal stem cells, NK cells, Collagen, LAIR-1.

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**PO-9**

*Track: Pharmaceutical Biotechnology*

**PHYTOCHEMICAL SCREENING AND ANTIPOROLIFERATIVE ACTIVITIES OF OCIMUM SANCITUM LINN**

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In this study, we screened for phyto-constituents and bioactivities of Ocimum sanctum Linn (OC) leaf, a Bangladeshi Medicinal Plant of traditional usage. The major volatile compounds and fatty acids indentified by GC-MS were oleic, linoleic and palmitic acid methyl esters from hexane (HE) extract. On the other hand, eupatorin, vanillic acid, 4-hydroxybenzoic acid and apigenin were the most abundant phenolics determined by HPLC-TOF/MS in chloroform (CH) and ethyl acetate (EA) extracts. Further, the bioassay guided fractions of CH extract afforded eugenol, p-methoxycinnamic acid ethyl ester and caryophyllene oxide, whose structures were identified by spectral data analyses. The antiproliferative effects of the extracts and isolated compounds were examined on human cervical cancer (HeLa) and colon cancer (HT29) cells at the concentrations of 50-250 μg mL⁻¹. The CH extract exhibited potent antiproliferative effect on HeLa cells at the tested concentrations followed by EA and ME extracts, whereas EA extract had potent anticancer effect on HT29 cells followed by CH and ME extracts. However, HE extract was found to be inactive or less active. The isolated compounds also displayed potent antiproliferative activities. The results of this study demonstrate the potential use of OC derived natural products in food, pharmaceutical, and/or other industries.
**PO-43**

*Track: Pharmaceutical Biotechnology*

**DISULFIDE-RICH PEPTIDE CYCLIZATION USING SORTASE A**

**Christina I. Schroeder**

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Peptides have many advantages over small molecules or antibodies as drug leads in terms of size, high affinity and potency for their physiological targets. Especially disulfide-rich peptides, isolated from plants, scorpions and cone snails, have attracted much interest because of their high specificity for targets including human voltage-gated ion channels, receptors and enzymes. However, linear peptides low stability against proteases *in vivo* has been a bottleneck to drug development. Therefore, disulfide-rich peptides have been engineered to incorporate a cyclic backbone to improve stability. An attractive alternative method of chemical cyclisation of peptides is enzyme-mediated ligation. Here, we describe the use of the bacterial transpeptidase sortase A (SrtA) which catalyses a new peptide bond by recognising a LPXTG sorting motif. We have successfully used SrtA to generate cyclic disulfide-rich peptides of interest for development as cancer therapeutics. Peptides containing one, two, three and four disulphide bonds have rapidly been cyclised in high yield highlighting the versatility of the methodology. Method development, activity, structure and future directions of SrtA-mediated cyclisation will be discussed.

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**PO-38**

*Track: Others - Beneficial effects of Natural Products*

**AMELIORATIVE EFFECTS OF RUTIN AGAINST METABOLIC, BIOCHEMICAL AND HORMONAL DISTURBANCES IN POLYCYSTIC OVARY SYNDROME IN RATS**

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The study was commenced to study the effects of Rutin on metabolic, biochemical, histological, and androgenic aspects of polycystic ovary syndrome in rats. The PCOS was induced by oral administration of Letrozole (1 mg/kg) on six weeks old female Sprague Dawley rats for 36 days. The control group received 0.5 % aqueous solution of carboxy methyl cellulose (CMC) for 36 days. PCOS, Metformin, Rutin-I & II groups received Letrozole (1 mg/kg) throughout the experiment and Metformin (2 mg/100g), Rutin (100 mg/kg, 150 mg/kg) post treatment was given to last three groups from day 21 to day 36 respectively. On 37th day, the animals were euthanised, and ovaries were taken out. Anthropometrical, metabolic and histological analysis was done. Biochemical and androgenic profiles were also evaluated. Both the doses of Rutin significantly reduced oxidative and androgenic levels. A complimentary lipid profile, CRP value and a decrease in the proportion of estrus smears were observed in treatment groups. Histopathological examination of ovary revealed a significant decrease in thickness and number of cystic follicles in post treated groups. The effects observed with Rutin were quite similar to that with Metformin. The study provides an evidence for the potential ameliorative effects of Rutin in PCOS.

**Keywords:** Rutin, Letrozole, Metformin, polycystic ovary syndrome, oxidative stress.
PO-12
Track: Plant and Environment

PHYSICOCHEMICAL AND PHYSIOLOGICAL CHARACTERISTICS OF THE WHEAT-MAKGEOLLI

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In order to investigate the effects of different milling degrees on the quality of wheat-Makgeolli, physicochemical and physiological characteristics of wheat-Makgeolli were evaluated. Samples of wheat-Makgeolli brewed from 100, 85 and 75% milling recovery rates of three Korean wheat cultivars were analyzed ethanol, pH, coloring degree, total acids, soluble solid, free sugars, organic acids, and adipocytes. As the milling recovery rates in wheat decreased, sugar contents increased and pHs decreased. The Makgeollis made from wheat exhibited 0.63~0.84% in acidity, 10.2~12.5 Brix in sugar, 14~16% in alcohol contents.

Free sugar contents of the wheat-Makgeolli significantly changed with fermentation, Glucose and mannitol showed the highest percentage of the makgeolli, 1593.53-5677.46 mg/L and 3701.37-5288.08 mg/L, respectively. Wheat-makgeolli contained excess lactic acid, which is produced by lactic acid bacteria (LAB). Our in-vitro results demonstrated that extracts inhibited the differentiation of 3T3-L1 adipocytes through down-regulation of adipogenic gene expression. Taken together, these findings suggest that makgeolli extract has inhibitory activities against adipogenesis.

Keywords: Makgeolli, free sugar, fermentation, extracts, in-vitro.

PO-23
Track: Pharmaceutical Biotechnology

PROGNOSTIC SIGNIFICANCE OF HORMONAL RECEPTOR STATUS OF MALIGNANT OVARIAN TUMORS

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Objective: To study hormonal receptor status of malignant ovarian tumor (MOT) and to evaluate its clinical and prognostic significance.

