6th International Conference on Drug Discovery & Therapy

February 10 - 12, 2014, Dubai, U.A.E.

Abstracts

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WELCOME MESSAGE

It is our pleasure to extend a very warm welcome to the honourable scientists and young researchers participating in the two conferences -- the ***6th International Conference on Drug Discovery & Therapy*** and ***3rd Biotechnology World Congress*** the here in Dubai.

This series of conferences has attracted twenty six Nobel Laureates and many other leading scientists to Dubai. The conferences are serving to nurture collaborations with scientists in the region and to establish linkages between scientists in the developing world with those in the advanced Western countries.

Challenges faced by researchers include diseases associated with ageing populations, the spread of transmissible diseases in an interconnected world and the growing threat of resistance to drugs.

We wish to convey our special thanks to **His Excellency Sheikh Hamdan Bin Mubarak Al-Nahayan,** Honourable Minister of Higher Education and Scientific Research and **His Excellency Mohd. Omran Al Shamsi,** Chancellor, Higher Colleges of Technology for their cooperation. We are also most grateful to all the scientists who have travelled from the four corners of the world to the UAE to participate in these scientific symposia.

We hope that you will find your visit to Dubai intellectually stimulating and socially enjoyable.

PROF. FERID MURAD
(Nobel Laureate)
Co-President

PROF. ATTA-UR-RAHMAN, *FRS*
(UNESCO Science Laureate)
Co-President

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PLENARY LECTURES

PL-109

CURRENT AND FUTURE DRUG TREATMENT OF OBESITY

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Obesity is a chronic disease, and like other chronic diseases, will require long term treatment. Single treatments, whether they be lifestyle changes or drugs generally have quite modest effects over the long term. Virtually all other chronic diseases are treated with more than one intervention and clearly obesity will require combination treatment as well. The combination of diet, exercise, and behavior modification ("lifestyle change") is viewed as "standard treatment", but has a poor long term success rate. Diet, exercise, and behavior modification combined with obesity drugs is somewhat more positive. The rigid structure of a dietary supplement as a meal replac ement helps some people. However, the future of the treatment of obesity likely will reside with drugs and particularly with combinations of obesity drugs. Drugs change the biochemistry of the body and it is clear that obese people have a different biochemistry than do non-obese people. Food intake, energy expenditure, and storage of calories as fat have been so essential to survival of all organisms on Earth that it is not surprising that there are multiple redundant systems to stabilize them. Single drug treatments usually affect only one biochemical pathway or physiologic system. Single drugs currently used for the treatment of obesity all show modest weight loss. The current drugs used singly are adrenergic agonists (eg phentermine); orlistat, a lipase inhibitor; and locaserin, a 5-HT2c serotonin re-uptake inhibitor. Phentermine may produce a 10% or more wt loss, but orlistat and locaserin produce only about a 5% wt loss. Until recently, there have been few combinations of obesity drugs studied or approved. The best known was the combination of phentermine and fenfluramine or dexfenfluramine. Phen-fen produced wt loss of ~16%, the largest wt loss of any obesity treatment except obesity surgery. The removal of fenfluramine and dexfenfluramine from the market relegated obesity treatment to single drugs again since the combinations of orlistat and either sibutramine or phentermine are reported to be ineffective. The combination of phentermine and fluoxetine attempted to reproduce the success of the combination of an adrenergic agent and a serotonergic agent. Phen-flu was not quite as effective as phen-fen, but since both drugs are available on the market, this combination may be used with caution for obese people by physicians willing to run the risk of displeasure of the governmental authorities. Recently the combination of phentermine and topiramate has been approved. Studies show a wt loss of 10%-13% at one year. The combination of bupropion and naltrexone is currently under consideration by the FDA and clinical trials show a weight loss of about 6%-8%. Locaserin is approved only as a single drug, but the combination with phentermine has a similar biochemical profile as phen-fen. It remains to be seen if this combination will give similar results as phen-fen. Potential future agents for obesity may fall into several categories, including CNS active agents, thermogenic agents, and nutrient partitioning agents. A particularly interesting possibility for combination drug therapy are gut hormones or analogues of gut hormones since it appears that the excellent clinical results seen with obesity surgery are due mainly to alterations of gut hormones. Gastric bypass and similar surgical procedures work by altering the biochemistry of the body and not by mechanical mechanisms. It is possible we eventually may be be able to reproduce these effects with drugs. In this category, liraglutide, a GLP-1 agonist has been shown to be quite effective for diabetes and is in clinical trials as an obesity drug. Initial reports suggest it alone causes an 8% wt loss. We are in our infancy of understanding obesity, its causes and its treatments. The belated interest of the drug companies and the more favorable attitude of the FDA for obesity drugs predict a bright future.

PL-110

NATURAL-PRODUCT BASED DRUG DISCOVERY - CAN WE AFFORD TO IGNORE CHEMICAL DIVERSITY OF NATURE?

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Biodiversity is the outward manifestation of chemical diversity. Nature's treasure house of diverse classes of chemical has been the main source of blockbuster drugs in most of the 20th century. However, use of various non-validated techniques and emphasis on arsenal of synthetic chemists has led to decline productivity and increased cost. Drugs for most of the tropical diseases and prevailing diseases are simply not available with pharmaceutical pipeline nearly dried out. Question is how

long we can afford to ignore nature's tremendous chemical source as primary source of new pharmacophores. During last two decades we have been focusing on natural products. This has led to the identification of novel lead molecules.

Prolonged hyperglycemia is recognized as the characteristic of diabetes and most important and core cause of diabetes related disorders. It is now recognized that chronic hyperglycemia may trigger long-term damage to different proteins in the body by undergoing non-enzymatic glycation process. There are many factors which increase the worldwide prevalence of diabetes, these includes sedentary lifestyles, obesity, an increase in the aging population, consumption of calorie-rich diets. Diabetes is the third most common killer of mankind, after cancer, cardiovascular and cerebrovascular diseases. According to WHO (World Health Organization) till 2030 about 366 million people will suffer from diabetes.

Glycation is the most common non-enzymatic process, results in the formation of advanced glycation end products (AGEs), which affect all the tissues in the body. Modifications due to glycation accumulate during the life span. Different proteins were reported to undergo glycation when exposed to elevated levels of sugars (e.g. serum albumin, hemoglobin, elastin, crystalline, collagen, tubulin, myelin, fibrinogen, immunoglobulin, insulin, and lipoproteins, etc. Glycation is not only implied to be a marker of the development of diabetic complications, but also found to be the main reason of diabetic associated disorders. No enzyme in the body system is capable of hydrolyzing the AGEs or making their formation a reversible process. Hence, the AGEs accumulate in the body with time. This leads to abnormalities, such as diabetic retinopathy, atherosclerosis, diabetic nephropathy, neuropathy, etc. Therefore inhibition of glycation of proteins and formation of AGEs has attracted considerable scientific attention as a novel approach towards delaying the on-set of the AGEs-mediated late diabetic complications. Keeping in view of the therapeutic significance of antiglycation agents, the prime objective of our on-going research is to evaluate the inhibitory potential of different compounds of natural and synthetic origins. Over 3,000 fully characterized chemical constituents (both of natural and synthetic origin), were systematically evaluated for their antiglycation activity. As a result, a number of new and novel antiglycation agents from Parmotrema cooperi J. Steiner & Zahlbr. (lichen), Ziziphus oxyphylla Edgw., Morus mesozygia Stapf., Aloe sinkatana Reynolds. etc. were identified. Along with the natural antiglycation agents, we also identified a number of new and novel classes of synthetic antiglycation agents like anthranilic acid, isatin-3-thiosemicarbazone, bis Schiff bases of isatin, oxindole, chelocardin, flavonoids, thiazolidinone, urea, and benzohydrazide Schiff bases. Similarly a large number of compounds was screened for a-glucosidase inhibition, which may be used for the management of type 2 diabetes, as they have the potential to slow down the absorption kinetics of carbohydrates in the small intestine.

Obesity is an emerging challenge and a serious health problem worldwide. It is associated with many chronic diseases, such as diabetes, cardiovascular disorders and certain cancers. Molecular cascade involves in obesity and associated disorders are still not fully understood. Proliferation of adipocytes plays an important role in the on-set and progression of obesity. Understanding the phenomenon of adipogenesis is of major importance as adipocyte dysfunction makes an important contribution to metabolic diseases. Differentiation of preadipocytes to adipocytes not only results in increasing number of adipocytes but also provide a large pool of fat depots in adipose tissues. Thus one strategy to treat obesity is to reduce the adipocyte numbers and fat content through targeting the mature adipocytes by diverse molecular entities.

Among different therapeutic interventions, the discovery of effective antiadipogenic compounds from various sources is considered to be a promising approach. Our recent research is focused on the study of the inhibitory effects of natural and synthetic compounds, such as steroids, flavonoids, terpenes alkaloids and sulfonamides, on the proliferation of adipocytyes, as well as to evaluate their effects on to the mature adipocytes and their capacity to initiate lipolysis process. This study has resulted in the identification of several new inhibitors of adipogenesis process.

During this plenary presentation, underlying philosophy and approach of our research on cost-effective discovery of lead molecules at the interface of chemistry and biology will be discussed.

PL-54

CELL SIGNALING BY PROTEIN PHOSPHORYLATION

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A rapid overview of the past, present and future of signal transduction by protein phosphorylation will be presented. This process represents one of the most prevalent mechanisms by which eukaryotic cellular events are regulated. It is involved in the control of many physiological processes and pathological conditions including various bacterial and viral diseases. After recalling how this field has originated and evolved in the last sixty years, the talk will focus on cellular regulation by protein tyrosine phosphorylation. This process is directly implicated in cell growth, differentiation

and transformation, bringing into play a diversity of tyro sine kinases of viral or cellular origin or linked to growth factor receptors. The receptors transduce their signal by recruiting a multiplicity of adapter proteins interacting with one another in a tinker-toy sort of way through a wide variety of binding modules (SH2, SH3, WW, PH, PDZ, *etc*.) thereby initiating a diversity of signaling cascade pathways.

Regulation also involves protein tyrosine phosphatases, an expanding family of transmembrane and intracellular enzymes that catalyze the reverse reaction. Most receptor forms have highly variable external domains that, surprisingly, display all the structural characteristics of cell adhesion molecules, suggesting that they must be involved in – or regulated by – cell-cell interaction, with the very exciting possibility that they might be directly implicated in contact inhibition that plays such a crucial role in carcinogenesis. Protein tyrosine phosphatases cannot be viewed as simply providing the "off" switch in an "on/off" kinase/phosphatase system: depending on their structure and where they localize within the cells, they can act either positively or negatively in eliciting a particular physiological response.

We begin to understand the links that exists between the disruption of protein kinases and phosphatases and the etiology of certain human diseases. Some of the attempts that are being made to develop therapeutic tools to target these enzymes will be presented.

PL-108

BIOLOGICAL BASIC RESEARCH AND ITS TRANSLATION INTO PRACTICE AND BUSINESS, MY EXPERIENCE

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As a student in the early nineteen sixties, I had the privilege to attend winter seminars organized by my mentor, W. Hoppe, and by M. Perutz, which took place in a small guesthouse in the Bavarian-Austrian Alps. The entire community of a handful of protein crystallographers assembled in a room which served as living and dining room and as auditorium for the lectures.

Today structural biologists organize large congresses with thousands of attendants and there exist many hundreds of laboratories specialized in this field. It appears to dominate biology and biochemistry very visibly if we count covers in scientific journals displaying macromolecular structures.

Structural biology was successful, because it was recognized that understanding biological phenomena at the molecular and atomic level requires to see those molecules.

Structural biology revealed the structure of genes and their basic mechanism of regulation, the mechanism of enzymes' function, the structural basis of immune diversity, the mechanisms of energy production in cells by photosynthesis and its conversion into energy- rich chemical compounds and organic material, the mechanism that makes muscle work, the architecture of viruses and multi-enzyme complexes, and many more.

New methods had an essential impact on the development of structural biology. Methods seemed to become available in cadence with the growing complexity of the problems and newly discovered methods brought biological problems within reach for researchers, a co-evolutionary process of the development of methods and answerable problems.

An important additional incentive for structural biology came from its potential application for drug design and development by the use of knowledge of drug receptors at the atomic level. The commercial interest in application spurred this direction of research enormously.

My lecture will start out with the history of protein crystallography and describe the major factors contributing to its development, illustrated with examples contributing to our understanding of the physical and chemical basis behind biological phenomena.

I then will let you share my experience with the foundation and development of two biotech companies with different business models, but both based on basic academic research in structural biology:

Proteros (www.Proteros.com) offers enabling technology services for Pharma- and Crop science companies imbedding all steps of the workflow molecular and structural biology can provide and commands and uses its platform for the generation of leads from identified targets to *in vivo* Proof of Concept (PoC).

Suppremol (www.Suppremol.com) specializes in the development of novel immunoregulatory therapeutics for the treatment of autoimmune diseases on the basis a recombinant, soluble, non-glycosylated version of the human Fcγ receptor IIB.

PL-3

TARGETING PAK1 KINASE IN HUMAN CANCER

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The process of cancer progression to more invasive phenotypes is profoundly influenced by dysregulation of pathways that control cytoskeleton remodeling, cell-cycle progression and mitosis, cell survival, transformation, chromatin remodeling, and genomic stability. Further, devastating influence of cancer invasiveness is also fueled by persistent stimulation of pathways that counteract commonly used cancer therapies targeti ng receptor-tyrosine kinases, mitogenic and/or survival signaling modules. One of the major signaling nodules of extracellular stimuli that plays an important role commending role in the above cancer phenotypes is p21-activated kinase 1 (PAK1), a widely overexpressed nodular molecule in human cancer. Recent studies have implicated PAK1 in the nucleus with new functions. Interestingly, PAK1 hyperstimulation also leads to mitotic abnormalities such as multipolar spindles and activation of Aurora kinase, an important mitotic regulator. In this context, emerging data suggest that a novel physiologic PAK1 substrate, could effectively regulate Aurora kinase activity and function, and in-turn, and participates in defective mitosis. Since mitotic defects leads to the development of aneuploidy and because such cells are likely to be resistant to anti-cancer drugs, these findings suggest that PAK1 and its targets could be effectively co-targeted to achieve a greater anti-cancer activity and possibly to sensitize tumor cells to anti-cancer modalities. Thus, the levels, subcellular localization, and activation status of PAK1 is likely to be an important determinants of tamoxifen resistance, and that raising the possibility that tamoxifen resistance might be prevented or reversed by PAK1 inhibition. The presentation will summarize the most exciting PAK1 data in the area of cancer biology and provide an up-to-date status of PAK1 as a cancer therapeutic target.

PL-2

SUPRAMOLECULAR AND ADAPTIVE CHEMISTRY BIORGANIC AND DRUG DISCOVERY ASPECTS – RECENT ADVANCES

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Supramolecular chemistry aims at constructing and implementing highly complex chemical systems from molecular components held together by non-covalent intermolecular forces. It has relied on the development of preorganized molecular receptors for effecting *molecular recognition*, catalysis and transport processes. The implementation of molecular recognition and transport processes in systems of biological significance will be described, in particular in the development of a bioactive molecule, *myo*-Inositol TrisPyroPhosphate (ITPP) displaying remarkable properties of interest in cardiovascular diseases and cancer.

Supramolecular chemistry is intrinsically a *dynamic chemistry* in view of the lability of the interactions connecting the molecular components of a supramolecular entity and the resulting ability of supramolecular species to exchange their molecular constituents. The same holds for molecular chemistry when the molecular entity contains covalent bonds that may form and break reversibility, so as to allow a continuous change in constitution by reorganization and exchange of building blocks. These features define a *Constitutional Dynamic Chemistry* (CDC) on both the molecular and supramolecular levels.

CDC takes advantage of dynamic constitutional diversity to allow variation and selection so as to achieve *adaptation*, opening the path towards *adaptive chemistry*. Its combinatorial features led to the development of a *dynamic combinatorial chemistry*, as a novel approach to drug discovery.

Supramolecular chemistry and CDC have also opened novel perspectives in materials science, in particular towards the development of supramolecular and dynamic materials for biological and medical applications.

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PL-56

REWRITING NATURAL PRODUCT DRUG DISCOVERY THROUGH SYNTHETIC BIOLOGY

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Natural product chemicals have historically been discovered based on their structural and biological properties. With the ease and affordability of genome sequencing today, a new era in natural product discovery is unfolding in which genomics and biosynthesis are together fostering new innovations in compound discovery. This orthogonal discovery approach takes advantage of the biosynthetic potential of a genomesequenced organism to design hypothesis-driven experiments to rapidly find new chemical entities that are desperately needed in the drug discovery and development pipeline. Examples from the author's laboratory will highlight the myriad of available and evolving genome mining approaches to connect orphan biosynthetic genes to new natural product molecules.

PL-1

APPLICATION OF NITRIC OXIDE RESEARCH TO DRUG DEVELOPMENT AND DISEASE THERAPY

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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 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 cofactors and regulators including NADPH, tetrahydrobioterin, 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 guanlyl cyclase and increasing cycling 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, while other reactions can lead to altered protein structure function and/or catalytic capacity. These effects 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 antacoid, 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 1870s. 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 discover 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 formulation 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 march to develop novel and important therapeutic agents. There are presently more than 80,000 publications in the area 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 industrials will also be discussed.