Materials and Methods. Retrospective analysis of the case reports of 284 patients with MOT of different histogenesis, stages I–IV; and immunohistochemical study of paraffin-embedded tissues were performed. Hormonal receptor status of tumors with different morphology genesis was studied and hormonal receptor phenotype of serous ovarian cancer (OC) was determined. The analysis of correlation between the expression of steroid hormone receptors (receptors to estrogens (ERs), progesterone (PRs) and testosterone (TRs)) in ovarian tumors; histological type of tumors and clinical morphological parameters was performed. Overall and relapse-free survival rates of the patients with serous OC depending on the hormonal receptor phenotype of the tumor were assessed.

Results. Presence of positive expression of steroid hormone receptors in serous OC (ERs – 66.4 %, PRs – 63.4 %, TRs – 53.0 %), mucinous OC (ERs – 88.0 %, PRs – 84.0 %, TRs – 60.0 %) and in sex cord stromal tumors (ERs – 74.1 %, PRs and TRs – 77.8 %) is proved by correlation of all steroid receptors expression with morphology type of ovarian tumors (ERs – r=0.4; PRs – r=0.4; TRs – r=0.3; p<0.05). Correlation of expression of ERs and PRs with age period in the patients (ERs – r=0.3; PRs – r=0.3; p<0.05) and disease stage (ERs – r=0.3; PRs – r=0.2; p<0.05) was identified; lack of relation between expression of steroid receptors, differentiation grade of tumors of different histogenesis and use of neoadjuvant chemotherapy was established.
Direct correlation between hormonal receptor phenotype of serous OC and the age period of the patients was observed ($r=0.5; \ p=0.002$): postmenopausal women patients reported the most increased frequency of serous OC with positive hormonal receptor tumor phenotypes (52.4 %), in particular during their late post-menopausal period (39.0 %), which is the evidence of higher susceptibility of these tumors both to endogenic sex steroids and hormonal therapy. Significantly low overall survival among the patients with positive hormonal receptor phenotype of serous OC was recorded (29.5±3.4 %) in comparison with the same score in the patients with negative phenotype of tumors (44.5±3.7 %) ($p<0.05$). Multifactor analysis of Cox-regression model has defined that positive hormonal receptor phenotype of serous OC increases the risk of disease relapse (HR 1.4; 95.0 % CI 1.1–1.7), significantly decreases overall survival rates in the patients (HR 1.4; 95.0 % CI 1.1–1.8) and is the factor of unfavorable course of tumor process.

**Conclusions.** Positive hormonal receptor status of MOT is an independent factor of unfavorable clinical progress of tumor process which can be regarded as the criterion for development of the methods of applying hormonal therapy in complex treatment of the patients and demands further large-scale multi-center studies in that direction.

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**PO.2**

**Track:** Pharmaceutical Biotechnology

**A PROBABILISTIC BOOLEAN NETWORK APPROACH FOR THE ANALYSIS OF CANCER-SPECIFIC SIGNALLING: A CASE STUDY OF DEREGRULATED PDGF SIGNALLING IN GIST**

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Signal transduction networks are increasingly studied with mathematical modelling approaches. Modelling the network behaviour with qualitative approaches, like Boolean networks, does not usually capture quantitative effects while applying detailed mechanistic modelling requires an extensive amount of data to infer the respective kinetic parameters. Probabilistic Boolean network (PBN) modelling might therefore be a promising compromise, as it allows capturing quantitative changes of molecular states at steady-state with minimal parameterisation. PBN modelling so far has not been explored for studying signalling networks.

We successfully applied the PBN approach to model and analyse the deregulated Platelet-Derived Growth Factor (PDGF) signalling pathway in Gastrointestinal Stromal Tumour (GIST). We experimentally determined a rich and accurate dataset of steady-state profiles of selected downstream kinases of PDGF-receptor-alpha mutants in combination with inhibitor treatments. Applying the tool optPBN, we fitted a literature-derived candidate network model to the training dataset consisting of single perturbation conditions. Model analysis suggested several important crosstalk interactions. The validity of these predictions was further investigated experimentally pointing to relevant ongoing crosstalk from PI3K to MAPK signalling in tumour cells. The refined model was evaluated with a validation dataset comprising multiple perturbation conditions. The model thereby showed excellent performance allowing to quantitatively predict the combinatorial responses from the individual treatment results in this cancer setting. The PBN model achieved with a minimal parameterisation a better or at least equal prediction power compared to other widely applied modelling frameworks.

We therefore propose the PBN approach as a promising method for analysing signal transduction networks, as it allows for modelling these networks in a simplified manner while still delivering quantitative predictions. The established optPBN pipeline is widely applicable to gain a better understanding of signalling network properties at steady-state in a context-specific fashion.

**Keywords:** Systems biology, probabilistic Boolean network, gastrointestinal stromal tumour.
**PO-55**

**Track: Industrial and Manufacturing**

**HOMOLOGOUS HIGH LEVEL LIPASE AND SINGLE CELL PROTEIN PRODUCTION AS PROMISING FEED FROM ENGINEERED YARROWIA LIPOLYTICA VIA SCALE-UP FERMENTATION**

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Aimed to simultaneously produce extracellular lipase and single cell protein (SCP) as promising feed, the fed-batch fermentation of engineered *Yarrowia lipolytica* was investigated from bench-scale to pilot-scale. Firstly, fermentation parameters for 500ml shaking flask culture were optimized with single factorial design. The obtained optimal conditions were: 5% sucrose, medium initial pH 5.5, inoculum volume 2%, fermentation duration 84 h. The resultant lipase activity reached 880.6 U/mL with 30.97 g of dry SCP/L at 84h. Using glycerol as sole carbon source, the highest lipase activity reached 10,266 U/mL, and a final dry SCP was 208.3 g/L at 118h in 10L. Using similar constant culture conditions, the lipase activities reached 11,100 U/mL with 173.3g of dry SCP /L in 30L and 8,532 U/mL with 170.3 g of dry SCP /L in 100L at 136h, respectively. These results indicate that the efficient fermentation strategy could promote further scale-up for industrial SCP production from the homologous engineered *Y. lipolytica* as feed.