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PL-55

TARGETING SOLUBLE GUANYLATE CYCLASE FOR THE TREATMENT OF CARDIOPULMONARY DISEASE

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The soluble guanylate cyclase (sGC) is a key signal-transduction enzyme in the cardiovascular system and activated by NO. It became apparent that many cardiovascular diseases are associated with a dysfunction of the NO/sGC system. Importantly, two different forms of sGC exist *in vivo*, the native and heme-free sGC. sGC activators, such as cinaciguat (BAY 58-2667) are capable of selectively activating the haem-free enzyme via binding to the enzyme's haem pocket. These new compounds selectively target the dysfunctional sGC that is prevalent under disease conditions. Cinaciguat has demonstrated efficacy in patients with acute decompensated heart failure (ADHF), reducing pre- and afterload and increasing cardiac output. sGC stimulators, such as riociguat (BAY 63-2521), show a dual mode of action: they sensitize sGC to the body's own NO while also directly stimulating sGC independently of NO. They may be beneficial in the treatment of a range of cardiovascular and non-cardiovascular disorders. Riociguat had beneficial effects on pulmonary haemodynamics, right heart hypertrophy, and remodeling of the pulmonary vasculature in different experimental models of pulmonary hypertension (PH). In phase III studies riociguat has demonstrated efficacy in patients with pulmonary arterial hypertension (PAH) and, remarkably, also in patients with chronic thromboembolic pulmonary hypertension (CTEPH). Very recently, the Food and Drug Administration (FDA) has approved Adempas® (riociguat) for use in these two forms of pulmonary hypertension: The treatment of adults with persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class; and the treatment of adults with PAH to improve exercise capacity, improve WHO functional class and delay clinical worsening.

KEYNOTE LECTURES

KN-8

Track: *Protein and Peptide Sciences*

TARGETING TAU PROTEIN AGGREGATION IN ALZHEIMER'S DISEASE

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Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by neurodegeneration in specific brain regions. Pathological hallmarks that accompany and/or precede neuronal death include neurofibrillary lesions, which develop intracellularly and correlate spatially and temporally with disease severity. The principal components of neurofibrillary pathology are filamentous aggregates composed of the microtubule-associated protein tau. Because of its utility as a surrogate marker for neurodegeneration in AD and other "tauopathic" neurofibrillary degenerative diseases, detection of tau aggregates is of practical importance for disease diagnosis and staging. Abnormalities in tau biology may also directly contribute to neurodegeneration, including synapse loss and cell death. If so, then pharmacological modulation of the aggregation pathway could have therapeutic utility. For these reasons, the search for disease-modifying therapies includes approaches for inhibiting and/or clearing tau aggregates.

Here two aspects of neurofibrillary pathology and pharmacology will be discussed. First, a wealth of animal studies point to size as being a major determinant of aggregate toxicity, but the species involved and their mechanism of action have been elusive. Using kinetic modeling methods, I will present evidence that filament ends are highly interactive and positioned to mediate length-dependent aggregate toxicity.

Second, although small-molecule inhibitors of tau aggregation have been reported, the common characteristics of these ligands and their mechanism of action have not been elucidated. Using biochemical and computational approaches, I will present evidence that planar, highly polarizable molecules inhibit tau fibril formation by interacting with partially folded tau intermediates to form soluble oligomers. The results suggest a route for optimizing the inhibitory potency of tau aggregation inhibitors while maintaining favorable pharmacokinetic properties.

KN-14

Track: *CNS Drug Discovery & Therapy*

ADVANCES IN DISCOVERY OF NOVEL DRUG TARGETS FOR NEURODEGENERATIVE DISEASES

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Neurodegeneration is defined as the progressive loss of structure or function of neurons, including neuronal death. Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), occur as a result of neurodegenerative processes. Many similarities exist between these diseases on a sub-cellular level. Discovering these similarities provide optimism for therapeutic advances that could ameliorate both AD and PD. Several recent advances are noteworthy in laying a solid biological foundation for understanding AD (Lahiri, Curr. Alz.. Res., 2013). Many parallels exist between various neurodegenerative disorders including atypical protein assemblies as well as induced cell death. AD is the most common form of dementia and characterized by the presence of amyloid-β (Aβ) peptide plaques and is believed to result from the misregulation of the production or clearance of Aβ. The rate-limiting step in the production of Aβ is the processing of amyloid- β precursor protein (APP) by a β-secretase called β-site APP-cleaving enzyme (BACE1). Dysregulation of proteins involved in Aβ production, such as APP and BACE1, may contribute to excess Aβ deposition. Elucidating how expression of these proteins is regulated will ultimately reveal new drug targets. We have utilized the novel approach of studying the regulation of these gene products by microRNAs (miRNAs). MiRNAs are an abundant class of small RNAs that mediate potent inhibitory effects on global gene expression. Recent advances in molecular methods allow us to study the contribution of these miRNAs to gene expression in CNS disorders, such as AD (Long and Lahiri, Exp. Neurol., 2012). Here we present data demonstrating

miRNA-mediated regulation of APP and BACE1. Using multiple bioinformatic tools and a series of functional studies in neuronal and glial cultures as well as in human brain tissue specimens, we reported specific microRNA species regulate APP levels, such as miR-101 and miR-153 (Long, and Lahiri, BBRC, 2011; Long, Ray and Lahiri, J. Biol. Chem., 2012). Furthermore, we examine neuroprotective and neuropreservative effects of pharmacological drugs, such as rivastigmine, and of nutraceuticals, such as nanocurcumin (Bailey *et al*., PLoS One, 2012) in neuronal cultures and *in vivo*. Specific compounds obtained from several nutrients have displayed beneficial roles in preserving and protecting neurons from degeneration and can have potential therapeutic efficacy in AD. Taken together, these results from molecular, cellular and pharmacological studies would accelerate further studies with these compounds in larger pre-clinical and clinical settings.

This work is supported by grants from Alzheimer's Association and NIH to Dr. D.K. Lahiri.

KN-84

Track: *Innovative Drug Discovery and Nanotechnology*

LIPOTEICHOIC ACIDS OF GRAM-POSITIVE BACTERIA - SYNTHESIS AND SOME BIOLOGICAL PROPERTIES

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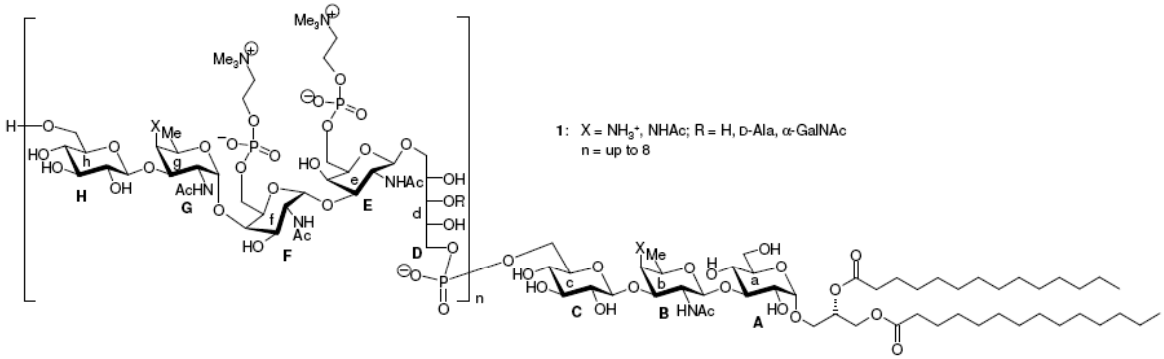
Gram-positive bacteria are causing many infectious diseases; nevertheless, these bacteria are not as well understood as Gram-negative bacteria. It is assumed that amongst the immunoactive constituents of the cell wall of Gram-positive bacteria are lipoteichoic acids (LTAs). They are amphiphilic, negatively charged, structurally quite different glycolipids that were classified into four types (type I-IV). The most frequently isolated Gram-positive pathogen causing infections is *Staphylococcus aureus* possessing an LTA classified as type I that has been synthesized in our group and biologically evaluated. LTAs that also gained great interest are type II LTAs isolated from *Lactococcus garvieae* and particularly type IV LTA **1** isolated from *Streptococcus pneumoniae*, respectively [1]. All three LTAs are structurally quite different, but they are believed to interact with the innate immune system in a similar fashion, which is by stimulation of TLR2. Hence, chemical syntheses leading to structurally defined material should have a major impact on these studies. The results will be discussed.



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INVITED LECTURES

IL-58

Track: *Pharmaceutical Research & Development*

POPULATION-BASED STUDIES OF REAL-LIFE COMPARATIVE EFFECTIVENESS AND SAFETY OF DRUGS: ADVANTAGES OF USING FLEXIBLE CUTTING-EDGE STATISTICAL METHODOLOGY

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Recent large governmental initiatives e.g. Canadian Drug Safety and Effectiveness Network emphasize the need to assess the real-life effectiveness and safety of drugs in population-based studies. Such studies are typically analyzed with conventional statistical models, adopted from phase III randomized clinical trials (RCT), or epidemiological studies, which use simplistic metrics of drug use, e.g. current dose, or any use in the past 3 months. These metrics ignore important variation in the patterns of drug use in real-life clinical practice, where daily doses, treatment duration, frequency of treatment interruptions, all vary substantially between subjects and within-subject over time. We present both simulation-based and real-life data illustrating how the above limitations of the models used in (comparative) effectiveness studies seriously hamper the ability to detect the important benefits or adverse effects of a new drug. We then demonstrate how our new, flexible statistical methodology, that accounts for variation in drug use patterns and cumulative effects, helps assessing accurately the causal effects of drugs in population-based studies and produces results consistent with the drug pharmaco-dynamics/-kinetics characteristics. The advantages of our new methodology are illustrated with empirical studies of the associations between (1) benzodiazepines and fractures, and (2) oral glucocorticoids and infections.

IL-85

Track: *Nutraceutical Drug Discovery & Therapy*

VITAMIN D REGULATES HIGH CHOLESTEROL HIGH FRUCTOSE-INDUCED CHANGES IN CORONARY ARTERY DISEASE

Devendra K. Agrawal

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Approximately 1 billion people worldwide are vitamin D insufficient or deficient. In the U.S. and Europe, 40-80% elderly population still living in the community is deficient in vitamin D. Serum 25(OH)D levels have been used as a surrogate measure of an individual's vitamin D status as it reflects both vitamin D intake from the diet and the intake from skin synthesis of vitamin D. There is a controversy over the cut-off-point values as determinants of 'deficiency' or 'insufficiency'. None-the-less, it is critical to evaluate the relationship between vitamin D deficiency/insufficiency with the pathophysiology and severity of the disease and determine whether supplementation with oral vitamin D would alleviate these problems.

Based on peripheral evidence, there is an association between vitamin D deficiency and cardiovascular disease. Decreased levels of 25(OH)D and calcitriol are independently associated with cardiovascular morbidity and mortality. Vitamin D can regulate endothelial dysfunction, vascular compliance, inflammation, and effects relating to parathyroid hormone, renin-angiotensin system. Indeed, an association between 25(OH)D deficiency and endothelial dysfunction and increased lipid peroxidation has been found in asymptomatic subjects and vitamin D supplementation improved endothelial function. Vitamin D supplementation may help in reducing the adverse cardiac events in patients with coronary artery disease. However, most of the studies which identified an association between lower vitamin D intake or lower 25(OH)D and increased risk of cardiovascular disease are observational or cross-sectional studies and hence their strength is limited. Also, the effect of vitamin D supplementation on blood pressure is still unclear and no effect of vitamin D supplementation on coronary heart disease has been clearly demonstrated. The evidence is inconsistent and

inconclusive as to causality. Therefore, vitamin D supplementation is not recommended in routine treatment for cardiovascular disease.

Although balloon angioplasty with stent implantation has been a successful strategy for the treatment of coronary artery disease (CAD), long-term prognosis has been less promising due to the development of intimal hyperplasia and restenosis**.** Both balloon angioplasty and stent placement cause injuries in the intima, media and sometimes adventitia. This results in a cicatricial process comprising proliferation and migration of smooth muscle cells (VSMCs) towards the intima and secretion of extracellular matrix forming a neointimal thickening of vessel leading to restenosis. However, introduction of drug eluting stents (DESs) seemed to address the restenosis problem by site-specific delivery of paclitaxel or sirolimus to prevent proliferation and migration of VSMCs. But, DESs are susceptible to another complication known as "late stent thrombosis" due to inhibition of re-endothelialization of stented segment. This condition can occur within a year after the placement of the DES and is characterized by blood clotting inside the stent. Thrombosis is very rare, but, it is extremely dangerous and fatal in almost over one third of cases.

Despite extensive research in the last decade, we are still not sure how to predict or prevent intimal hyperplasia and restenosis.

We have recently made several novel observations: (i) porcine coronary artery smooth muscle cells express VDR and vitamin D metabolizing enzyme machinery. Calcitriol inhibits PGDF-BB-induced proliferation and migration of coronary artery SMCs. Thus, it is possible that the patients prone to develop intimal hyperplasia following coronary intervention are vitamin D-deficient and vitamin D supplementation prior to interventional procedures might be helpful in the prevention of intimal hyperplasia in coronary artery disease patients, (ii) Calcitriol decreases the expression of importin-α3 thereby decreasing the import of NF-κB to the nucleus, (iii) both CYP27B1 (enzyme that converts 25(OH)D into calcitriol) and CYP24A1 (catabolizing enzyme for calcitriol) are present in human white blood cells and vitamin D administration for 1 year in 78 women (59-80 yr old) with vitamin D insufficiency (<20 ng/ml) increased the mRNA transcripts of these enzymes in WBCs, suggesting the presence of the machinery for vitamin D metabolism in human WBCs, and (iv) vitamin D supplementation for one year significant increased VDR and cathelicidin expression and decreased importin-α3 in the WBCs. These *in-vitro* and *in-vivo* data further support the theory that vitamin D administration decreases importin-α3 resulting in decreased import of NF-kB into nucleus. This could be one of the underlying mechanisms for the anti-inflammatory and immunoregulatory effects of vitamin D in inflammatory diseases.

Together, these observations support the anti-inflammatory effects of vitamin D and thus could maintain the immune response following injury due to balloon angioplasty or intravascular stenting. Vitamin D deficiency will exacerbate the immune response leading to increased inflammation and uncontrolled proliferation of the intimal cells towards lumen, resulting in restenosis. Accordingly, vitamin D deficiency might predict CAD patients who develop restenosis following coronary intervention and therefore, vitamin D supplementation will decrease pro-inflammatory markers and increase anti-inflammatory mediators, resulting in significant decrease or no intimal hyperplasia.

In my presentation, I will share recent findings on the effect of high fructose high cholesterol diet on the development of atherosclerotic lesions in coronary arteries and changes in the phenotype of epicardial adipose tissue, and how the vitamin D status affect such changes and the outcome results following interventional procedures in atherosclerotic coronary arteries.

Briefly, Yucatan microswine were fed with high fructose high-cholesterol diet. Atherosclerotic lesions were confirmed by coronary angiography and histology. Immunostaining was performed in the adipose tissue and coronary arteries for macrophage phenotype. Contraction and relaxation of coronary arteries was examined in organ bath studies. In obese swine fed with high-fructose high-cholesterol diet, there was significant infiltration of CD86+ cells (M1 macrophages) with minimal immunostaining to CD206 (M2 macrophages) in adipocytes, which was increased in adipocytes of vitamin D-supplemented swine. Similar pattern was found in coronary arteries. Compared to vitamin D-sufficient high-cholesterol diet, vitamin D-deficient high-cholesterol swine EAT showed dense inflammatory cell infiltrate with significantly decreased expression of SOCS3 protein and marked increase in TNF-α, MCP-1, and IL-6 expression in EAT. The contractile response to serotonin in both carotid and coronary arteries of atherosclerotic swine was much higher in the vitamin D-deficient than in vitamin D-sufficient group. Norepinephrine (NE)-induced contraction in carotid and dilatation in coronary arteries, which was lower in vitamin D-deficient than vitamin D-sufficient swine. We conclude that high-fructose high-cholesterol diet enhances pro-inflammatory macrophages, increases vasoconstriction and decrease vasodilatation. Vitamin D supplementation could be beneficial in preventing metabolic effects in atherosclerosis.

IL-61

Track: *Hot Topics in Medicinal Chemistry*

STRUCTURE-BASED DRUG DESIGN OF POTENT BACE1 INHIBITORS: POSSIBLE DRUG LEADS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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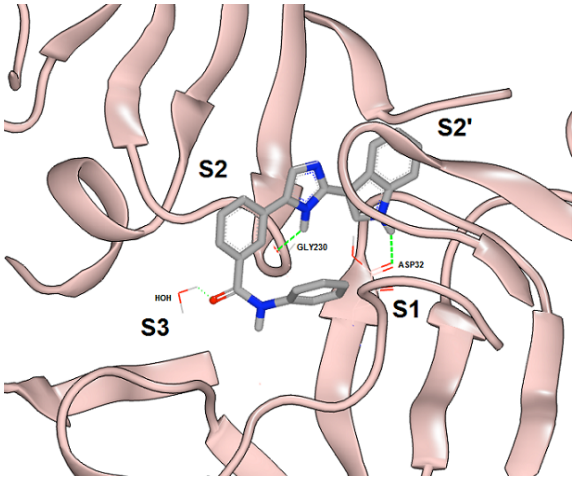
Alzheimer's disease (AD) is a progressive, neurodegenerative disorder and considered the most common form of irreversible dementia. To date, treatment of AD only partly reduces the symptoms and does not affect the underlying progression of the disease. More than 25 million people are suffering from dementia and the annual socioeconomic worldwide costs have been estimated to exceed US$200 billion. Although, the cause of AD remains unknown, a large body of evidence is beginning to in the pathogenesis of the β accumulate that highlights the central role of A disease. Recently, we have disclosed the discovery of small molecules isophthalic acid and imidazopyridine derivatives as potent BACE1 inhibitors. In early SAR investigations we quickly learned that the truncation of the benzimidazole portion on isophthalic acid led to the more compact scaffold, possessed a 10-fold enhancement in potency (IC50 = 3.4 nM). Soon afterward we carried out detailed structure-activity relationship studies that ultimately led to 1900-fold improvement of ligand affinity for BACE1 enzyme (Figure **1**) [1]. In this presentation, we will disclose our efforts gained over the years in this regard.



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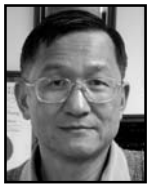
IL-97

Track: *Stereoselective Synthesis of Bioactive Compounds*

NANOSTRUCTURED SUPPORT AND MEMBRANES FOR CHIRAL ENZYMATIC AND ORGANIC SYNTHESES

Steven S.C. Chuang



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The reaction and adsorption of bioactive compounds on the supported enzymes/catalysts has been a subject of extensive studies because of its potential applications in lowering the production cost of chiral compounds and allowing efficient screening of the potential candidate materials for the development of the active catalyst. This presentation will discuss (i) the approaches for immobilization of enzymes and preparation of chiral selective catalysts and (ii) the mechanisms of enzyme immobilization and catalyst preparation as

well as associated synthesis reactions. Specific examples to be discussed will include immobilization of oxidase by micro/nanoporous polyvinyl alcohols and chiral modification of supported nanoscale metal catalysts. The kinetics and dynamics of the reactions catalyzed by immobilized enzyme and modified catalysts were studied by the in situ infrared and Raman spectroscopy. The results of the spectroscopic studies showed that the ratio of the hydroxyl and amine function groups and their density on the surface of micro/nanoporous polyvinyl alcohols affects the infrared intensity of amide I and II in the oxidase, an indicative of the conformational changes of the enzymes, which govern their activity. The results also showed the nature of supports and metal particle sizes control the activity and selectivity of the synthesis of chiral β-amino acid, a precursor for the synthesis of biologically active compounds. Emphasis will be placed on how to design in situ experiments for mechanistic studies and for enzyme/catalyst screening as well as how to use mechanistic information to develop chiral selective synthesis and separation processes.

IL-80

Track: *Anti-Infectives*

THE FUTURE CHALLENGES FACING ANTIMICROBIAL THERAPY: RESISTANCE AND PERSISTENCE

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The emergence of resistance to antimicrobial agents is a pressing concern for human health that increases the need for the development of novel antimicrobial drugs. Antimicrobial resistance means that microorganism keep on growing even in the presence of a drug due to specific defense mechanisms (e.g. efflux-pumps). Many of infectious diseases are difficult to be treated with antimicrobials not due to resistance but persisters (non-multiplying cells). Distinction is important as persistent cells need an entirely design of new antimicrobial agents. Non-multiplying cells, do not cause overt disease but prolong the duration of therapy, increasing the chance of the emergence of resistance (i.e. bacterial or fungal biofilms and latent tuberculosis) resulting in therapy failure. Persisters are phenotypic variants of the wild type that present in all microorganisms which are able to survive antimicrobial treatment without acquiring resistance or conferring genetic changes and upon re-growth they produce a population of sensitive cells and new persisters. Persistence may arise spontaneously regardless to the presence of drug or environmentally induced due to starvation, DNA damage, oxidative stress and quorum sensing. Many approaches targeting non-multipliers would shorten the duration of therapy and decrease the emergence of resistance. Some depends on studying the effectiveness of the existing therapeutics against non-multipliers (i.e. pyrazinamide and gatifloxacin) and others depend on the discovery of new compounds targeting microbial genes that might be essential to non-multipliers viability or specific enzymatic or metabolic pathway (i.e. TG44 targets outer membrane of *Helicobacter pylori* and TMC207 targets proton pump of the ATP synthaes in *Mycobacterium tuberculosis*). Clinical trials and studies are needed to produce a marketed antimicrobial agent active against both multiplying and non-multiplying organisms and to know whether the approach of targeting non-multiplying bacteria is clinically relevant and will produce compounds that reduce the rate of emergence of bacterial resistance.

Keywords: Antimicrobial resistance, non-multiplying microorganisms, *M. tuberculosis*, persisters.

IL-114

Track: *Recent Advances in Spectroscopy*

SIMULTANEOUS USE OF SEVERAL CHIROPTICAL METHODS IN CONFIDENT STRUCTURE ELUCIDATION OF PHARMACEUTICALLY PROMISING MOLECULES

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Determination of the molecular structure of isolated natural products or synthesized compounds continues to be an important challenge in the organic and medicinal chemistry. This is undoubtedly

due to the close dependence between the biological activity and the stereostructure of bioactive compounds. Therefore, the access to the methods allowing simple and unequivocal determination of their absolute configuration and/or conformation is of high importance. The circular dichroism spectroscopy is the technique of choice for elucidating chirality, and, in particular, for monitoring and characterizing even smallest changes of a molecule in solution and solid state. It is also commonly well known that the use of more than one chiroptical method considerably increases the reliability of stereochemical assignment. Therefore, during the present lecture, the most recent results on the combined application of both the electronic (ECD) and the vibrational circular dichroism (VCD) in the structure elucidation of a broad variety of important bioactive compounds will be presented.

The scope of the -lactam antibiotics, β lecture includes, among others, *cis*- and *trans*-enones, DNA bases, vitamins, sugars, etc. (Figure **1**). Special emphasis will be placed on the effectiveness of such a combined ECD and VCD approach in solving structural problems, which with other spectroscopic methods, such as e.g. NMR, cannot be unambiguously resolved. The studies are supported by a thorough conformational analysis and TD-DFT calculations.

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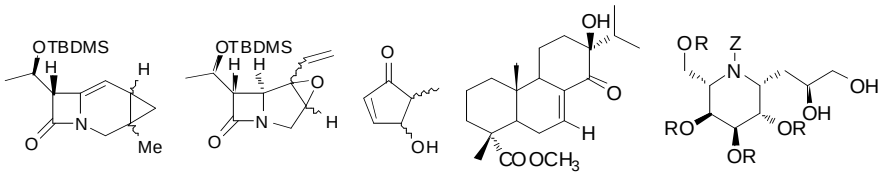

Figure 1. Selected structures of the compounds under discussion.

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IL-129

Track: *Diabetes and Obesity Drug Discovery & Therapy*

DIETARY TREATMENT OF TYPE 2 DIABETES

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Our research group is interested in the dietary treatment of people with type 2 diabetes. We have developed diets we refer to as Low Biologically Available Glucose Diets, or LoBAG Diets. The general concept is, that of the dietary mono-, di- and polysaccharides, only glucose (or potential glucose) is responsible for the elevated blood glucose in people with type 2 diabetes. The LoBAG diets consist of 30% protein, which is higher than traditionally ingested. In various studies, the carbohydrate content has been 20%, 30% or 40%. The remainder was fat (10% saturated). The carbohydrate content of the diet is indicated by a subscript – thus a LoBAG30 diet is composed of 30% carbohydrate, 30% protein, and 40% fat. The control diet consisted of 55% carbohydrate, 15% protein, 30% fat (10% saturated). The LoBAG30 diet has been studied for the longest period (10 weeks). In addition, more metabolic parameters have been studied using the LoBAG30 diet. In randomized, crossover designed short-term studies of 5-10 weeks the decrease in glycated hemoglobin (HbA1c) is similar to, or greater than that obtained with commonly prescribed oral medications. This occurred without deleterious changes in blood lipid profiles or in kidney function, as determined by creatinine clearance.

IL-112

Track: *Medical Imaging*

CONTRAST FREE MAGNETIC RESONANCE IMAGING (MRI) FOR EARLY DETECTION OF HYPOXIA INDUCED ACUTE KIDNEY INJURY (AKI)

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Background: Acute kidney injury (AKI) is common and often fatal. Severe blood loss during major operations and sepsis are common causes of AKI. Detection of AKI oftentimes is delayed due limited sensitivity of diagnostic methods. Here, we present new magnetic resonance imagining (MRI) techniques to detect and to monitor experimental AKI characterized by decrease of renal perfusion and edema formation. The MRI techniques were validated in patients with AKI after lung transplantation.

Methods: Renal ischemia reperfusion injury (IRI) was induced in mice by transient unilateral clamping of the left renal pedicle. MRI was performed prior to surgery and at different time points thereafter (day 1, 7, 14, 21, 28). Renal morphology, glomerular filtration rate, renal blood flow, expression of alpha-SMA and as well as inflammatory cell infiltration was investigated. For further validation, two weeks after lung transplantation patients were investigated by functional MRI.

Results: AKI induced renal perfusion impairment was detectable 24h after injury and deteriorated until day 7. Edema formation and changes in apparent diffusion coefficient (ADC) correlated with inflammation and fibrosis. Histological dramatic increase infiltrating cells were observed. Reduction of MRI measured renal perfusion was verified by PAH clearance to investigate systemic renal blood flow (RBF). The MRI techniques also were save in patients after lung transplantation and showed clearly that also in patients AKI can be classified and detected by renal blood flow impairment.

Conclusion: Our study proves that contrast free MRI is a new and safe technique for early detection of AKI without contrast media.

IL-82

Track: *Anti-Cancer Drug Discovery & Therapy*

PHYTOCHEMICALS IN COMBINATION WITH TARGETED THERAPY CAN PROVIDE A MEANS TO OVERCOME DRUG RESISTANCE IN OVARIAN CANCER

Fazlul Huq

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Whereas platinum resistance is associated with increased expression of anti-apoptotic factors and pathways such as NF-kB and AKT, a number of phytochemicals serve to dampen their expressions so that they may act synergistically in combination. In this study we investigated synergism from combination of widely used platinum drugs and selected tumour active phytochemicals including curcumin, EGCG, thymoquinone, resveratrol and genistein in human ovarian tumour models. Generally sequenced combinations with 2 to 4 h time gap are found to be synergistic whereas the bolus is often antagonistic. The variation in nature of the combined drug action with change in sequence of administration clearly indicates that the action of one drug modulates that of the other. Proteomic studies have identified over thirty proteins that are believed to be associated with platinum resistance in ovarian cancer. They belong to six major groups including cytoskeletal proteins, molecular chaperone and stress related proteins, proteins involved in detoxification and drug resistance, proteins involved in metabolic processes and mRNA processing proteins. Synergistic outcome from combinations of cisplatin with phytochemicals is found to be associated with down-regulation of mRNA

processing proteins that play a variety of roles in tumour development and progression, and up-regulate molecular chaperones that are needed for constant surveillance to ensure normal protein homeostasis. Detoxification and drug resistance proteins are found to be up-regulated after treatment with synergistic combinations of Cis with other phytochemicals, indicating that the phytochemicals have served to sensitize resistant A2780^{cisR} cancer cells towards platinum action by targeting various cellular pathways.

IL-4

Track: *Chemistry*

DEOXYGENATIVE OLEFINATION REACTION AS THE KEY STEP IN THE SYNTHESES OF DEOXY CARBOHYDRATES

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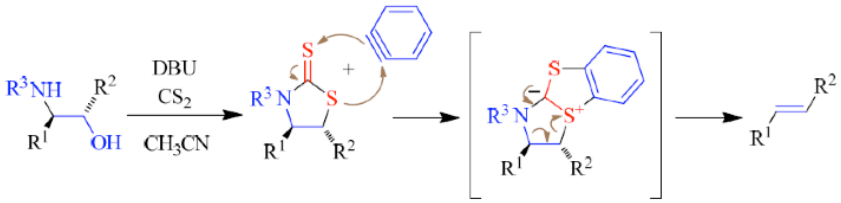
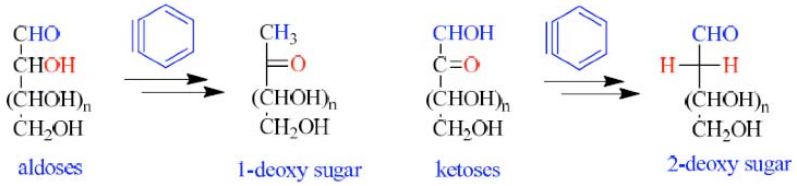
Our success in the development of a novel benzyne-induced method for the generation of the C=C from β-amino alcohols is reported in this talk (see Scheme **1**). This new method was developed as the key step in the newly developed strategy for the syntheses of deoxy- and imino-carbohydrates.

Carbohydrates with significant biological activities are discovered in profusion; some of which possess special structures of deoxy sugars and iminosugars. In deoxy sugars, one or more carbon atoms have been reduced, thus losing their hydroxyl groups. Iminosugars are analogs of sugars having a nitrogen atom at the position of the endocyclic oxygen atom. Some of these sugars possess immense therapeutic potential in various diseases, such as cancer, diabetes, and viral infection. As shown in Scheme **2**, the new synthetic strategies involves deoxygenation, olefination, and cleavage of an endocyclic O–C single bond at the glycosidic carbon center. In this talk, we report new results on approval of the feasibility and generality associated with the deoxygenative olefination by a benzyne-induced method in carbohydrate syntheses.



Scheme 1



Scheme 2

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IL-140

Track: *Pharmacogenomics*

TRENDS IN DIAGNOSTIC BIOCHIP DEVELOPMENT

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Technological advancements in biochips for diagnosis and prevention lead to improved healthcare cost containment with a decreasing birth rate and an aging population. Biochips have been attracting attention as a tool for improving healthcare costs. There are technological, standardization-related, ethical and societal problems in biochip development. For biochip market expansion, in addition to technological problems, it is necessary to overcome social, institutional, marketing and economic problems all together. It is expected that the application of biochip technologies will facilitate not only 'super' early diagnosis of diseases and disease prevention based on the diagnosis, but also early treatment.

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IL-105

Track: *Hot Topics on HIV Research*

RIBONUCLEOSIDE CHAIN TERMINATORS: HIV-1 RESERVOIR SPECIFIC ANTI-VIRALS FOR HIV-1 CURE

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Terminally differentiated/non-dividing macrophages are well known long-lived reservoirs of HIV-1, and blocking HIV-1 replication in these viral reservoir cells is essential for HIV-1 eradication and cure. Unlike activated CD4(+) T cells, this nondividing HIV-1 target cell type contains a very low level of the deoxynucleoside triphosphates (dNTPs) required for proviral DNA synthesis whereas the ribonucleoside triphosphate (rNTP) levels remain in the millimolar range, resulting in an extremely low dNTP/rNTP ratio. Biochemical simulations demonstrate that HIV-1 reverse transcriptase (RT) efficiently incorporates ribonucleoside monophosphates (rNMPs) during DNA synthesis at this ratio, predicting frequent rNMP incorporation by the virus specifically in macrophages. Indeed, HIV-1 RT incorporates rNMPs at a remarkable rate of 1/146 nucleotides during macrophage infection. In contrast, little or no rNMP incorporation is detected in CD4(+) T cells. Repair of these rNMP lesions is also substantially delayed in macrophages compared with CD4(+) T cells. Therefore, the frequent incorporation of rNMPs makes them an ideal candidate for development of a new class of HIV RT inhibitors, specifically targeting non-dividing long-living HIV-1 reservoirs.

IL-103

Track: *Enabling Technologies*

A UNIQUE MODEL FOR TESTING NANO-MODULAR DNA APTAMERS AS THROMBIN INHIBITORS

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Nucleic Acid Aptamers are alternative to antibodies in growing enabling technology - theranostics. Set of DNA aptamers for human thrombin (thrombin binding aptamers, TBAs) was developed by SELEX, but there is no rationale for 'Structure-Function'. All aptamers have pharmacophore - 15-mer G-quadruplex linked to

short duplex: 31-mer TBA31 and 26-mer NU172. We have design novel two-modular DNA aptamer, RA36. RA-36 had been previously characterized with enzymatic and coagulation tests. Here we present unique data on *in vivo* activity of aptamers. RA-36 in Kusada electric injury model of murine arterial thrombosis has been studied. Transient current electrical injury was induced in common carotid artery of adult mice 1-2 min after bolus injection of substance. Apparent white thrombus was registered with digital video recorder for 30 min after injection. Thrombus area was measured using UTHSCSA ImageTool program at 30 sec intervals. Average area of thrombus was significantly larger in saline versus aptamer-treated group (7 mg/kg) in the time interval 5-14 min after injection, then convergence of thrombus areas was observed. To elucidate effects of DNA aptamers on human coagulation cascade we used thrombin generation assay. In this assay aptamer RA-36 was demonstrated to have high efficiency that was similar to bivalirudin one"s.