**Keywords:** *Yarrowia lipolytica*; homologous expression; scale up; fermentation; single cell protein.

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**PO-15**

**Track: Industrial and Manufacturing**

**GENETIC ENGINEERING IMPROVED PERFORMANCE IN TRICHODERMA HARZIANUM USING AQUAPORIN OVEREXPRESSION**

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Genetic engineering has brought about insights on the biology of Trichoderma species as well as improvements on their use in industrial processes. It has previously been reported that a gene encoding an aquaporin identified in *Trichoderma harzianum* during biocontrol of phytopathogen has biotechnological applications. Here, we report on the cloning and overexpression of this gene in *T. harzianum* in order to enhance its tolerance to biotic and abiotic stresses. Following transformation of *Trichoderma harzianum* via biobalistics, fungi expression analysis was performed using real-time PCR (qPCR) approach. Also, fungi phenotype were evaluated under different abiotic (ethanol, hydrogen peroxide, sorbitol and sodium chloride) and biotic (*Fusarium solani, Sclerotinia sclerotiorum* and *Rizoctonia solani*) stresses. Analysis under stress-free condition showed that *T. harzianum* overexpressing aquaporin did not present differences in growth and germination rates when compared with wild type. However, mycoparasitic potential against phytopathogens was increased when assessed in plate confrontation assays. Furthermore, evaluations under abiotic stresses revealed that transformants overexpressing aquaporin presented high tolerance to ethanol (10%), H$_2$O$_2$ (5%), and salt (5%) stresses. Our results underscore the high potential of aquaporin from *Trichoderma harzianum* in biotechnology processes such as biofungicides and industrial fermentations.

**Keywords:** Biocontrol, biofungicide, mycoparasitism, abiotic stress.
TARGETED CHEMOTHERAPY USING PLURONIC NANOPARTICLES TO OVERCOME TUMOR MICROENVIRONMENT

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For effective chemotherapy, two types of attempts were introduced to overcome tumor microenvironment which had heterogeneous and evolutionary features. The Pluronic nanoparticles (NPs) were used as delivery vehicles for each treatment.

A combination therapy consisting of radiotherapy and chemotherapy was demonstrated using the Pluronic NPs containing gold NPs and doxorubicin (DOX). Although radiation therapy has been a major treatment in cancer therapy, many patients do not undergo radiation because of serious radiation-associated risks. One strategy for maintaining the therapeutic index of radiation therapy with reduced radiation-associated side effects can be accomplished using radiosensitizers. Gold NPs used as a radiosensitizer and DOX were successfully incorporated into the Pluronic NPs with core/shell structure. Because Pluronic F-68 utilized as a polymeric shell was mainly composed of PEO, the prolonged systemic circulation and enhanced targeting of the Pluronic NPs at tumor tissue were observed with significant improvement in antitumor efficacy. This indicated that the Pluronic NPs containing gold NPs and DOX can be utilized as a nanomedicine for the combination therapy [1].

The concept of DOX induced apoptosis-targeted chemotherapy (DIATC) was introduced and demonstrated by co-delivery of DOX and DEVD-S-DOX at the tumor tissue using the Pluronic NPs. DEVD-S-DOX, DOX linked to a peptide moiety (DEVD: Aspartic acid-Glutamic acid-Valine-Aspartic acid), is a prodrug that is cleaved into free DOX by caspase-3 upon apoptosis. DEVD-S-DOX has no therapeutic efficacy, but it changes into free DOX with the expression of caspase-3. To immobilize DOX and DEVD-S-DOX in the same frame, heparin was utilized to form a heparin/DOX/DEVD-S-DOX complex through an ionic interaction. Subsequently, the heparin/DOX/DEVD-S-DOX composite was stabilized with Pluronic F-68 to form the Pluronic NPs. With the accumulation of the Pluronic NPs in the tumor tissue by the enhanced permeation and retention (EPR) effect, a small exposure of DOX in the tumor cells initiated apoptosis in a localized area of the tumor tissue, which induced caspase-3 activation. Cleavage of DEVD-S-DOX into free DOX by caspase-3 continued with repetitive activation of caspase-3 and cleavage of DEVD-S-DOX at the tumor site. The Pluronic NPs successfully accomplished DIACT in the tumor-bearing mice with a minimal level of cardiotoxicity, which limited the usage of DOX [2].

ACKNOWLEDGEMENTS

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Keywords: Targeted chemotherapy, pluronic nanoparticles, doxorubicin, tumor microenvironment.

REFERENCES

PO-44

Track: Pharmaceutical Biotechnology

ANTIBODY-PROTEASES AS TRANSLATIONAL TOOLS (BIOMARKERS AND TARGETS) OF THE LATEST GENERATION TO MINIMIZE RISKS OF CHRONIFICATION OF AUTOIMMUNE DISORDERS AND THUS THE DISABLING RATES OF THE PATIENTS

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Among the best-validated proteome-related predictive biomarkers, antibodies (Abs) are the best known. A combination of different panels of auto-Abs in the diagnostic practice has become a great significance to predict risks of chronification of the autoimmune disorder since most of the latter are preceded by a long subclinical (symptom-free) phase when the patients or persons-at-risk could be identified via specific sets of auto Abs. Of particular interest would be algorithms which would employ panels of targeted Abs for screening patients and their relatives at risks for the presence of preclinical (lab proof-based) signs and for thus having the data translated into the daily practice.

The methodological bricks of subclinical diagnostic protocols should include basic algorithms to differ essentially from those employed in traditional clinical practice, i.e., (i) to confirm a diagnosis of subclinical stage of the disease course and (ii) to select a mode for preventive treatment to quench the autoimmune inflammation.