IL-79

Track: *Regenerative Medicine*

STEM CELL THERAPY AS ONE OF TEMPORARY MEASURES FOR MANAGEMENT OF HEART FAILURE AND PULMONARY HYPERTENSION IN CHILDREN

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Objective: The aim of this report is to assess efficacy and safety of two methods for delivery of autologous bone marrow derived stem cells, considering their potential use in critically ill patients.

Methods: We used intrapulmonary delivery of stem cells in children with severe pulmonary hypertension and intramyocardial implantation in children with dilated cardiomyopathy. For assessment we used various visual diagnostics as well as functional and laboratory tests.

Results: Two patients (9 and 15 years) with severe pulmonary hypertension due to uncorrected large ventricular septal defects had been admitted for intra-pulmonary bone marrow stem cell implantation. Both patients underwent radionuclide scintigraphy before the procedure, followed by re-examination 6, 12, 24 and 36 months after it. Latest test results show improvement in lungs' vascularization. Seven patients (4 months – 17 years) with dilated cardiomyopathy had been admitted for transcutaneous intra-myocardial transplantation of bone marrow derived progenitor cells. All the patients underwent repeated clinical examination before and after the procedure. We observed improvement in LVEF, decrease of LVDd on 2D and 3D echocardiography and CTI on chest X-ray, reduction of serum BNP and decrease of the stage of heart failure. No serious periprocedural side effects were observed.

Conclusions: The preliminary results are promising. We suggest using transplantation of bone marrow derived stem cells as a safe and effective way for stabilization of critically ill patients with both severe pulmonary hypertension and idiopathic cardiomyopathy. This method provides additional opportunities for symptomatic treatment and serves as a bridge for potential heart or lung transplantation.

IL-59

Track: *CNS Drug Discovery & Therapy*

RELEVANCE OF THERAPEUTIC STRATEGIES TARGETING NMDA RECEPTORS AND APP PATHWAY IN CNS DISORDERS

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The predominant features of Alzheimer's disease (AD) include the amyloid-β peptide (Aβ) deposition, hyperphoshorylated tau, cholinergic deficit, oxidative stress and glutamate excitotoxicity. Aβ is a cleaved proteolytically from the transmembrane amyloid precursor protein (APP) by secretase enzymes. Deposited Aβ causes microglial activation that results in the generation of reactive oxygen species (ROS) and cytochemokines, which

finally lead leading to widespread neuronal damage. Modulating APP pathway is considered to be a rational strategy in the treatment of AD. We have reported that memantine (Namenda), a partial N-Methyl-D-aspartate (NMDA) receptor antagonist and a FDA-approved AD drug, displayed APP pathway modulatory property (Alley *et al.* 2009, Ray *et al*. 2010). We showed that memantine treatment decreased levels of secreted APP and Aβ peptides in human neuronal cell line and primary rat neuronal cultures; however, the exact mechanism remains unclear. Herein, we treated human primary fetal brain (HFB) cultures (Long *et al.*, 2013) with memantine and observed significant decrease in levels of secreted APP (both sAPPα and sAPP-total) and Aβ peptides (both 1-40 and 1-42 forms) in the drug-treated group *vs.* vehicle group. Contrarily, memantine treatment increased levels of brain derived neurotrophic factor (BDNF) *vs*. vehicle group in the HFB culture. To study the mechanism, memantine-mediated effects on APP metabolites were reversed when the HFB cultures were co-treated with anti-BDNF IgG, which indicates that APP modulatory property of memantine is mediated by BDNF. Then we checked this effect of memantine on different protein levels in autopsied human brain tissue specimens. Importantly, BDNF level was significantly increased in brain extracts samples from AD patients who were treated (clinically) with memantine *vs.* brain extracts samples from AD patients who were treated with no AD medications. A similar APP-modulating property was observed in acamprosate (Campral), a widely used drug to treat alcoholism in the United States. Acamprosate is an NMDA receptor blocker, and our pre- and post-treatment blood biomarker analyses looking at BDNF levels revealed a significant increase in BDNF with treatment in in fragile X patients (Erickson *et al.*, 2013). Acamprosate may also affect APP and BDNF proteins in cultured neurons. Taken together, these results suggest that targeting NMDA receptor by multiple therapeutic agents can have potential effects in several neurological disorders.

This work is supported by grants from Alzheimer's Association and the NIA/NIH. We sincerely thank Jason Bailey, Yokesh Balaraman, Craig Erickson, Nigel Greig, Kumar Sambamurti and Peter Nelson.

IL-124

Track: *Diabetes and Obesity Drug Discovery & Therapy*

INCRETINS IN THE THERAPY OF DIABETES MELLITUS TYPE 2

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The treatment of hyperglycemia in type 2 diabetes involves a wide spectrum of different approaches to be used in an attempt to achieve normoglycemia. However, the long-term studies have shown that the sustainable achievement of the persistent normoglycemia with any of those particular agents or their combinations is not yet feasible and that there is a need for new tools enabling the achievement of optimal glycoregulation. In this context, the agents acting on the level incretin effect have been introduced in the treatment of type 2 diabetes, offering new therapeutic advantages.

The incretin effect, defined as the amplification of nutrient-induced insulin secretion, is mediated by the hormones from the gut, among which glucagon-like peptide 1 (GLP-1), secreted by L cells in the distal small intestine and colon, plays a major role. GLP-1 was proven to exhibit a strong and glucose-dependent insulinotropic activity in humans. In addition, it has been shown in animal models that GLP-1 might have a trophic effect on β cells by stimulating the proliferation of preexisting and differentiation of new β cells in the pancreatic duct epithelium, together with an inhibition of apoptosis. However, in human subjects GLP-1 is shown to be able to inhibit the β cell apoptosis *in vitro*, but the data are not available to confirm its regenerative potential. Moreover, GLP-1 suppresses glucagon release in a glucose-dependent manner, and exhibits a strong effect on gastrointestinal function by inhibiting gastric emptying with powerful subsequent reduction effect on postprandial glucose excursions. Also, GLP-1 has been found to be very rapidly degraded by an enzyme, dipeptidyl-peptidase 4 (DPP-4), and the degradation occurs within minutes, which represents an important determinant both regarding its physiological effects and its pharmacological use.

Type 2 diabetes is characterized by a marked blunting of the incretin effect, associated with defective glucose-stimulated insulin secretion, reduced glucose clearance, increased levels of glucagon, and quicker gastric emptying. The first step towards the use incretin-based treatment in type 2 diabetes were the results showing that intravenous infusion of GLP-1 had dramatic effects on insulin secretion and was able to completely normalize fasting blood glucose level in a glucose-dependent manner. After those initial data, we have seen the development of the two distinct groups of incretin-based pharmatocological agents: GLP-1 mimetics and DPP-4 inhibitors. The GLP-1 mimetics represent parenteral agents, GLP-1 analogs or GLP-1 receptor agonists. The group of DPP-4 inhibitors includes several oral agents being selective

inhibitors of this enzyme isoform. The GLP-1 mimetics are shown to induce a potent stimulation of insulin secretion and consecutive decrease of glycemia, together with an important weight decrease and their implementation is accompanied with differing degree of nausea, which usually in manageable in the course of treatment. The DPP-4 inhibitors also induces a significant decrease in glycemia, although to lesser extent than GLP-1 mimetics, their effect is weight neutral while they do not cause nausea nor other adverse effects. The initial studies have strongly suggested multiple beneficial effects of the use of both groups of agents on other organs and tissues in patients with type 2 diabetes, especially cardiovascular system and brain, but these influences are still under intensive investigations. Although different therapeutic guidelines for the type 2 diabetes still disagree in positioning of incretin-based therapy, the prevailing opinion is that they are identified as new classes of efficacious, glucose-dependent insulin secretagogues, weight reducing or weight neutral, which are to be used in the second step of the treatment, i.e. after the failure of metformin alone therapy, or in the third step when they might be combined with insulin treatment.

IL-113

Track: *Anti-Cancer Drug Discovery & Therapy*

APOPTOSIS INDUCTION THROUGH DOWN REGULATION OF BCL-2 AND AKT SIGNALING OF PYRROLO[1,2-b][1,2,5]BENZOTHIADIAZEPINES IN MEC1 CELLS

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B cell chronic lymphocytic leukemia (B-CLL) is a neoplastic disorder characterized by accumulation of B lymphocytes due to uncontrolled growth and resistance to apoptosis, indicating the need for development of new drugs to treat the disease. Pyrrolo[1,2-b][1,2,5]benzothiadiazepine (PBTDs) have been shown to have antitumor activity, but the mechanism of this activity is not fully understood. The effects of PBTDs (RS2778) on the proliferation and apoptotic induction of B-cell leukemia cells using the DNA fragmentation assay were evaluated. In addition, we found RS2778 mediated apoptosis in MEC1 (human chronic B cell leukemia) through the activation of the caspase-9 and -3, and cleavage of poly (ADP-ribose) polymerase (PARP). The bax:bcl-2 ratio was increased as a consequence of down-regulation of bcl-2 and up-regulation of bax proteins in response to treatment with RS2778. Furthermore, such compound impeded hyper phosphorylation of Akt as were determined by Western blot. In this study, we demonstrated that RS2778 induced apoptosis through down-regulation of the expression of antiapoptotic protein Bcl-2, making it a promising candidate for clinical applications in the treatment of B-cell leukemia.

IL-7

Track: *Anti-Cancer Drug Discovery & Therapy*

PERSONALIZED PATHWAY- SPECIFIC STRATEGY FOR SOLID TUMORS

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Cancer is public enemy number one for United States and worldwide. With tremendous outpouring of resources into drug development, we have not met expectation of our patients.

While it is often claimed that we need new drugs to treat cancer, a more fundamental problem may be the way we classify cancer. We may have many excellent drugs, but they work poorly because we are not matching the drugs to the mutations that patients have.

We believe:

(1) Treatment is not disease-based but target-based.

(2) Correlative/translational aspects are critical.

(3) Treatment is not conventional. Virtually all patients can be on trial.

Our presentation will focus on personalized pathway-specific treatment for solid tumors. We have previously presented in Moffitt Cancer Center in Tampa and Istanbul, Turkey. We believe your meeting would be a good avenue. Furthermore it can potentially help establish collaboration in the near future.

IL-117

Track: *Medical Imaging*

THE EVOLVING CLINICAL ROLE OF MEDICAL IMAGING

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The field of Medical Imaging evolved with many advanced features. The evolution is evident from initial discovery of X-ray in early 1900, adapting new generation of computer system in the 1970s and incorporating digitization technology in the 1990s. The progress of imaging technology then, marked an important milestone achievement in clinical practice placing a major role for medical imaging in routine clinical procedure for diagnostic work up. The fundamental bio-physiology property of each modality is exploited in characterizing normal and diseased tissues. X-ray and sound wave interaction with matters in CT and ultrasound, proton magnetization in MR and *in vivo* tissue uptake of isotopes in SPECTS and PET systems to be named a few. Recent imaging technology advancement is geared towards early detection of anatomical and functional tissue alteration especially in cancer imaging. The Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Nuclear Imaging systems are most common non invasive modality used in cancer imaging at initial staging and post-treatment monitoring. To increase the clinical value, mono-dality imaging system are now combined, integrating various modalities into a single hybrid system with improved accuracy in cancer imaging. The success story is partly contributed by the discovery of 2-deoxy-2-(^{18}F)fluoro-D-glucose (^{18}F-FDG), a potential imaging bio-tracer in Positron Emission Tomography (PET) imaging. Farther to this, the recent thera-nostic concept of medical imaging has created a new path in innovating the future role of medical imaging in molecular medicine. Perhaps, the future direction of clinical medical imaging will be directed toward the development of multifunctional nano-medical platforms for targeted imaging or simultaneous diagnosis and therapy including CT and MR where the therapeutic effect of drug delivery can be visualized during personalized therapy.

Keywords: Medical Imaging Technology, PET, CT, MRI, cancer imaging, nano particles.

IL-9

Track: *Drug Discovery in Preclinical Research*

THE DISCOVERY OF POTENT SMALL MOLECULE GK-GKRP DISRUPTORS FOR THE TREATMENT OF DIABETES

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Glucokinase (GK) is an enzyme that converts glucose to glucose-6-phosphate (G6P) and is predominately expressed in pancreatic β-cells and liver hepatocytes. It's endogenous inhibitor, glucokinase regulatory protein (GKRP), binds to and sequesters GK in the nucleus, preventing glucose phosphorylation at fasting. Thus the GK↔GK-GKRP equilibrium plays an important role in regulating glucose uptake and glycogen synthesis. As a result, modulating blood glucose via the GK pathway presents a promising treatment of type II diabetes mellitus (T2DM). The prevailing approach has

focused on compounds that directly hyperactivate GK via allosteric binding (GK activators – GKAs). One potential liability associated with this class of compounds is the development of hypoglycemia upon alteration of the intrinsic enzyme kinetics of GK. To mitigate this risk, we explored an alternative mechanism that increases GK-mediated glucose phosphorylation by disrupting the binding of GKRP to GK. In this presentation, we will describe the identification of a screening hit that led to the discovery of the initial tool compound (AMG-1694) with a suboptimal PK profile. Subsequent metabolic profiling along with structural-based optimization resulted in the discovery of a novel and stable small-molecule GK-GKRP disruptor (AMG-3969). This compound potently induced the dissociation of the GK-GKRP complex as well as promoted GK translocation in both *in vitro* and *in vivo* assays. Furthermore, AMG-3969 reduced blood glucose levels in rodent models of diabetes while showing no effect in euglycemic animals. These results represent the first successful discovery of a small molecule that targets the GK-GKRP complex as a novel pathway for managing blood glucose levels.

IL-111

Track: *CNS Drug Discovery & Therapy*

VISUALIZATION OF THE BRAIN STATE USING CALCIUM IMAGING USEFUL FOR THE DRUG SCREENING

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To evaluate the effects of the drugs on diseases in central nervous system, the neuronal activities should be diagnosed. Traditionally, the electrophysiological method with single electrode was widely used for recording the neuronal activities. However, this method can record only single or a few cell activities. For the high-throughput drug screening, the multineuronal activities, or the behavior of the neuronal networks should be diagnosed, with or without a drug. For this aim, the spatio-temporal activities of multiple neurons have to be measured. In this regards, multicellular Ca^{2+} imaging with a fluorescent dye is one of the most promising techniques. Ca^{2+} enters through voltage-dependent Ca^{2+} channels opened by action potentials, thus the changes in the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) indicates the neuronal activities. On the other hand, Ca^{2+} is a universal and versatile signal transduction molecule. Ca^{2+} can modulate the functions of proteins such as enzymes and receptors, gene expression, and morphological changes in cellular processes. Therefore, multicellular recording of $[Ca^{2+}]_i$ provides the information, i.e. the state, concerning the behavior of the neuronal circuit and/or the intracellular signal transduction.

We conduct the Ca^{2+} imaging study in the brain slice preparations. In the cortical slice preparation, we observed the signal propagation in the neuronal network of the visual cortex, and investigated the role of the inhibitory synaptic transmissions in the cortex. The inhibitory synaptic transmissions are known to be involved in the seizure and the depression. In the striatal slices, we found the metabotropic glutamate receptor (mGluR) dependent-spontaneous $[Ca^{2+}]_i$ changes from individual neurons and glial cells. mGluR has been suggested as a therapeutic target for Parkinson's disease. Recently, we have developed the ultrafine endoscope for Ca^{2+} imaging. This endoscope makes it possible to record the multicellular activities in the deep brain region, allowing functional neuroimaging.

The Ca^{2+} imaging method provides the useful information for drug discovery and can be powerful tool for the high-throughput drug screening.

IL-29

Track: *Drug Delivery and Targeting*

A FEW ASPECTS OF MOLECULAR PROGRAMMING DEVOTED TO THE SELECTIVE DELIVERY OF ANTICANCER DRUGS

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Despite several years of intensive research devoted to the discovery of novel anticancer agents, chemotherapy is still not entirely effective for the treatment of many solid tumors. Most of the drugs used clinically act by anti-proliferative mechanisms and lack any intrinsic selectivity, leading to severe adverse effects due to the destruction of normal tissues. Therefore, the development of more selective therapeutic approaches has become a major goal in cancer chemotherapy.

In recent years, a wide spectrum of drug carriers have been investigated with the aim to increase drug deposition in tumor while reducing its concentration in healthy tissues. Such compounds were designed to meet two key requirements: (1) the efficient recognition of malignant specificities and (2) the controlled release of anti-neoplastic agents exclusively at the tumor site. Within this framework, Brentuximab Vedotin has reached the market in 2011 for the treatment of lymphomas demonstrating the validity of this targeting strategy.