Antibodies are the best known ones to represent one of the principal immune effectors and thus key mediators of inflammatory responses to generate the events. Most of autoimmune disorders including multiple sclerosis (MS), autoimmune myocarditis (AIM) and autoimmune thyroiditis (AIT) are preceded by a symptom-free subclinical stage in which the disorder can be identified by specific autoAbs.

Proteolytic Abs are multivalent immunoglobulins (IGs) endowed with a capacity to proteolyze the antigenic substrate. Abs against myelin basic protein (MBP), cardiac myosin (CM) and thyroid globulin (TG) endowing with targeted proteolytic activity (Ab-proteases) are of great value to monitor a stepwise autoagression (e.g., demyelination in MS or chronic myocarditis in AIM) at either of the stages (subclinical and clinical ones) to illustrate the evolution of the disorder.

Those Ab-proteases at either of the disorders mentioned are capable of demonstrating Ab-associated targeted proteolytic activity to attack and thus destroy the targeted Abs whilst correlating with the severity and course of the disease. The activity of the targeted Ab-proteases markedly differs between: (i) the patients and healthy controls; (ii) different clinical courses; (iii) scales of disabling to correlate with the disability of the patients to predict transformation prior to changes of the clinical course. The latter means that when we saw a stable growth of the activity, we could predict transformations in the clinical course prior to changing in a pattern of the clinical manifestations. Bursts of the Ab-associated proteolytic activity have been confirmed at the pre-early stages of the exacerbation to predict the latter, or prior to changing type of the clinical course, i.e., from a remitting type into the progradient one. Ab-proteases may serve as biopredictors to monitor subclinical stages of MS to predict the outcome and as a promising target for newer therapeutic tools to produce preventive therapeutic effects at subclinical stages of MS.

It is so important to stress that the close association between the proteolytic sensitivity of the targeted autoAbs and post-translational modifications of the latter may represent one of the key regulatory mechanisms in the epitope generation. For sure, a combinative (enzyme- and Ab-mediated) proteolysis may illustrate a crucial pathway to exert a concerted attack on the autoAbs, although mechanisms responsible for the activation of these potential activities are not known yet.

Ab-proteases can be programmed and reprogrammed to suit the needs of the body metabolism or could be designed for the development of principally new catalysts with no natural counterparts. And thus two logical questions would arise: (i) Would the original potential for the Ab-mediated proteolysis relate to natural Ab-related function? (ii) Could that potential be translated into the clinical practice to suit the need of clinicians?

Canonical Abs play neither predictive nor discriminative role to affect the subclinical stage of MS. Meanwhile, sequence-specific Ab-proteases have proved to be greatly informative and thus valuable as translational biomarkers to monitor MS at both subclinical and clinical stages. Moreover, of tremendous value in this sense are Ab-proteases directly affecting the physiologic remodeling of tissues with multilevel architectonics (for instance, myelin or cardiac
muscle). And autoAb-mediated proteolysis could thus be applied to isolate from IG molecules the efficient catalytic domains directed against particular autoimmune epitopes pathogenically and clinically relevant.

Further studies may provide a supplementary tool for predicting autoaggression, biomarkers of new generations and thus a supplementary tool for assessing the disease progression and predicting disability of the patients and persons-at-risks. So, the activity in combination with the sequence-specificity would confirm a high subclinical and predictive value of Ab-proteases as applicable for personalized monitoring protocols.
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ADDITIONAL ABSTRACTS
IMPACT OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY ON LIVER FUNCTION OF UNDER-FIVE HIV-POSITIVE CHILDREN IN SOUTHERN NIGERIA


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Background: Hepatotoxicity deserves serious attention due to treatment discontinuation in HIV-seropositive patients.

Objectives: Study aimed at evaluating the impacts of Highly Active Antiretroviral Therapy (HAART) on liver function of under-five children.

Method: In five hospitals, 238 under-five children were enrolled after ethical permission from the hospitals and written consent from participants' caregivers. Participants were divided into six groups: the HIV-seropositive either on HAART (group A, n= 91) or co-trimoxazole (group B, n= 11) and four other groups who were HIV-seronegative. Among this second cohort were those commenced on nevirapine for six weeks post-exposure (group C1, n= 24) and co-trimoxazole at 6 months (group C2, n= 18) or 18 months (group C3, n= 48) post-exposure. No medication for group D (n= 46). Blood sample of 2ml was obtained from each participant and assayed for alanine aminotransferase (ALT) and aspartate aminotransferase (AST). After three- and six-months post initial study, group A participants were restudied for ALT and AST. Mean and standard deviation of the parameters of group A participants were compared with those from other groups by using ANOVA. Significance was considered at p ≤0.05.

Results: ALT was significantly higher in group A compared to group B (12.8±11.0 IU/L vs 6.5±2.6 IU/L, p= 0.245), group C1 (12.8±11.0 IU/L vs 10.9±7.8 IU/L, p= 0.910), group C2 (12.8±11.0 IU/L vs 11.7±20.7 IU/L, p= 0.995), group C3 (12.8±11.0 IU/L vs 11.2±6.9 IU/L, p= 0.868), and group D (12.8±11.0 IU/L vs 5.8±3.4 IU/L, p= 0.001). After three and six months of monitoring, ALT of group A was significantly decreased by 39.3% (p= 0.001) and 50.6% (p= 0.000) respectively.

Conclusion: The elevated ALT of under-five HIV-infected children on HAART lowered after six months of monitoring.

Keywords: Under-five HIV children, Alanine aminotransferase, Aspartate aminotransferase, Highly Active Antiretroviral Therapy.
cell growth and heighten the biocompatibility. Beside the wettability we studied the surface morphology of the obtained multifunctional thin films by: Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM). This joint analysis leads to interesting conclusions, which can help to improve the biocompatibility of TiCr films, leading to an increase in their medical applications.

Keywords: TVA, biomaterial, wettability, Transmission electron microscopy, selected electron microscopy, topography.

THE BIOOPEN- A MULTIFUNCTIONAL PIPETTE FOR SINGLE CELL ANALYSIS

Aldo Jesorka

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In my talk I present the Biopen, a novel turn-key research instrument based upon the principle of hydrodynamically confined microfluidics, which my laboratory developed for contamination-free superfusion of single cells in adherent cultures and tissues [1].