In this context, we developed a novel drug delivery system composed of four distinct units including a potent anticancer drug, an enzymatic trigger and a targeting moiety articulated around a self-immolative linker. Design as such, the targeting assembly is programmed to (1) transport potent anticancer agents in an innocuous manner toward safe tissues (2) recognize a malignant specificity located either at the surface of cancer cells or in the tumor microenvironment and (3) release the drug in a stringently controlled fashion upon a specific enzymatic stimulus.

The originality of this technology relies on the structure of the central linker that includes three different chemical functionalities suitable for the successive introduction of each part of the device. This allows the on-demand synthesis of a wide variety of drug-trigger-targeting device combinations and permits the custom design of the perfect assemblies for the treatment of particular cancers based on their unique tumor-associated specificities.

IL-10

Track: *Chemistry*

THE ANTIPROLIFERATIVE AND CYTOTOXIC ACTIVITIES OF SUBSTITUTED TETRAHYDROISOQUINOLINES ON MDA-MB-231 CELLS

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Breast cancer is a leading cause of mortality among women, resulting in more than half a million deaths worldwide each year. The taxanes, paclitaxel and docetaxel, a microtubule-stabilizing drug has emerged as an important chemotherapeutic agent in the treatment of breast cancer. This taxane interacts with β-tubulin and arrests cells at G2/M phase, blocking normal spindle assembly and cell division, but long-term treatment is limited due to the toxic side effects. Discovery of new antimicrotuble drugs with novel mechanism of action may be helpful to overcome these challenges. Steroidomimetic tetrahydroisoquinoline moieties were reported recently to be selective estrogen receptor modulators (SERMs) and microtubule disruptors. N-amination of substituted isoquinolines by an aminating agent *O*-mesytelene sulfonylhy-droxylamine followed by ylide formation and reduction yielded the desired substituted tetrahydroisoquinolines in moderate to good yields. These compounds were also evaluated for *in vitro* antiproliferative activity on MDA-MB-231 cell lines. In particular, 4-Ethyl-*N*-(7-hydroxy-3,4-dihydroisoquinolin-2(1H)-yl)benzamide showed a significantly effective IC_{50} value of 0.51 µg/mL and 4-Ethyl-*N*-(3,4-dihydroisoquinolin-2(1H)-yl)benzamide showed IC_{50} value of 0.64 µg/mL. This research was supported by the National Center for Research Resources and the National Institute of Minority Health and Health Disparities of the National institutes of Health through Gant Number 8 G12MD007582-28.

IL-40

Track: *Protein and Peptide Sciences*

DESIGNER PROTEINS FOR TARGETED BIOMEDICAL FUNCTION

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Rational protein design is a powerful tool for elucidating biomolecular phenomena at different time and length scales. Traditionally used in structural biology and for applications in biotechnology and biomaterials industry designer proteins provide an efficient strategy for relating molecular structure with function. Particular attention is being given to novel membrane-active polypeptides with broad spectra of biological activity.

Notable examples are antimicrobial polypeptides which are seen as promising drug candidates in post-antibiotic era. Their clinical potential is largely attributed to that widespread microbial resistance against them has yet to emerge. The peptides are innate immune regulators found in all multicellular organisms. Many of them fold into membrane-bound α-helices and function by causing cell wall disruption in microorganisms. Here we highlight novel mechanisms of antimicrobial action and antagonism at the molecular and nano-to-microscales with applications in antimicrobial therapies [1,2], tissue engineering [3] and gene delivery [4].

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IL-26

Track: *CNS Drug Discovery & Therapy*

EFFECTS OF CEFTRIAXONE, β-LACTAM ANTIBIOTIC, IN RELAPSE-LIKE ALCOHOL DRINKING BEHAVIOR: A POSSIBLE ROLE FOR xCT AND GLT-1 ISOFORMS MODULATION OF GLUTAMATE LEVELS IN P RATS

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Rationale: We recently demonstrated that ceftriaxone treatment induced upregulation of glutamate transporter 1 (GLT1) levels as well as attenuated ethanol intake. **Objectives.** In this study, we investigated the effect of ceftriaxone on the levels of cystine/glutamate exchanger (xCT), GLT-1 isoforms, and another glial cell protein such as glutamate aspartate transporter (GLAST) in relapse-like ethanol-drinking behavior. **Methods:** P rats were exposed to free choice of 15% and 30% ethanol, and water for five weeks, and then deprived from ethanol for two weeks. Furthermore, P rats treated with ceftriaxone (100 mg/kg, i.p.) or vehicle during the last five days of the two-week deprivation period. **Results:** We found that ceftriaxone treatment significantly attenuated relapse-like ethanol-drinking behavior that persisted for nine days upon re-exposure to ethanol drinking. However, water intake increased significantly in ethanol ceftriaxone-treated rats compared to ethanol vehicle-treated rats. Importantly, ceftriaxone-mediated attenuation in relapse-like ethanol-drinking behavior was associated in part with upregulation of the levels of GLT-1α and GLT-1β isoforms, and xCT in the PFC and the NAc. We did not observe any significant differences in GLAST expression among all groups, which indicated the specific action of ceftriaxone on xCT and GLT-1 isoforms expression. **Conclusion:** These findings suggest that xCT and GLT-1 isoforms might be target proteins for the treatment of relapse to alcohol consumption.

Keywords: Relapse, glutamate, ethanol intake, GLT-1α, GLT-1β, xCT.

IL-20

Track: *CNS Drug Discovery & Therapy*

DNA-APTAMER AS NEW TYPE OF DRUGS

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Intravascular clot formation causes serious diseases such as stroke and myocardial infarction, postoperative complications, etc. Today, the basic means for treatment of these pathological states include anticoagulants, or drugs affecting blood coagulation by inhibiting fibrin formation (heparin and its derivatives, indirect anticoagulants, direct thrombin inhibitors); thrombolytics, which activate the fibrinolytic system and clot dissolution (streptokinase, urokinase, etc.); and antiaggregants, or drugs inhibiting blood platelet aggregation (e.g., aspirin).

Thrombin is a protease that plays a key role in the coagulation cascade. Direct thrombin inhibitors are a promising class of antithrombotic agents, and their development and introduction into clinical practice can significantly contribute to treatment and prevention of various thrombotic disorders. Using the SELEX methods there are created fragments DNA (aptamers) a new class of drugs with high affinity to the target molecule. In essence, aptamers are functional equivalents of monoclonal antibodies [1, 2].

DNA aptamers against thrombin, the central enzyme of the blood coagulation system [3-6], inhibit its activity in reactions with fibrinogen and blood platelets. We have studied a single-stranded DNA aptamer RE31 consisting of 31 nucleotides, estimating its inhibitory activity from the activated partial thromboplastin time (APTT) and prothrombin time (PT) in human blood plasma. RE31 proved to inhibit clot formation. In experiments with rats, its effective life span in circulating blood was about 10-15 min. [6]. Aptamers administered in the form of protamine-containing polyelectrolyte complexes remained active *in vivo* for up to 12 hours, compared to the control.

Using the SELEX technique [1, 2], we produced a family of DNA aptamers against interleukin-6 (IL-6). To this end, recombinant IL-6 in active form was produced [7]. This cytokine interacts with the cell-surface receptor complex containing signal-transducing glycoprotein gp130. In particular, IL-6 signaling is responsible for proliferation of precursor blood cells [8], and its increasing concentration in the circulating blood creates the risk of more aggressive cancer development. The affinity of aptamer 120G to IL-6 was estimated by means of surface plasmon resonance, a modern physical method. The apparent dissociation constant of the IL-6-120G complex reached 9 nM, being comparable to those of IL-6 complexes with monoclonal antibodies. The method of flow cytometry was used to evaluate the inhibitory effect of this aptamer on the formation of a complex between IL-6 and gp130.

Prospects for using DNA aptamers for therapeutic purposes are discussed.

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IL-28

Track: *Innovative Drug Discovery and Nanotechnology*

NOVEL BRAIN-CHIP TECHNOLOGY PROVIDES BREAKTHROUGH FOR HIGH TO MID-THROUGHPUT DRUG SCREENING OF NEURONAL AND CARDIAC CELLS

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To understand brain function and how best to regain lost nervous system function, we have developed several novel neuron-chip technologies. These chips also offer opportunities for drug discovery at the mid-throughput level. Planar patch-clamp chips have been developed to screen drugs targeted at ion channels embedded in neuronal and cardiac cells. However, the available planar patch-clamp chip approach is limited only to suspended cell lines transfected with ion channels – thus limiting their physiological and pathological utility. We report here for the first time, on the development of planar patch-clamp chips suitable for recording ion channel activity from cultured neurons placed either at single- (silicon: Si chips) or dual-sites (polyimide: PI chip). This approach allows us not only to monitor ion channel activities underlying intrinsic membrane properties but also provides access to synaptic currents between the paired cells. We successfully recorded evoked post-synaptic potentials (EPSPs) and currents (EPSCs), and

synaptic potentiation that form the basis for learning and memory in the nervous system. Simultaneous, dual-site chip recordings were obtained over days from synaptic pairs, and dedicated cytoplasmic perfusion of individual neurons *via* on-chip subterranean microfluidics was possible without disrupting the whole-cell configuration. Recordings of synaptically connected neurons on a patch-clamp chip have tremendous value as a model to investigate synaptic function, and also as an advance drug development tool for diseases such as Epilepsy, Parkinson, Alzheimer's and mental disorders.

IL-60

Track: *Biologics*

THERAPEUTIC TARGETING OF INTERLEUKIN-6 RECEPTOR FOR IMMUNE-MEDIATED DISEASES

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Interleukin (IL)-6 is a typical cytokine featuring redundancy and pleiotropic activity. A transient expression of IL-6 contributes to host defense against pathogens and tissue injuries. However, dysregulated continual IL-6 production plays a significant pathological role in various immune-mediated diseases, so that tocilizumab, a humanized anti-IL-6 receptor antibody was developed. Clinical trials have demonstrated the outstanding efficacy of tocilizumab for patients with rheumatoid arthritis, Castleman's disease or systemic juvenile idiopathic arthritis, resulting in approval of this innovative biologic for the treatment of these diseases. Moreover, various recent favorable results from off-label use of tocilizumab suggest that it can be widely applicable for other chronic inflammatory and autoimmune diseases including systemic sclerosis, polymyositis, relapsing polychondritis, giant cell arteritis, polymyalgia rheumatica, and amyloid A amyloidosis. I will present current evidence as well as future perspectives of IL-6 receptor blockade therapy for immune-mediated diseases.

IL-88

Track: *Anti-Cancer Drug Discovery & Therapy*

SERUM BIOMARKER PANELS FOR TARGET THERAPY IN BRAIN TUMORS

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One of the main goals of oncology is the development of biomarkers that have the potential to identify cancer risks, to help with the early detection and target therapy.

Proteomic profiling has recently become one of the most important areas in cancer research, and a majority of currently available methodologies, such as xMAP technology and SELDI-TOF-MS, increasingly gains field in brain tumor research. These technologies may provide a panel of serum biomarkers for early detection and monitoring of disease progression.

Our data were obtained using xMAP technology (cytokine panels, signaling molecules) and SELDI-TOF-MS (protein profile).

By multiplex assay, we have identified a panel of overexpressed cytokine/growth factors and signaling pathways dysregulation.

SELDI-TOF proteomic profiling led to the selection of 110 protein peaks; a panel of 4 molecules has revealed a significant difference between brain tumors and controls.

Biomarker panels can discriminate between tumor types and control groups.

These techniques can be used for a rapid and efficient method in the discovery of serum biomarkers in brain tumors diagnosis. Among the advantages there are: early detection of the biomarkers/screening for molecular biomarkers, identification of potential therapeutic targets.

Study supported by Grant POSCCE-685/2010-2014.

IL-83

Track: *Traditional Chinese Medicine*

THE CURRENT RESEARCH AND DEVELOPMENT OF TUJIA ETHNOMEDICINE

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Tujia ethnomedicine is one of the gems of Chinese folk medicine. 8 million the Tus live in the rural Wulin mountain area. They have developed their special ethnomedicine for the prevention and treatment of kinds of disease during thousands of years. The Tus trust the effect of the Tujia ethnomedicine and many folk medicines still are used widely in their ghetto so far. For example, typical Tujia "Qi (seven)" herb, which local trivial name includes the Chinese character "qi", is good at curing the arthritis and inflammatory diseases. There are four major issues existing in the Tujia ethnomedicine. Firstly, how to protect the rare and endangered species? Secondly, many herbs have not been carried out the bio-guided phytochemistry investigations. Thirdly, majority of Tujia ethnomedicine have not established the quality control methods. Fourthly, there are safety concerns on these folk medicines. Anyway, the in-depth research and development of Tujia ethnomedicine will not only benefit the Tus, but also benefit the human beings.

IL-102

Track: *Topics in Drug Targets*

ADVANCES IN THE TREATMENT OF SCHIZOPHRENIA IN COMPLIANCE WITH THE CLASSICAL NEUROTRANSMITTERS AND NEUROPEPTIDES INVOLVED

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Introduction: The paranoid and hallucinatory form of schizophrenia is due to alterations of classical neurotransmitters and neuropeptides in the mesolimbic system, the hippocampus and the prefrontal cortex. A question arises whether it is possible to derive new pharmacotherapies.

Methods: The alterations of classical neurotransmitters and neuropeptides and their effects on specific subreceptors are described. In the mesolimbic system, the susceptibility gene GAD 67 leads to GABA hypoactivity, and neuregulin-1 and dysbindin-1 lead to glutamate deficiency *via* NMDA receptors. The genes monoamine oxidase and COMT are associated with dopamine hyperactivity in the mesolimbic sytem and the hippocampus. A neural network in the involved brain centers is derived. In the mesolimbic system, GABAergic neurons weakly inhibit *via* GABAA receptors dopaminergic neurons which exert a high activity *via* D2 receptors. Tachykinin neurons strongly activate dopaminergic neurons *via* NK3 receptors. Glutaminergic neurons weakly inhibit *via* NMDA receptors 5-HT2C serotonergic neurons. But other subreceptors are also of importance. M4 Muscarinic cholinergic neurons antagonize D1 dopaminergic in the prefrontal cortex. Alpha4beta2 and alpha7 nicotinic cholinergic neurons activate GABAergic neurons in the hippocampus. CB1 cannbinoid neurons strongly inhibit cholecystokinin neurons in the prefrontal cortex, while an association between the CCKA gene and persistend auditory hallucinations has been found.

Results: A survey of the mechanism of action of the conventional and newer antipsychotic drugs is given. Antipsychotic drugs such as risperidone have a stronger D2 than 5-HT2A antagonistic effect and often cause dyskinesia. The antipsychotic drugs such as olanzapine and quetiapine have a stronger 5-HT2A antagonistic effect and have less extrapyramidal effects. It has to be examined whether OSU-6162 which exerts a partial agonism at the D2 and 5-HT2A receptors has a sufficient antipsychotic effect. Besides, it should be examined the susceptibility genes in a large cohort of

schizophrenic patients in order to answer the question which patients better respond to a pharmacotherpay with antipsychotic drugs: those with a stronger D2 antagonistic or those with a stronger 5-HT2A antagonistic effect. The mechanism of action of antipsychotic drugs to be developed is indicated: an agonism at M4 receptors, an agonism at $\alpha4\beta2$ or $\alpha7$ nAchR's, an antagonism at CB1 receptors, an antagonism at NK3 receptors and an agonism at CCKA receptors in order to treat persistent auditory hallucinations.

Conclusion: It is important to examine neural networks in the brain regions involved in schizophrenia in order to improve the understanding of the coherence between the function of susceptibility genes and the pathophysiology of the disease and to optimize a multimodal antipsychotic treatment.

IL-81

Track: *Inflammation & Immunology*

CONTROL OF INFLAMMATION AND TUMORGENESIS BY CYTOGUARDIN A NOVEL TRYPTOPHAN METABOLITE

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We previously proposed that human fibroblasts produce small molecule soluble factors which suppress Cyclooxygenase-2 (COX-2) and control inflammation. The soluble factors were named cytoguardin. Using comparative metabolomic analysis, we recently identified 5-methoxytryptophan (5-MTP) as cytoguardin (Cheng etal PNAS 2012) and mapped the 5-MTP synthetic pathway in human fibroblasts and endothelial cells. 5-MTP inhibited proinflammatory mediator-induced COX-2, inducible nitric oxide synthase and proinflammatory cytokine expressions by suppressing p300 histone acetyltransferase (HAT) and NF-KB activation. 5-MTP was effective in controlling sepsis *via* suppression of cytokine storm in murine model. Furthermore, it reduced cancer cell proliferation, migration and invasion *in vitro* and cancer growth and metastasis in a murine xenograft tumor model. Our findings indicate that 5-MTP is a valuable lead compound for new anti-inflammatory drug development and for cancer chemoprevention.

IL-6

Track: *Combinatorial Chemistry*

SYNTHESIS AND FUNCTION OF MULTIDOMAIN OLIGOMERS CONTAINING HELICENE

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Proteins are multidomain compounds containing different structures and properties at domains, and function emerges as their combination. It is therefore interesting to study how the combination of domains affects the property of multidomain compounds, and use of synthetic multidomain oligomers can promote our understanding of protein function. It was found that, when each domain exhibits different properties under well-designed system, the whole molecule can exhibit property not observed in the single domain oligomer: Such phenomena may be noted as synthesis of properties or function. Using bidomain oligomers containing helicene, synthesis of $\alpha\alpha\beta\beta$ tetermeric aggregates [1] and development of reversible organogel shrinkage were conducted.

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IL-90

Track: *Innovative Drug Discovery and Nanotechnology*

PREPARATION OF THE ELECTROSPUN PCL BASED ANTI-INFECTION DRUG-LOADED GUIDED TISSUE REGENERATION MEMBRANES AND COMPARISON OF THEIR STRUCTURE AND PERFORMANCE

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Infection is the major reason causing the GTR/GBR membrane failure in clinical. Herein, we developed a localized anti-infection drug delivery system to prevent the occurring of infection by inhibiting the bacterial colonization and reducing the foreign body response. An antibiotic, metronidazole (MNA), was successfully incorporated into different kinds of nanofibers at different concentrations (0, 1, 5, 10, 20, 30 and 40 wt.% polymer), in a single-step electrospinning process.

The physical-chemical and mechanical properties of the electrospun MNA-loaded PCL nanofibrous membranes were systemic investigated in-depth. In vitro drug release studies demonstrated that MNA released in a controlled sustained manner over 2 weeks. The electrospun PCL-MNA nano-fibrous membranes showed antibacterial activity over 30 days which was assessed by *in vitro* static experiment against Fusobacterium nucleatum bacteria. L929 Cells could adhere to and proliferate on all membranes while cells proliferated best on the membrane with 30% MNA. *In vitro* results indicated that 30% drug loaded nano-fibrous membrane possessed best comprehensive properties. Analysis of subcutaneous implants demonstrated that the PCL nanofibers encapsulating 30% MNA evoked a less severe inflammatory response than the pure PCL nanofibers examined. To improve the biocompatibility and biodegradation rate of the PCL-MNA membrane, natural material gelatin was introduced into the system. We developed PCL/gelatin-MNA (PCL:gelatin=5:5) electrospun biomimetic nano-fibrous membranes. *In vitro* and *in vivo* characterization results of the membranes showed a significant improvement of the biocompatibility and biodegradation rate of the membranes while the sustained drug release profile, mechanical property, antibacterial activity and cells barrier function still maintained. However, phase separation between PCL and gelatin was found during the electrospinning process, which will influence the nanofiber performance and the quality control of the product. A tiny amount (0.1%) of acetic acid was introduced into the electrospinning solution to improve the miscibility and compatibility of PCL and gelatin. Nanofibers thus obtained appeared to be homogeneous with enhanced performance in naofibers morphology, drug dispersion and mechanical properties of the membranes. Subcutaneous implantation of the PCL/gelatin-MNA and PCL/gelatin/HAc-MNA membranes demonstrated that the drug-loaded membranes evoked a less severe inflammatory response and inhibited the bacterial colonization with a proper biodegradation rate matching the tissue regeneration rate. Through comparison of these three kinds of membranes, the PCL/gelatin/HAc-MNA membranes could be the most suitable material system for anti-infection GTR membrane. This localized drug delivery system may also be broadly applied to more biomedical applications such as wound healing and anti-adhesive membranes.

Keywords: Guided tissue regeneration, electrospinning, PCL, metronidazole, anti-infection, controlled delivery.

SESSION LECTURES

SL-86

Track: *Anti-Infectives*

ANTIMICROBIAL ACTIVITY OF ESSENTIAL OILS ALONE AND IN COMBINATION WITH SOME STANDARD ANTIMICROBIALS AGAINST DIFFERENT PATHOGENS ISOLATED FROM SOME INFECTIOUS DISEASES

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The clinical effectiveness of most of the marketed antimicrobials is found to be threatened by the rapid emergence of multidrug resistant pathogens which increase the need to find alternatives. Hundred years ago, essential oils have been known for their biologic activities in the folkloric medicine in many countries. The objective of our study was to investigate the antibacterial activity of some essential oils against different microorganisms and to study the possible effects between the tested oils and some standard antimicrobials. The antibacterial activity of 11 essential oils was evaluated against *Staphylococcus aureus*, *E. coli*, *Klebseilla pneumoniae* and *pseudomonas aeruginosa* and 50 clinical strains isolated from different infections each alone and in combination with some standard antimicrobials using well diffusion method. Minimum inhibitory concentrations were determined using linear regression analysis. Results showed that all tested essential oils have good antimicrobial activity. As Coriander oil showed the highest antimicrobial activity against *Staphylococcus aureus* and *Klebseilla pneumoniae* followed by Origanum and Ivy oil. Cumin oil showed the highest activity against *E. coli* followed by Origanum oil while Chammomile and Onion oil showed the highest activity against *Pseudomonas aeruginosa*. *In-vitro* interaction between the tested antimicrobials and oils showed variable results against the tested bacteria. The results are of significance in health care system and microbial diseases treatment. As our study showed that essential oils posses good antimicrobial activity against the tested strains. Most of essential oils/antimicrobials combinations showed synergistic effects. Essential oils can be used as adjuvant to antibiotic therapy.

SL-37

Track: *Anti-Cancer Drug Discovery & Therapy*

CATHETER-RELATED BLOODSTREAM INFECTIONS: UPDATE ON MANAGEMENT AND PREVENTION

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Central venous catheters (CVCs) are an essential tool in adult intensive care (ICU), providing means to monitor patient hemodynamics and to administer fluids, nutrition, blood products and medications. Because multiple factors contribute to the high risk of catheter related infection, a multi-strategy approach is required to prevent such infections. The incidence of catheter-related blood stream infection (BSI) ranges from 2-5 per 1000 CVC days [1], with attributable mortality rates of 4-20% [2]. It prolongs hospital stay with an average cost of 3,700 to 29,000 dollars per catheter infection [3].

A CVC bundle that incorporates the Center for Disease Control (CDC) Guidelines for Prevention of BSI that incorporates best practices in order to prevent BSI4. The central line bundle has five key components: 1. Hand hygiene 2. Maximal barrier precautions 3. Chlorhexidine skin antisepsis 4. Optimal catheter site selection, with subclavian vein as the preferred site for non-tunneled catheters 5. Daily review of line necessity, with prompt removal of unnecessary lines.

This CVC bundle is an effective way to decrease BSI. Prevention of BSI requires concerted efforts on the part of hospital administration, physicians, and ICU personnel. The PI program must be evidence-based, maintained, and accepted by ICU personnel. Continued education and feedback are crucial to maintain a low CRBSI rate.

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SL-122

Track: *Medical Imaging*

HOPE AND INNOVATIVE CANCER DIAGNOSTICS BY RAMAN SPECTROSCOPY AND RAMAN IMAGING

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There is strong interest in the development of highly sensitive optical imaging technologies that would shift medical diagnosis to the next level in pathogen detection, gene identification, gene mapping and DNA sequencing. The optical imaging systems are ideally suited for early detection of intraepithelial diseases, including most cancers, and to assess tumor margins and therapy response. Raman imaging is an emerging field that has generated a lot of interest both for the label free Raman methods, as well as for the unique properties of nanoparticles applied as Raman reporters of proteins and nucleic acid targets. The medical applications of Raman imaging are a rapidly developing area of molecular biospectroscopy that create new possibilities in human cancer diagnostics. Raman imaging provides with remarkable possibilities as a label free method, nanoparticle enhanced for *in vivo* cancer detection, as well as for monitoring of treatment response. In the presentation, we give an overview of the use of Raman imaging in oncology, with particular focus on the diagnosis of breast cancer. We will present recent progress obtained in our laboratory on understanding a vibrational fingerprint from the biological tissue which can be used to identify, characterize and discriminate structures in breast tissue, both in the normal (noncancerous) and cancerous environment by confocal Raman imaging and IR spectroscopy. The most important differences between the noncancerous and cancerous tissues were found in regions characteristic for vibrations of carotenoids, fatty acids, proteins, and interfacial water. The contribution demonstrates that Raman imaging has reached a clinically relevant level in regard to breast cancer diagnosis applications.

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SL-78

Track: *Hot topics in Medicinal Chemistry*

NOVEL 1-[4-(AMINOSULFONYL)PHENYL]-1*H*-1,2,4-TRIAZOLE DERIVATIVES WITH REMARKABLE SELECTIVE COX-2 INHIBITION: DESIGN, SYNTHESIS, MOLECULAR DOCKING, ANTI-INFLAMMATORY AND ULCEROGENICITY STUDIES

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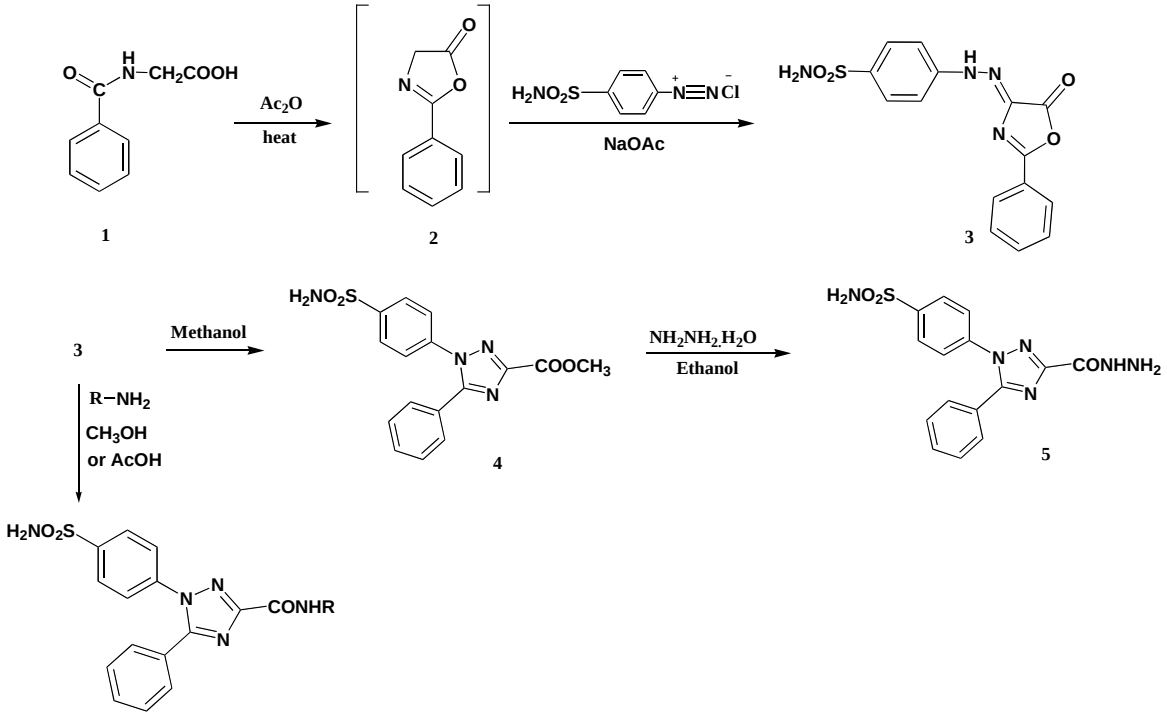
A group of novel 1-[4-(Aminosulfonyl)phenyl]-1*H*-1,2,4-triazole amide derivatives **6a-j** in addition to their corresponding ester **4** and hydrazide **5** were prepared as shown in scheme 1. The target compounds are designed to fulfill the best pharmacophore for selective COX-2 inhibitors using triazole as a bioisostere for the heterocyclic ring. In addition, they contain an amide group, or its bioisosteres, the ester and hydrazide moieties as extra-binding sites towards COX-2 that may enhance the selectivity. The prepared compounds experienced significant anti-inflammatory activity using carrageenan-induced rat paw edema method compared to celecoxib and indomethacin. Calculation of ulcer indices showed minimum gastric ulceration. Moreover, studies of molecular docking and selectivity to COX-1 and COX-2 isozymes showed remarkable COX-2 selectivity.



6a, R = H; 6b, R = Isopropyl; 6c, R = Cyclohexyl; 6d, R = Benzyl; 6e, R = 4-CH_3-Phenyl; 6f, R = 4-OCH_3-Phenyl; 6g, R = 3,4-Di-OCH_3-Phenyl; 6h, R = 4-Cl-Phenyl; 6i, R = 4-CH_3CO-Phenyl; 6j, R = 2-Benzothiazolyl.

Scheme 1: Synthesis of the target compounds 4, 5 and 6a-j.

SL-67

Track: *Hot topics in Medicinal Chemistry*

NITRIC OXIDE DONOR HYBRIDS: RECENT APPROACH IN DRUG DEVELOPMENT

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Nitric oxide (NO) is a magic molecule endogenously discovered as endothelium derived relaxing factor. Besides its vasodilatation effect, NO is involved in many physiological and pathophysiological processes like inhibition of platelets aggregation and immune defense against viruses, bacteria and cancerous cells. A number of disorders are associated with impaired synthesis and/or increased degradation of vascular NO, such as hypertension and hypercholesterolemia. The so called NO donors which are compounds having the ability to produce NO *in vivo* were introduced because of the short half-life of NO in biological systems and somewhat cumbersome nature of delivery of NO gas in controlled manner. One strategy in the development of new drugs is to combine a well-established bioactive molecule with a nitric oxide donor moiety, the produced hybrid molecule will dissociate releasing the bioactive molecule and NO, which may lead to synergistic effect, induce binary biological action and/or abolish detrimental side effects. This strategy was applied in the literature in several fields such as reduction of ulcerogenic liability of NSAIDs, potentiation of anticancer activity of 5-Fluorouracil and increasing the activity of calcium channel blockers Moreover, this approach was applied with several known drugs like aspirin, corticosteroids, ketoconazole, nicorandil, captopril; or with biologically active chemical moieties like pyrazole, pyrazoline and chalcone or NO-generating materials that show particular promise.

SL-120

Track: *Drug Delivery and Targeting*

COLON CONTROLLED RELEASE DRUG DELIVERY SYSTEMS OF INDOMETHACIN USING HYDROPHILIC CARRIERS

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This study aimed to investigate the efficacy of both xanthan gum (XG) and guar gum (GG) controlling the release rate of the poorly water soluble drug, indomethacin (IDM) from colon target drug delivery systems. Binary mixtures of the drug and the hydrophilic carrier (XG) in the ratios of 1:1 and 1:2 and tertiary mixture in the ratio of 1:1:1 IDM: XG: GG were prepared using three different approaches namely, physical mixture, co-grinding and solid dispersion. The prepared binary and tertiary systems were compressed into core tablets. The core tablets were evaluated for their drug content, weight variation, hardness, friability and *in-vitro* dissolution rate study. The dissolution profiles in pH 6.8 buffer solutions revealed that increasing the gum content in the core tablet resulted in a decrease in the IDM release rate. The core tablets were then coated with two different type of coat (inner and outer). The inner coat consisted of guar gum solutions of different concentrations (0.2, 0.4, 0.6, 0.8% w/v) to prevent the drug release in pH 7.4. Tablets were then coated with an enteric coat by dipping in 5% Eudragit (ER L100) ethanolic solution to inhibit the drug release in pH 1.2. The coated tablets were then dried using hot air. The prepared coated tablets were subjected to release rate study which indicated that the release of the drug was inhibited in pH 1.2 whereas; a low percentage of the drug was released in pH 7.4. In pH 6.8 the release profiles showed a sustained release of the drug over 18 hours. The coated tablets that showed the promising sustained release profiles were further evaluated in pH 6.8 buffer solution containing rat cecal content to study the effect of bacterial degradation on the polysaccharide gums.

SL-99

Track: *Inflammtion and Immunology*

NOVEL TARGETS IN THE IMMUNOMODULATION OF INFLAMMATORY DISEASES

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Our immune system serves as a surveillance mechanism that is responsible for monitoring invasion by foreign antigens, recognizing them, and protecting the body against their ill effects. The healthy immune system distinguishes between self and non-self antigens and thus protects the body's healthy cells and tissues permitting normal function. Defense against foreign antigens takes place by activation of both innate (natural) and adaptive (specific or acquired) immune responses. The immune system evolves over time to recognize specific pathogens more efficiently to trigger adaptive immune responses and create immunological memory characterized by the induction of antibodies and memory cells. Disorders in the immune system can result in diseases. Thus, a properly functioning of the immune system has the greatest impact on human health, and it is not surprising that the immunobiology and the modulation of immune response in human diseases is currently receiving the most intense investigation, both on the basic and applied front. The Human genome project has advanced the field of genes responsible for body's reaction to insults. Indeed, genetic variants between individuals could be one reason why some subjects develop disease and others do not. These responses could also be significantly influenced by micronutrients, such as folic acid, vitamin D, magnesium, anti-oxidants, in our diet and environment. However, there is an urgent need to increase our knowledge on the underlying cellular and molecular mechanisms of the disease by examining blood and tissue samples from the patients at opposite ends of various disease spectrums to identify specific targets for therapy. This would provide potential target sites for treatment.