Cellular heterogeneity is a limiting factor in further understanding how biological cells function within tissues. In recent years it has become clear that individual cells can display considerable variability. Treating of cell populations as an ensemble average infers an unnatural homogeneity to the cellular functions. Individual events occurring infrequently are hidden due to this averaging effect. For example, the hypothesis of a unique role of rare cancer stem cells has been consistently supported by experimental evidence [2-4]. This particular model implies the hypotheses that cancer stem cells are rare, well defined populations, and that they may be resistant to conventional cancer chemotherapies.

New technological solutions for single cell analysis are driving advanced, increasingly detailed investigations, both from fundamental biochemical and analytical perspectives. In order to manipulate and analyze the cellular machinery, new enabling technologies, which provide convenient access to individual entities, their chemical environment and internal contents, are increasingly in demand. One aspect, for example, is controllable and reversible permeabilization of the cell membrane in connection with transfection, and delivery of active material to the immediate environment of a single cell without affecting other cells nearby. While many examples of single cell analysis techniques for cells in suspensions have been developed, most of them using microfluidic devices [5], similar technology for adherent cells is still in its infancy. Here, glass capillaries, or “puffer needles”, are the most commonly utilized instruments for manipulation of the cellular environment, with obvious disadvantages such as fragility, and continuous build-up of active solution in the culture dish.

The Biopen, or multifunctional pipette, is a pen-shaped microchip device, which generates a virtual flow cell of ~100 µm size at its tip [1]. A fluid stream, containing the desired active compound to be delivered, is injected from a microchannel into the immediate environment of an adherent cell, and simultaneously aspirated back into the device. The laminar flow of the injected fluid features a sharp boundary between the injected fluid and the medium in the open volume, which efficiently prevents the escape of solutes from the injected stream. The Biopen can be positioned, similar to a conventional glass needle, in the vicinity of a single selected cell, or a group of cells in a tissue sample. The functions defined by the on-chip microfluidic circuitry allow for rapid switching between different solutions, which are stored in reservoir wells on the device. Sequences of treatments with different active compounds, including cell permeabilization, delivery of active compounds, and viability testing, become instantly possible. The instrument combines the benefits of conventional glass needles, namely the ability to target individual cells, to release minute amounts of material, and to allow simultaneous use of other probes on the same cell, with the functional diversity modern microfluidic chip technology offers. Here the economic use of reagents, the solution switching ability, and the low risk of contamination due to the one-time use of the consumable device, are distinct advantages. Hydrodynamic confinement allows for sequential investigation of many cells in the same culture dish over prolonged periods of time, effectively preventing the build-up of injected material over time.
In addition to a short introduction to the technological foundation of the Biopen, multiple application examples will be presented, including single cell enzymology studies [6], ion channel investigations, activation of blood platelets, mitochondria dynamics in single muscle fibres [7], and single cell electroporation with subsequent internalization of material [8]. The Biopen is currently in use in more than a dozen research laboratories worldwide, enabling the creation of new experimental approaches which are required for advanced single cell investigations.

REFERENCES


PO-49
Track: Pharmaceutical Biotechnology

SYNTHESIS AND CHARACTERIZATION OF THE TI-MG NANOCOMPOSITES OBTAINED BY LASER THERMIONIC VACUUM ARC (LTVA) METHOD FOR BIOMEDICAL APPLICATIONS

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There is an increasing interest in the development of new biocompatible and biodegradable materials for medical applications. Magnesium has been identified as a promising biodegradable implant material because it does not cause systemic toxicity and can reduce stress shielding. On the other side, titanium is already used for implants, was chosen as the alloying element because of its proven biocompatibility and corrosion resistance in physiological environments. Therefore, from combining titanium with magnesium is expected an improvement of physical and chemical properties.

The aim of this paper is to investigate the growth and structure properties of Ti-Mg thin films deposited by Laser Thermionic Vacuum Arc (LTVA) method on silicon, glass and OLC 45 special substrate. LTVA method is the extension of Thermionic Vacuum Arc technology to coatings using laser beam focused on the solid materials from anode (in our case Ti and Mg). The main advantages of this technology are: the plasma is localized just above the anode; the ignition of the plasma discharge in LTVA system is easier than in the TVA technology since the present on laser focused on the material to be evaporated and the state of gas being achieved faster; the deposition rate is high, and the thin film are smooth, uniform and pinhole-free. The samples were characterized using Atomic Force Microscopy (AFM), Scanning Electron Microscope (SEM) accompanied with energy dispersive spectrometer, transmission electron microscope (TEM) and See System apparatus for the wettability (assessed by measuring the contact angle).

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Keywords: Ti-Mg coatings, Laser Thermionic Vacuum Arc method, TEM.
**PO-45**

*Track: Marine Biotechnology*

**MOLECULAR CLONING, GENOMIC ORGANIZATION AND PROMOTER ANALYSIS OF THE VITELLOGENESIS-INHIBITING HORMONE (SPVIH) FROM THE GREEN MUD CRAB, SCYLLA PARAMAMOSAIN**

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Vitellogenesis-inhibiting hormone (VIH) is known to regulate ovarian maturation by suppressing the synthesis of vitellogenin (Vtg) in crustaceans, which belongs to a member of crustacean hyperglycemic hormone (CHH) family synthesized and secreted from the X-organ/sinus gland complex of the eyestalks. In this study, the genomic DNA and the 5'upstream regulatory (promoter region) sequences of VIH gene were obtained by conventional PCR, Genome walker and Tail-PCR techniques, according to the cDNA sequences which were identified from our previous study. The full length gDNA of SpVIH is 790 bp containing two exons and one intron. The 5'-flanking promoter region of SpVIH is 3070 bp from the translation initiation (ATG) and 2398 bp from the predicted transcription initiation (A), which consists of putative core promoter region and multiple potential transcription factor binding sites. As lacking of the cell lines of crabs, we chose the mature transfection system HEK293FT cell lines to explore the mechanism of transcription regulation of SpVIH in crabs. Sequential deletion assays using luciferase reporter gene in HEK293FT cells revealed that the possible promoter activity regions (including positive and negative transcription factors binding sites simultaneously) presented between pSpVIH-4 and pSpVIH-6. In order to further identify the crucial transcription factors binding site in this region, the site-directed mutagenesis of Sox9 binding site of pSpVIH-4 was created. The results demonstrated that the transcriptional activity of pSpVIH-4△ decreased highly significantly (p<0.05), suggesting that the Sox9 may be the essential positive transcription factor which regulates the expression of SpVIH.