Despite tremendous interest in the immunobiology of human diseases, even today we know little about the complex interplay of the functional response of immune cells in regulating defensive and pathophysiological events in the disease process. Immunomodulators have been developed and some of them are currently in the clinics, including monoclonal antibodies against IgE, TNF-α receptor antibody, and others in phase II and III clinical trials. However, in recent years, many new potential sites/molecules for immunomodulation have emerged. These include: (1) Toll-like receptors, (2) Triggering Receptor Expressed on Myeloid Cells (TREM-1 and TREM-2), (3) Receptor for Advanced Glycation End Products (RAGE), (4) High Mobility Group Box 1 (HMGB1), (5) Prohibitin, and (6) Contact sensitizing agents. In addition, potential role of micronutrients, including vitamin D, as potent immunomodulators is recognized. Indeed, Vitamin D is one of the key micronutrients of modern times. The importance of this micronutrient began with elucidating the role of vitamin D in the maintenance of musculoskeletal health by regulating calcium homeostasis, and thus bones formation and resorption. Only recently the role of vitamin D in extraskeletal tissues has been recognized. Vitamin D is a potent regulator of both innate and adaptive immunity as it relates to host defense from infections as well as auto-immunity in which the immune cells turn against self-antigens. There is a fine balance between a protective and pathogenic immune response in a healthy human host. If this balance is altered it can lead to disease induction.

In my presentation, goal is to discuss the underlying pathophysiological mechanisms of cardiovascular and metabolic diseases involving various immune cells and cytokines and point out the role of novel immunomodulators to produce more effective clinical response in pre-clinical studies. New knowledge on the potential target sites in the prevalent cardiothoracic, vascular and metabolic diseases will provide an opportunity to develop novel therapeutic modalities to significantly reduce the health care cost for society and better life.

SL-104

Track: *Anti-Infectives*

ANTIMICROBIAL ACTIVITY OF TWO WOOD DECAYING FUNGI

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Introduction: Treatment failures due to pathogens resistant to antibiotics have been reported all over the world [1]. This has necessitated the need to search for new and effective antimicrobial agents. Fungi have, over the years, been a source of novel compounds with proven antimicrobial efficacy [2].

Aim: To investigate the antimicrobial activity of the methanol extracts of two wood decaying fungi; *Trametes gibbosa* (Pers.) Fr. and *Trametes elegans* (Spreng.) Fr.

Method: The mushroom species (*Trametes gibbosa* and *Trametes elegans)* were collected from bushes and farms in and around Ayeduase (Kumasi, Ghana). They were separately dried, powdered and extracted using 70% methanol and then filtered and filtrates lyophized. The antimicrobial activity of the extracts were determined against *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* NTCC 4853, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 4853 and clinical isolates of *Streptococcus pyogenes, Klebsiella pneumonia* and clinical isolate of *Candida albicans* using the agar well diffusion method and micro-dilution method [3].

Results: Methanol extract of *T. gibbosa* and *T. elegans* had antimicrobial activity against all the test organisms with minimum inhibitory concentration (MIC) ranging of 4 to 20 mg/mL for *T. gibbosa* and *T. elegans* had MIC of 6 to 8 mg/mL against test organisms. For *T. gibbosa* extract, the most susceptible organism was *B. subtilis* and the least active against *C. albicans* with MIC of 4 mg/mL and 20 mg/mL respectively. *T. elegans* demonstrated the least MIC value of 6 mg/mL each against *S. aureus, K. pneumonia, C. albicans* and *B. subtilis* and the highest MIC value of 8mg/mL each against *E. coli, P. aeruginosa* and *S. pyogenes*. The antimicrobial activity of *T. gibbosa* and *T. elegans* extract at the concentration of 30 mg/mL showed mean zone of growth inhibition with standard mean error (SEM) of 21.12 ± 0.55 to 18.33 ± 0.133 mm against test Gram-positive bacteria, 20.83 ± 0.83 to 17.00 ± 1.03 mm against test Gram-negative bacteria, 19.50 ± 0.55 mm against *C. albicans* and zone of growth inhibition ranging of 22.33±0.52 to 18.00 ± 0.75 mm against Gram-positive bacteria, 23.50 ± 0.52 to 20.33 ± 0.55 mm against Gram-negative bacteria, 18.00 ± 0.75 mm against *C. albicans* respectively.

Conclusion: Methanol extracts of *T. gibbosa* and *T. elegans* exhibited broad spectrum activity against the test organisms.

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SL-52

Track: *Anti-Cancer Drug Discovery & Therapy*

PREFERENTIAL KILLING OF CANCER CELLS USING NANOPARTICLES

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Cancer is a leading cause of death globally. The common treatments of cancer are surgery, radiation and chemotherapy. However, chemotherapy agents also show unexpected toxicity to tissues, and the patient can suffer from serious side effects. Consequently, there is an urgent need to develop new classes of anticancer drugs with new modes of action that better target cancer cells while sparing normal cells. In this regard, newly emerged field of nanomedicine can offer unique approaches. Nanomedicine deals with the application of nanotechnology in medicine, aims to overcome problems, related to human diseases, at the nanoscale (1-100 nm) where

most of the biological molecules exist and operate. Particularly, nanotechnology application to cancer aims to bring significant breakthroughs in diagnosis, treatment, and monitoring of cancer. Nanoparticles are increasingly being recognized for their potential applications in biomedicine such as imaging, drug/gene delivery and cancer therapy, due to their unique physicochemical properties. We investigated whether zinc oxide and iron oxide nanoparticles have potential to induce toxicity in a cell-specific and proliferation-dependent manner with rapidly dividing cancer cells being the most susceptible and quiescent cells being the least sensitive. We have utilized different types of cancer cells and normal cells. Results showed that both zinc oxide and iron oxide nanoparticles exert distinct effects on cell viability *via* killing of cancer cells while posing least toxicity on normal cells. Molecular data suggested that nanoparticles selectively induce apoptosis in cancer cells, which is likely to be mediated by reactive oxygen species via p53 pathway, through which most of the anticancer drugs trigger apoptosis. This study provides preliminary guidance for the development of nanoparticles as anticancer agents.

SL-43

Track: *Anti-Cancer Drug Discovery & Therapy*

UPDATE ON HEPATOCELLULAR CANCER

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Hepatocellular carcinoma (HCC) is annually diagnosed in more than half a million people worldwide. The highest incidence rates are seen in areas where hepatitis B is endemic, primarily in sub-Saharan Africa and Southeast Asia. Hepatitis C related HCC is a rapidly growing group, particularly in the West. The treatment of HCC is complicated by the wide variety of associated underlying liver diseases and by the need to balance efficacy with toxicity in patients with underlying advanced liver disease, including often, decompensated cirrhosis and portal hypertension. The Barcelona Clinic Liver CAncer staging is widely recognized as the standard system for evaluating and determining the prognosis of patients with HCC. There are five accepted therapeutic modalities: resection, transplantation, radiofrequency ablation (RFA), chemoembolization (TACE), and Sorafenib. Surgical resection is an option for a small subset of patients with solitary tumors and no portal hypertension. Otherwise, the best outcomes for patients with early-stage HCC is liver transplantation, with 5 year survival rates of up to 75%. Liver transplantation is resource intensive and although commonly used for HCC in the West, it is not as accessible in developing countries. If liver transplantation is not possible then local ablation is the next best option. TACE and RFA are good options for patients with intermediate-stage HCC. Perhaps the greatest advance in recent years is the introduction of Sorafenib, a small molecule multikinase inhibitor and which has antiproliferative and antiangiogenic properties. It is indicated in patients with advanced HCC and has been associated with a 37% increase in overall survival, apparently 2-3 months life gained. Other small molecules, including brivanib and erlotinib, and the monoclonal antibodies bevacizumab and cetuximab are currently being studied for HCC. Genomic analysis has been used to identify possible prognostic biomarkers, but further study is required for validation but further research is required for validation. Future research must focus on a better understanding of the molecular regulation of HCC which will assist in the identification of new molecular targets. The future of HCC treatment lies in personalized, likely combination, therapy administered by accessible, specialized multidisciplinary teams. Finally, prevention must be emphasized by hepatitis B vaccination, antiviral therapy, and HCC screening. Although many gaps exist in the data supporting such a program, screening for the early detection of HCC is widely endorsed.

SL-94

Track: *Anti-Cancer Drug Discovery & Therapy*

SCREENING FOR NATURAL ANTI-HYPERTENSIVE DRUGS IN *S. DISTICHUM*

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Hypertension is one of the most frequent cardiovascular diseases all over the world. In Egypt there is a high incidence of hyper-tension, and there is a major focus on finding alternatives to classical medication.

Extracts and fractions from *S. distichum* were subject to *in vitro* studies in order to identify the anti-hypertensive fractions, to further assess citotoxicity and to estimate the potential of action. The assessment evaluated the modulation of secretory cytokines, feature that is often present in various polyphenolic extracts, and also the inhibition of serum angiotensin converting enzyme. Cytotoxicity was assessed *in vitro* on Huvec cells and total blood, with MTS assay as end-point. Secretory cytokines were determined in total blood cultures by Luminex-xMAP assay.

Based on ACE inhibition, a first assay classiffied the primary extracts, followed by a series of tests on fractions. One isolated compounds displayed 50% of the activity of Ramipril, while some of the fractions displayed 12-15% of Ramipril activity. Considering the perspective of long – term administration, the natural extract may prove a viable alternative to synthetic drugs, due to the lack of adverse effects.

The study was supported by the E.U. FP7 Grant PIRSES-GA-2008-230816.

Keywords: *In vitro*, anti-hypertensie, *S. distichum.*

SL-21

Track: *Drug Discovery in Preclinical Research*

(1Z)-2-(HYDROXYMETHYL)DODEC-1-ENE-1,3-DIOL ISOLATED FROM INTEGUMENT OF THE RED PALM WEEVIL RHYNHOPHORUS FERRUGINEUS FOR TREATMENT OF CALCIUM- INDUCED DYSRRHYTHMIA

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The red palm weevil was collected, dried and extracted with different organic solvents such as acetone, chloroform, ether and ethyl acetate. The different organic extracts were evaporated under reduced pressure and low temperature of 40°C to obtain the dry residues. These were suspended in 0.25% aqueous sodium carboxy methyl cellulose. Each residue was investigated in rats and mice via the intraperitoneal administration. The results revealed that the insect extract obtained using acetone that was extracted with ethyl acetate proved to be active as it decreased the heart rate in mice as revealed by the ECC recording. Further ECG studies revealed the ability of this extract to antagonize $CaCl_2$- induced cardic dysrhthmias. Chemical analysis was performed in the extract to reveal the nature of the active insect substance. Thin layer chromatography (TLC) on silica gel plates followed by column chromatography using sephadex LH20 enabled the isolation of a single compound that was identified using standard physical and chemical methods to be (1Z) -2- (hydroxymethyl) dodec -1- ene-1,3-diol. Studies were performed using this substance in mice. ECG results revealed the ability of this substance to decrease the heart rate and to protect the animals from $CaCl_2$-induced dysrrhythmia in mice.

SL-116

Track: *Advances in Neuroscience Technique Useful for Drug Discovery and Therapy*

THYMOQUINONE PROTECTS CULTURED HIPPOCAMPAL AND HUMAN INDUCED PLURIPOTENT STEM CELLS-DERIVED NEURONS AGAINST α-SYNUCLEIN-INDUCED SYNAPSE DAMAGE

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Thymoquinone (TQ) is the major active component of the medicinal plant *Nigella sativa* seed's oil also known as The Black Seed. This natural antioxidant has recently received considerable attention for its potent protective properties and has demonstrated several neuropharmacological attributes. Using cultured rat primary hippocampal and human induced pluripotent stem cell (hiPSC)-derived neurons, the present study aims to investigate whether TQ could provide protective effects against alpha-synuclein (αSN)-induced synaptic toxicity, a

presynaptic protein that is implicated in Parkinson's disease, dementia with Lewy Body and other neurodegenerative diseases. Cultured hippocampal and hiPSC-derived neurons were treated simultaneously with αSN and TQ for 72 h. The results showed that co-treatment with TQ efficiently attenuated αSN-induced synaptic toxicity, as evidenced by the restored major synaptic protein synaptophysin, using synaptophysin immunostaining for quantification of synapses. In addition TQ restored synaptic vesicle recycling in the presence of αSN as evidenced by the fluorescent dye FM1-43 and therefore, restored synaptic activity. Using a multielectrode array, we further demonstrated that the treatment of hiPSC-derived neurons with αSN induced a reduction in spontaneous firing activity, and the co-treatment with TQ partially reversed this loss. We also demonstrated that the addition of mutated beta-synuclein (P123H-βSN) to hippocampal neurons induced the inhibition of synaptic vesicle recycling and thus inhibited synaptic activity. However, the addition of TQ decreased the inhibitory effect of P123H-βSN on synaptic vesicle recycling and restored synaptic activity. Our findings suggest that TQ has neuroprotective effects, and may be worth looking into further as a potential agent in lowering the risks of Parkinson's disease and other neurodegenerative disorders.

SL-53

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

OPIOID ANTAGONIST NALOXONE NASAL SPRAY TREATMENT FOR PATIENTS WITH BINGE EATING DISORDER (BED): CONTROLLED RANDOMIZED STUDY

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Binge eating disorder (BED), characterized by an addictive behaviour towards food, is one of the major causes of obesity. At least 10 million people in the USA meet the criteria for BED, which is undertreated with no approved pharmacological therapies.

Naloxone, an opioid antagonist, delivered nasally, can block the endorphin mediated opioidergic reinforcement that occurs when foods high in fat, salt, or sugar are consumed.

The efficacy, safety, and tolerability of intranasal naloxone in the treatment of BED was assessed by a phase II randomized, double-blind, placebo-controlled 6 month trial of 127 subjects. Patients were simply instructed to spray naloxone each time they binged.

Whilst on an intention to treat analysis, there was no significant difference between naloxone and placebo, on a per protocol analysis, Naloxone produced a significantly ($p=0.024$) greater reduction than placebo in time spent binge eating: a decrease of 125 minutes /week with naloxone *Vs* 84 minutes/ week with placebo.

These findings support a new strategy for BED. Naloxone blocks the opioidergic reinforcement from the consumption of foods high in fat, salt, or sugar, so patients gradually binge less. Intranasal naloxone acts rapidly, selectively targeting the extinction of bingeing behavior without any adverse events observed.

SL-30

Track: *Hot Topics in Natural Products*

EFFECT OF THE RESIN OF *DRACAENA CINNABARI* ON THE HEALING OF FULL-THICKNESS SKIN WOUNDS IN MICE

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The resin of *Dracaena cinnabari* (known in Arabia as damalachawin) has been used in traditional medicine for the treatment of diarrhea, dysentery, ulcers of the digestive tract, skin diseases such as eczema, fever, and as hemostatic, anti-ulcer, antispasmodic, analgesic and anti-inflammatory remedy. Wound healing is a complex biological process that involves inflammation, re-epithelialization, angiogenesis, granulation tissue formation, and deposition of interstitial matrix, beside the activities of different types of cells such as keratinocytes, fibroblasts, inflammatory cells, and endothelial cells. The purpose of this study was to investigate the effect of the resin of *Dracaena cinnabari* on the

healing of full-thickness excisional skin wounds induced experimentally in mice. Full-thickness excisional skin wounds were inflicted on the back skin of mice (n=75) and the animals were divided into three equal groups. Group 1 served as negative control (untreated group), group 2 was treated with resin (resin treated group) and group 3 served as positive control (antibiotic treated group). Results indicated that early epithelialization, increased collagen deposition and decreased inflammatory cellular infiltrate at 1st week in the resin treated group. Wounds of the resin treated group also showed earlier remodeling. Angiogenesis was greater at the 1st week but not in the subsequent weeks. It was concluded that the resin of *Dracaena cinnabari* has a beneficial effect on the healing of wounds.

SL-133

Track: *Clinical Trials and Regulatory Affairs*

ENSURING PARTICIPANTS SAFETY AND ENHANCING THE CLINICAL TRIAL EFFICIENCY

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How to ensure that it would be safe to give an investigational medicinal product to healthy volunteers (participants) and, later on to patients? The answer to this question is based on ethical principles and on scientific knowledge. Based on the latter two pillars the long process of drug development can be made much more efficient. To reach this goal, a full cooperation between academics, investigators, Pharmaceutical companies, CROs and the regulatory authorities is needed.

An overview of ethical aspects and Good Clinical Practice (GCP) together with some real life examples of clinical study design will be given.

A First in Man clinical trial should be run in a Phase-I unit that complies with GCP standards.