**Keywords:** Scylla paramamosain, Vitellogenesis-inhibiting hormone, Genomic DNA, promoter, Transient transfection, Transcriptional regulation.

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**SL-195(a)**

*Track: CNS Drug Discovery & Therapy*

**PROTEIN SEPARATION, ISOLATION AND ANALYSIS OF NEUROTROPIC FACTOR FROM THE MU BIE ZI (MOMORDICA COCHINCHINENSIS) SEEDS**

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Nerve Growth Factor 7S (NGF 7S) is a 130-140 kDa protein with the capacity to sustain maintenance of neurons in CNS. It is widely used as a model to investigate aspects of nerve differentiation through NGF signaling. Previously, we conducted a high-through-put (HTP) screening of > 1100 natural products to determine if any plant-based dietary substance could induce neurite outgrowth in a similar fashion to NGF (Neurotropic Factor, NTF) in PC12 cells over 7 days at <200µg/mL (Neurochemical Research 40:2102-2112, 2015). This work showed a rare frequency of naturally occurring NGF mimetics, with only one single hit elucidated: that being: Mu Bie Zi, *Momordica cochinchinesis* seed extract (MCS). In the current study, we further explore the components of ground seed pit (aril removed) responsible for the NGF mimetic effects. The data showed that chemicals isolated by solvent fractionation (methanol, ethanol, ether, ethyl acetate) failed to induce neurite outgrowth in PC-12 cells. Next, a pure protein isolate was evaluated and found to induce dose-dependent neurite outgrowth. To determine the active protein constitute, the purified protein was then subject to one-dimensional gel electrophoresis, gel staining, sectioning / excision, electro-elution back into solution and re-evaluation for NTF effects on PC-12 cells. All major stained bands had no biological consequence, and through the
process of elimination – NTF was found to reside in a low abundant gel band at around 17-20 KD. This gel band was excised and subsequently evaluated for peptide/protein identification using UPLC-MS/MS – with a Q Exactive Hybrid Quadrupole - Orbitrap Mass Spectrometer. The data show 100% sequence match for > 30 annotated functionally uncharacterized proteins from Cucumis Sativus (garden cucumber), with 2 sequence matches leading to the identification of proteins of Momordica charantia (bitter melon) and the Cucumis melo (honeydew/muskmelon). Given that the Cucumis Sativus proteome is annotated (proteome ID UP000029981) while Momordica cochinchinensis is not, identification is limited to potential homologous proteins in related species. While every protein identified in the trophic fraction was under the (Cucurbitaceae / Cucumber family), none had sequence similarities to 7S NGF. Future research will be required for in-depth sequencing, isolation of this active protein and to determine if it is intact, or a cleavage protein product, and determine clinical relevance in reducing the risk of human degenerative diseases such as Parkinson’s disease or Alzheimer’s disease (Supported by NIH grants from NIMHD G12 MD007582 and P20 MD00677).

**SL-54**

**Track:** Systems Biology in Drug Design

**ANTIBODIES WITH INTEGRATED ENDOSONME ESCAPE AND NUCLEAR-DIRECTIONAL INTRACELLULAR TRAFFICKING CONTROL CAPABILITIES FOR IMPROVED PAYLOAD DELIVERY AND EFFICACY AGAINST SPECIFICALLY TARGETED CANCER CELLS/TUMORS**

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Antibody-drug conjugates (ADCs) are a transformative class of biopharmaceuticals for improving cancer detection and therapy due to the ability of an antibody to transport molecular payloads such as radioisotopes and small molecule/biological toxins to targeted cancer cells. Thanks to the detailed understanding of the “three key components” (Antibody-Linker-Payload), ADC technology has evolved into a firmly established science driving biopharma expansion. Despite this success, there are clear limitations that result in less-than-ideal patient survival and poor tumor detection.

The ability to develop novel transport systems at subcellular-level is of paramount importance and will enable the exploration, engineering, and thus the further advancement of ADCs. Upon binding to target receptors on the cell surface, endocytosis and subcellular trafficking is highly efficient resulting in the deposit of ADCs in the lysosome where they are degraded terminating the directed intracellular transport of attached cargo. Unfortunately, this delivery system is inefficient for effective treatment of imaging of cancer as tumor cells can either recycle ADCs to the extracellular space or upregulate multidrug resistant proteins. The ultimate result is reduced intracellular accumulation of the delivered payload that results in tumor cell resistance and low tumor-to-nontumor background signals for therapy and imaging applications, respectively.

I will present work from my laboratory that optimizes the design and study of ADCs functionalized with a novel technology (cellaccumulator™ [CA]) as a 4th easily attachable component that enables ADCs to escape the endosomal-lysosomal trafficking pathway and re-direct subcellular transportation to the nucleus. Results from exploring CA and its mechanisms to different ADC-cancer systems and the relationship between endosome escape-cargo nuclear localization and intracellular accumulation and efficacy will be presented and discussed.
PO-55

Track: Academic CRO/Industrial Collaborations in Drug Discovery

PHARMACOKINETICS AND SAFETY OF A LONG-ACTING SUBCUTANEOUS FORMULATION OF 2-METHOXYESTRADIOL IN HEALTHY VOLUNTEERS

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2-Methoxyestardiol (2ME), a major estradiol metabolite, is the product of the sequential C-2 hydroxylation and methylation of estradiol. 2ME has no estrogenic activity and exhibits estrogen receptor-independent, cardiovascular and renal protective effects in experimental models of cardiovascular and renal injury, diabetes and pulmonary hypertension.

The two objectives of the present study were (i) to evaluate the safety and tolerability of a subcutaneously administered long-acting formulation of 2ME in healthy male volunteers and (ii) to assess the pharmacokinetic profiles of ascending dose levels of subcutaneously administered 2ME in this population.

Thirty-six healthy male volunteers were randomized in a placebo-controlled, double-blind, dose escalation study to evaluate the safety and pharmacokinetics (PK) of a single SC injection with a long-acting crystalline suspension of 2ME formulated to release drug over several weeks. Four cohorts of 9 subjects each (7 treatment, 2 placebo) underwent safety assessments and blood samples were collected for laboratory evaluations and measurement of testosterone, estradiol, estrone and sex hormone binding globulin levels. Levels of 2ME and its principal metabolite, 2-methoxyestrone, were followed for 6 weeks after dosing using a LCMS assay (detection limits 0.1 ng/mL). Subjects were dosed at 0.8, 2.5, 5.0 or 10.0 mg/kg.

All subjects completed the study and there were no serious adverse events. Other than transient stinging and bruising at the injection site, there were no significant clinical observations. Hematology, serum chemistry and endocrinology parameters were not adversely affected. 2ME levels above the detection limit were observed in 9 of 36 subjects prior to dosing. There was good linearity between dose levels for Cmax (R² = 0.995) and AUC0-984h (R² = 0.885). The PK of 2-methoxyestrone was similar to that of 2ME with drug: metabolite ratios of 8 to 5:1 for Cmax and 16 to 4:1 for AUC depending on dose level.

This study suggests that normal males have baseline levels of 2ME and that the tested formulation can safely be given at doses of up to 10 mg/kg resulting in 2ME levels exceeding baseline for at least 42 days post-injection.

SL-00

Track: CNS Drug Discovery & Therapy

UNTANGLE IT WITH A FENAMATE: TOLFENAMIC ACID AN TAUPATHIES

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Alzheimer’s disease (AD) is a disorder found predominantly in the aging population with dementia and progressive neurodegeneration. The hallmark of AD includes amyloid beta (Aβ) plaques formed from the cleavage of the Amyloid Precursor Protein (APP) and tau tangles. In addition, a whole group of neurodegenerative diseases with primarily tau pathology have no approved treatments. Specificity protein1 (Sp1) is a transcription factor which plays important roles in the expression of key genes associated with AD and taupathies. Our research has demonstrated that targeting Sp1 with a non-steroidal anti-inflammatory drug (NSAID), Tolfenamic acid (TA) reduces AD-related biomarkers regulated by Sp1 such as: APP, BACE1, Tau and CDK5. TA also improves spatial learning, as well lower plaque and tangle burden. TA has now been designated by both the European Medicine Agency (EMA) and the US FDA as a potential treatment for two neurodegenerative diseases (2016), frontotemporal dementia (FTD and Progressive Supranuclear Palsy (PSP), and is under review for clinical trials.
VALUE ADDITION OF JATROPHA CURCAS CAKE: DETOXIFICATION AND SIMULTANEOUS PROTEIN ENRICHMENT

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Jatropha curcas cake (JC) is a toxic residue derived from the extraction of the oil from J. curcas seeds. This residue is rich in proteins, starch and aminoacids, but cannot be used as animal feed mainly due the presence of phorbol esters and antinutritional compounds. One way to add value to JC is to use it as a culture medium for solid-state fermentation (SSF). Through this process, it is possible to detoxify and to reducing other toxic/antinutritional components such as phytic acid and mycotoxins. In this way, the SSF was used in an attempt to detoxify the JC through the Penicillium simplicissimum. The fermentations were carried out in tray bioreactors. The fungal growth was able to reduce the amount of phorbol esters in 86% after 120h. The maximum protein content was observed after 48h, reaching 21, 13±0, 88 of protein (g/100g). The fungus was also able to eliminate the presence of ochratoxin A and aflatoxin B1 in JC and reduce 75% of aflatoxin G2. Moreover, the fungus was also able to reduce 93.1% of the phytate and 92.1% of lipids present content in JC after 120h of cultivation, reaching a final concentration of 1.28g / 100g and 0.84g / 100g, respectively. Thus, using SSF it was possible to aggregate value to an undesirable residue, making it safe for further applications, as animal feed for instance.

Keywords: Jatropha curcas, solid-state fermentation, protein enrichment.
TARGETING EPGENETIC PROTEINS FOR CANCER THERAPY

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In cancer, epigenetic proteins are intensely studied targets for drug discovery owing to the general view that it is not just the DNA sequence that is altered in epigenetics-based diseases. Studies to date have indeed been focused on developing small molecule inhibitors of chromatin modifying enzymes, so-called epigenetic “writers” and “erasers”. Perhaps owing to the perception that it is difficult to interfere with protein-protein interactions, epigenetic proteins have received comparatively little attention. Motivated by this challenge, we have been focusing on developing small molecule inhibitors of epigenetic proteins, such as BET (bromomain and extraterminal domain), an epigenetic reader, which recognizes the acetylated lysine side chain on histones, and EZH2, an epigenetic writer, which modify the histone tail with methylation marks. For the bromodomain, we designed and synthesized a thienodiazepine based small molecule called JQ1, which exhibits excellent inhibition against the BET subfamily with low nanomolar binding potency, especially targeting the BET protein, BRD4. A medicinal chemistry campaign around this prototype drug further optimized the molecule to produce a clinical candidate that has entered clinic trials for BRD4-dependent cancers and hematologic malignancies. Furthermore, we have developed novel tool compounds to degrade BET bromodomains (dBET), techniques for assessing small molecule localization to chromatin (Chem-Seq) and assay platforms to characterize bromodomain selectivity (BromoScan). These tools will allow us to study alternate epigenetic reader proteins, both within and beyond the BET subfamily of bromodomains. We are further expanding our interests to other epigenetic targets.

PO-50

Track: Pharmaceutical Biotechnology

PVT1-DERIVED NON-CODING RNAs IN PROSTATE CANCER IN MEN OF AFRICAN ANCESTRY

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Prostate cancer (PCa) is the most common non-skin cancer and the second leading cause of cancer related death for men in the U.S. Males of African Ancestry (MoAA) have a higher incidence and a 2.5 fold greater risk of lethal PCa, compared to Caucasian males (CM). In fact, African ancestry is a confirmed, nonmodifiable risk factor for PCa. Discovery of biomarkers with diagnostic, prognostic, and therapeutic applications are necessary to address this profound health disparity. The chromosomal region 8q24 is associated with aggressive PCa in MoAA and variants of this region have been identified to interact with the PVT1 non-coding gene in PCa. PVT1 is located at 8q24 and is transcribed into a long non-coding RNA that has been implicated in PCa. In previous work where we identified at least 12 exons of PVT1, we observed that exon 9 of PVT1 is significantly upregulated in aggressive PCa cell lines derived from MoAA and that silencing expression of PVT1 exon 9 induces apoptosis and cell cycle arrest in aggressive PCa cells derived from MoAA. Furthermore, we found that PVT1 exons 4A and 4B are overexpressed in PCa cell lines derived from aggressive PCa in MoAA. Functional studies upon silencing of PVT1 exons 4A and 4B showed an inhibition of cell proliferation when PVT1 exon 4B was silenced in aggressive PCa cells derived from MoAA. Moreover, a PVT1 encoded microRNA, miR-1207-3p, has prognostic value in PCa, which is differentially expressed in the prostate tumor tissues of MoAA versus CM, and directly binds to the 3’ UTR of Fibronectin type III domain containing 1 (FNDC1) to regulate a novel FNDC1/fibronectin (FN1)/androgen receptor (AR) pathway upregulated in metastatic PCa. To discover all the molecular targets of miR-1207-3p, we designed and synthesized a novel synthetic biotinylated miR-1207-3p duplex (miR1207-3p duplex) and a novel synthetic biotinylated scramble duplex (scramble duplex) as control, and then we proceeded to validate these novel tools. Our data show that the miR-1207-3p duplex directly binds to the 3’ UTR of FNDC1 and
inhibits the FNDC1/FN1/AR pathway. Wound healing assays revealed that our miR1207-3p duplex significantly inhibits cellular migration in PCa cells derived from MoAA by up to 40% when compared with the scramble duplex. Furthermore, Annexin V staining analysis demonstrated that our miR1207-3p duplex increased apoptosis by nearly 2-fold in PCa cells derived from MoAA compared to scramble duplex. These data demonstrate the importance of PVT1-derived non-coding RNAs in PCa in MoAA, and provide the basis for larger studies to evaluate prognostic, diagnostic, and therapeutic applications of miR1207-3p, PVT1 exon 9, PVT1 exon 4A and PVT1 exon 4B in PCa.

PO-47
Track: Nutraceutical Drug Discovery & Therapy

ANALYSIS OF THE GALLIC ACID TREATMENT ON THE PROTEOMIC PROFILES EXPRESSION IN HUH7 CELLS INFECTED WITH HEPATITIS C VIRUS


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The hepatitis C virus (HCV) proteome and its interrelation with HCV-infected cells proteome have been studied to find new antivirals. Therefore, we evaluated gallic acid (GA) effect, a natural phenol, on Huh7-HCV cells proteome. Huh7-HCV cells were exposed to 200μM GA for 0-72 h. Total proteins were extracted and resolved in two-dimensional electrophoresis gels to separate by isoelectric point (pI) and molecular weight (MW). Gels were analyzed by PDQUEST-v8.0.1 software and protein expression using TagIdent software. Differential proteomic profiles were found in Huh7-HCV treated with GA at different times. Profiles denoting a basal expression of proteins that showed differential profile (35%), such as cellular stress response and antiviral activity proteins (Hsp72, HSP7C). At 24h, an overexpression (30%) of liver regeneration and anti-angiogenic proteins (GAS6, RASF7) was observed. After 48h, apoptotic and mitochondrial proteins expression increased (40%) (CRLS1, NDUAA). Finally, at 72h, we identified an overexpression (60%) of cell protection and DNA repair proteins (KAD2, TNF14), that are necessary for cell survival after DNA damage. Our study identified that GA decreases HCV-replication and induces proteins expression involved in stress response, antiviral activity, apoptosis and anti-angiogenesis. These results will allow identify proteins associated with HCV that could be molecular targets to treatment.

PO-72
Track: Cancer Targeted Drug Delivery

NEW EFFECTIVE FORMULATION OF LIPOSOMES ENCAPSULATED DOXORUBICIN-GLUCAN REDUCED CELL VIABILITY IN SEVERAL CELL CANCER LINES

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Many issues remain concerns about doxorubicin (DOX) anticancer activity and cardiovascular toxicity. Glucans are abundant in many organisms with significant bioactive properties toward immune responses and inflammatory. This study meant to fabricate a new liposomal formulation that can deliver DOX and glucan together in attempt to enhance DOX effectiveness and thereafter reduce its cardiovascular toxicity.
The formulation prepared by DRV method. Encapsulated glucan determined by glucan kit and DOX measured by spectrophotometer. Toxicity of liposomal formulation evaluated using MTT assay.

The liposomal nanoparticles were about 905 ± 45 nm sizes. Liposomal formulation encapsulated both of glucan / DOX with encapsulation efficiency of 35.2 ± 8.7 and 20.4 ± 3.1 μg/ml respectively. MTT assay illustrated significant reduction for cell viability at concentrations of 40, 20, 10, and 5 mg/L in each of lung carcinoma epithelial cell (A549), breast cancer cell (MCF7), and colorectal adenocarcinoma cell (HT29) by liposomal formulation compared to free DOX and free DOX-glucan (P value < 0.05).

In conclusion, encapsulation of DOX-glucan in liposomal formulation improved DOX's activity and might reduce its cardiovascular toxicity, since it works with less amount of DOX. However, formulation stability, physicochemical properties, and cardiovascular toxicity studies for this formulation are still needed.