SL-118

Track: *Anti-Cancer Discovery & Therapy*

IN VITRO AND *IN VIVO* VALIDATION OF NANOPARTICLE-BASED DRUG DELIVERY SYSTEMS TO IMPROVE THE CHEMOSENSITIZING EFFICACY OF CURCUMIN IN PACLITAXEL CHEMOTHERAPY

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The efficacy of curcumin as a chemosensitizer in paclitaxel chemotherapy has already been reported from our lab. However, poor bioavailability (due to reduced aqueous solubility and retention time) limits their biological effects *in vivo*. Nanoparticle-encapsulated formulations of paclitaxel and curcumin are readily dispersed in aqueous media and exhibit all the biological activities of their free counterparts. The present study evaluates the chemosensitizing efficacy of curcumin in paclitaxel chemotherapy using polymer nanoparticles loaded with paclitaxel and curcumin. Confocal microscopic pictures clearly indicate that cellular uptake of curcumin-loaded PLGA nanoparticles of size 140-200 nm and curcumin-adsorbed poly acrylic nanogels of the size 50-100 nm, when suspended in aqueous medium is equivalent or slightly more effective than that of curcumin dissolved in DMSO. Both nanocurcumin and nanopaclitaxel dissolved in aqueous media induce similar or even better cytotoxicity and apoptosis in cervical cancer cells compared to their free counterparts dissolved in DMSO. From these results we conclude that nanocurcumin and nanopaclitaxel formulations resolve the problem of insolubility of these compounds in aqueous media. Hence it is safe to assume that synergistic combinations of nanocurcumin and nanopaclitaxel formulations can have enhanced chemotherapeutic outcome. *In vitro* and *in vivo* studies are going on in this direction.

Keywords: Curcumin, Paclitaxel, Nanoencapsulation.

SL-128

Track: *Anti-Cancer Discovery & Therapy*

MODULATING METABOLIC HOMEOSTASIS IN CANCER CELLS

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Genetic studies in humans and rodents support the notion that alterations in metabolic homeostasis can directly contribute to carcinogenesis and metabolic processes may be targets for therapy. The nuclear hormone receptors (NR) control a wide variety of metabolic processes by regulating the expression of genes encoding key enzymes, transporters, and other mediators. Therefore we explored potential links between cellular metabolic control by NRs and viability of cancer cells. In this study we tested the effect of 127 NR modulators, targeting receptors known to be important in regulating metabolism or known to be viable cancer targets on the growth of different cancer cells lines. Of the compounds tested 8, mainly targeting ER and RAR, induced significant apoptosis in these cell lines. The effects of the 8 active compounds on mitochondrial metabolism were tested in Jurkat cells and 5 compounds significantly reduced lactate levels. However, only the synthetic retinoid (CD437) significantly affected pyruvate dehydrogenase complex activity. CD437 also effected the expression of genes involved in leukemia development and therapeutic responses with the PKC pathway being the primary target. CD437 induced PKC Kinase activity and activated its downstream signals AKT and JNK. CD437 downregulated CPT-1a, and decreased the overall O_2 consumption rate. Additional CD437 induced genes included those involved in the mitochondrial respiratory complex I and III and increased the production of ROS. Our results indicate that the apoptotic effect of CD437 can be linked to its regulation of mitochondrial oxidative metabolism.

Keywords: Metabolism, leukemia, apoptosis, CD437.

SL-22

Track: *Chemistry*

$GABA_B$ AGONISTIC ACTIVITY OF CERTAIN NOVEL AMINO ACIDS STRUCTURALLY RELATED TO BACLOFEN

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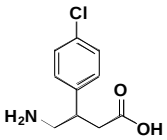
Baclofen (**1**) is the prototypic selective agonist for bicuculline-insensitive $GABA_B$ receptors and is used clinically as an antispastic and muscle relaxant agent. In the search for new bioactive chemical entities that bind specifically to $GABA_B$ receptors, we report herein the synthesis and $GABA_B$ receptor agonistic activity of certain novel amino acids **1a-k** structurally related to baclofen. Compound **1a** emerged as the most active congener among all the synthesized compounds as $GABA_B$ receptor agonist with an EC_{50} value of 32 μM on tsA201 cells transfected with $GABA_B$1b/ $GABA_B$2/ Gqz5.



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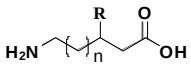

(*RS*)-**1a-k**

1a-j: R = aryl **1K**: R = CH_3
n = 0 or 1

SL-46

Track: *Recent Advances in Patient Treatment and Care*

USE OF ADENOSINE IN DENTISTRY: A NEW INTERESTING TREATMENT

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Adenosine preparation containing the following components:

- Mannuronato of Silanol
- Nucleotides (Adenosine)
- Glycerol
- Nisin
- Lactic Acid

Mannuronato, belonging to the Silanols family, acts directly on the metabolism of the dermis , especially in "liquid" form , composed of collagen and glycosaminoglycans (GAG) and is to a long time an adjuvant to the treatment of dermis desease.

Nucleotides are phosphate esters of nucleosides and are constituted by : a nitrogenous base that can be purine or pyrimidine; a carbohydrate pentose (which together with the nitrogenous base is a nucleoside); a phosphate group (which together with the nucleoside is the nucleotide).

The nucleotides constitute the monomers of DNA and of RNA : the pentose is ribose in RNA and Deoxyribose in DNA.

The presence of one or two other phosphate groups in the chain gives acidity and produces the nucleoside diphosphate and triphosphate (NTP and NDP). Is vital for cellular energy metabolism : the most important of these are are the ADP and ATP.

Glycerol, however, is a trivalent alcohol, which by binding to carboxyl groups of fatty acids, form the Triacylglycerols (TAG) or triglycerides.

This substance have an osmotic action and is able to bind water and favor the tissue hydration. Lactic Acid and Nisin, however, are used for a long time as food additives preservatives stable at acid pH.

Due to its composition , therefore, Adenosine is used with the following information:

- Healing of wounds in general and in particular of those complicated by sepsis

- Adjuvant in the treatment of major dystrophies mucocutaneous

For several years, in fact, galenicals analogues are used in surgery to facilitate and speed restitutio ad integrum of gunshot injuries, cuts and grazes, burns, etc.

Also to these reasons it was decided to use Adenosine as an aid in improving the healing of lesions within Dentistry. And in particular, Oral Pathology in the main directions relate to the treatment of the following diseases:

- Oral ulcers

- Lichen Ruber Planus

- Prosthetic sores

- Oral mycosis

- Degenerative diseases of oral cavity

In Oral Surgery, however, Adenosine is indicated as an additive to the treatment of any surgical wound , including teeth avulsion and also in Periodontal and Implant Surgery.

The aim of the lecture is , therefore , either through a small review of the Literature, both through a case series, illustrate our clinical experience about the use of Adenosine in Dentistry not only as therapy replacement, but rather an alternative to those already fully described in Literature.

SL-96

Track: *Innovative Drug Discovery and Nanotechnology*

SULFONATED ALUMINUM PHTHALOCYANINE AS AN EFFECTIVE DRUG FOR TWO-PHOTON PHOTODYNAMIC CANCER THERAPY

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Sulfonated aluminum phthalocyanine (AlPcS) was a photosensitizer (PS) which was widely used in research and clinical application of the photodynamic therapy (PDT) of cancers. Conventionally, one-photon excitation (OPE) was used. Whether two-photon excitation (TPE) of AlPcS under the near infrared (NIR) wavelength was equally effective was not known. Since the NIR region (700-900 nm) has the best tissue penetration depth, the TPE PDT with the NIR wavelength is promising for solid tumor treatments. In this study, the two-photon absorption cross section (TPACS) of AlPcS at near infrared (NIR) wavelengths were deduced from NIR femto-second (fs) laser-induced fluorescence. We found that TPACS of AlPcS reached a high value of 855 GM at 750 nm. The 750 nm induced fluorescence images of AlPcS in KB and Hela cancer cells were clearly visible. The considerable singlet oxygen ($^1O_2$) production was also observed under TPE of 750 nm fs laser. The *in vitro* experiments showed that 750 nm TPE PDT can effectively damage KB and Hela cells with the PTD killing efficiency approaching that of commonly used OPE at visible wavelength. These results demonstrated for the first time that AlPcS had good TPE PDT potential.

SL-13

Track: *Anti-Cancer Drug Discovery & Therapy*

IN VIVO DISTRIBUTION OF ^{131}I AND ^{125}I DUAL-LABELED GELATIN MICROSPHERES AFTER IMPLANTATION INTO RABBIT LIVER

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After the ^{131}I and ^{125}I dual-labeled gelatin microspheres (^{131}I and ^{125}I-GMSs) had been implanted in rabbit liver, radionuclide distribution and metabolism *in vivo* were examined using single photon emission computed tomography (SPECT) and by blood and urine radioactivity counting. ^{131}I and ^{125}I were labeled into GMSs in accordance with the mixture ratio of batch feeding. After the GMSs had been implanted in rabbit liver, small amounts of ^{131}I and ^{125}I were released into the blood and excreted *via* the urine within 24 days. The radionuclides in the injection site could be detected by SPECT until day 48. The microspheres could be observed by histological methods on day 32. No signs of thyroid damage were observed throughout the entire experimental period. ^{131}I and ^{125}I-GMS can be retained long term in the injection site, and ^{131}I and ^{125}I-GMS may be a safe and effective choice for cancer brachytherapy.

SL-139

Track: *Diabetes and Obesity Drug Discovery & Therapy*

EFFECTS OF CHRONIC (TRAINING) EXERCISE AND ADMINISTRATION OF QUERCETIN ON ENDOTHELIAL DYSFUNCTION IN ANIMALS WITH STREPTOZOTOCIN-INDUCED DIABETES

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Introduction. Diabetes mellitus (DM) is one of the most common endocrine-metabolic disorders. Due to population ageing, urbanization, increased prevalence of obesity and physical inactivity, the number of individuals affected by DM is increasing all over the world. Over the last few years, many experimental and clinical studies suggest that oxidative

stress is involved in the pathogenesis and progression of diabetic tissue damages and diabetic complications. Endothelial dysfunction, characterized by the impairment of endothelium-dependent relaxation, is now recognized as a critical initiating factor in the development of diabetes-induced vascular complications. Quercetin (3,5,7,3'4'-pentahydroxy flavon) is an effective antioxidant that exerts endothelium-independent vasodilator effects, protective effects on the nitric oxide and endothelial function and anti-atherogenic effects in the presence of inflammatory lesions and oxidative stress. This study investigated the endothelial function and measures the levels of vascular oxidative and nitro-oxidative stress in streptozotocin-induced diabetic rats, in view of mounting evidence for an association between DM and accelerated vascular disease. The study evaluated the possible effects of chronic (training) moderate exercise and Quercetin treatment in restoring nitric oxide-mediated endothelium-dependent-relaxation in streptozotocin-induced diabetic rats. In the same time this study investigated the protective effects of Quercetin treatment on oxidative stress and the expression of inducible nitric oxide synthase (iNOS) in streptozotocin-induced diabetic Wistar rats.

Methods. Adult male Wistar rats were divided into seven groups: Group I: non-diabetic, sedentary control rats; Group II: non-diabetic, trained control rats; Group III: non-diabetic, trained control rats treated with Quercetin; Group IV: diabetic, sedentary control rats; Group V: diabetic, trained control rats; Group VI: diabetic, sedentary rats treated with Quercetin; Group VII: diabetic, trained rats treated with Quercetin. Quercetin was administered *via* an intragastric tube (0.6 ml/rat), at a dose of 20 mg/kg body weight/day for 4 weeks after the induction of diabetes mellitus. Diabetes was induced by a single *i.p.* injection of streptozotocin (40 mg/kg body weight). Animals were sacrificed at the end of a 4-week swimming training program (1 hour/day, 5 days/week, 4 weeks). The glycemic profile, oxidative status (lipid peroxidation and protein oxidation), antioxidant levels (catalase, SOD and glutathione peroxidase) and expression of iNOS in the serum were evaluated.

Results. When compared to diabetic sedentary rats, the diabetic trained rats treated with Quercetin rats presented significantly lower glycaemic values accompanied by a remarkable reduction of oxidative markers and endothelial dysfunction.

Conclusion. The results suggested that chronic exercise training associated with Quercetin administration could lower blood glucose levels and reduce endothelial dysfunction in diabetic rats.

Keywords: Endothelial dysfunction, diabetes, exercise, oxidative stress, Quercetin.

SL-62

Track: *Anti-Infectives*

LOCK THERAPY WITH ETHANOL AND MICAFUNGIN TO SAVE CENTRAL VENOUS CATHETER IN VERY SICK NEWBORNS WITH INVASIVE FUNGAL INFECTION

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Background and Aims: Fungi are able to adhere to the internal catheters biofilm in case of bloodsteam fungal infection. Failure to promptly remove or replace CVC in infants with invasive fungal infections places them at higher risk of prolonged infection, mortality, and long-term neuro-developmental impairment, because. *In vitro* studies support the efficacy of ethanol solutions and echinocandins lock therapy to eliminate fungal biofilms; therefore lock therapy with ethanol can be proposed in life threatening conditions, when catheter removal involves high risks for the instable patient. Systemic echinocandins are increasingly used as antifungal agents due to their property to destroy the biofilm. As micafungin has an enhanced clearance in neonates, especially in preterm infants, the dose to administer to neonates is still uncertain. We therefore developed a micromethod with EDTA for the measurement of plasmatic micafungin levels even in neonates, with the goal of withdrawing only small amounts of blood.

Methods: We describe three neonates with fungal catheter associated bloodstream infection successfully treated with systemic micafungin combined with lock therapy for catheter salvage. We also describe the validity of the micromethod to assess plasmatic levels of micafungin. Having the aim to perform a combined lock therapy with micafungin and ethanol to increase LT effectiveness, micafungin stability test in ethanol 70% was performed by serial dosages carried out at the beginning of the test and then after 2, 6, 12, and 24 hours.

Results: Systemic therapy with liposomal amphotericin-B (5 mg/Kg) and micafungin (10 mg/Kg) was started as soon as candidemia was detected As these neonates were critically ill, catheter removal was strongly contraindicated; therefore lock therapy was performed to save the catheter. A solution containing ethanol 70% and mycamine 5 mg/L was instilled and the catheter was closed for 4 to 12 hours. 2 locks were performed in each patient with a distance varying from 24 to 48 hours. Sterilization was obtained in all patients allowing catheter salvage. Drug concentration, analyzed by high performance liquid cromatography (HPLC), was unchanged at all timepoints.

Conclusions: Neonatologists should attempt to remove a CVC as soon as candidemia is detected unless it cannot be removed or replaced because of severe generalized or unstable critical conditions. Our experience suggests that the ethanol-micafungin lock therapy associated with systemic treatment may allows salvage of the catheter. Nevertheless further experience is needed to determine the appropriate length of duration of the lock and the number of locks necessary for catheter sterilization.

SL-32

Track: *CNS Drug Discovery & Therapy*

DEVELOPMENT OF NOVEL ANALGESIC AGENTS TARGETING PDZ DOMAINS INVOLVED IN NEUROPATHIC PAIN

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PDZ domains are invovled protein–protein interactions and are almost always associated with the cell membrane where they play an essential role in the clustering of proteins and signal transduction [1]. Disrupting interaction between PDZ-containing protein PSD-95, and its natural ligand 5-HT_{2A} receptor, was found to reduce hyperalgesia in a rodent model of neuropathic pain [2]. Thus, inhibiting this interaction could lead to the development of a novel class of analgesic agents.

Starting from a lead indole, previously identified by our laboratory [3-5], we carried out a structure-activity relationship (SAR) study. The analogues were evaluated by NMR for their ability to interact with the PDZ domain and by affinity chromatography as inhibitors of the PSD95 PDZ1/5-HT_{2A} receptor interaction. One compound showed promising results and possessed *in vivo* analgesic activity. We have also determined an NMR structure of this compound bound to the PDZ domain [6].

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SL-130

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

ANALGESIA PARTNERSHIP, A UNIQUE PUBLIC-PRIVATE INITIATIVE DEDICATED TO PAIN INNOVATION

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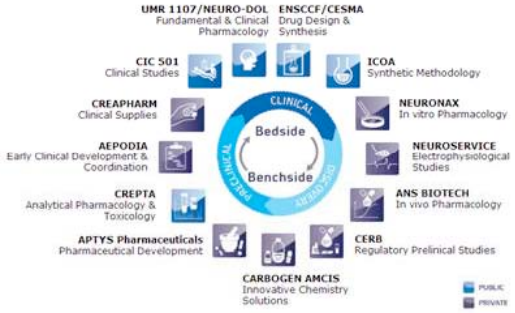
Analgesia Partnership[1] is a unique integrated platform of discovery, preclinical and clinical services fully dedicated to Research & Development of products in pain's management. The Cluster involves both Private and Public structures in order to benefit of a scientific and cultural synergism in the field of pain management by analgesics. The main objective of the 13 members is to perform R&D activities focused on methodological aspects (e.g. relevant animal or human models of analgesic effect assessment) and on new concepts for innovative analgesic drugs. This activity benefits of the multidisciplinary organization of the cluster mixing chemists, fundamental and clinical pharmacologists, toxicologists, and pharmaceutical developers. Moreover, the cluster has developed outside collaborations especially with clinical departments at the university hospital.



[1]Analgesia-Partnership, http://www.analgesiapartnership.com/. A Cluster powered by Public-Private Synergy pushing the boundaries of Innovation.

SL-49

Track: *Hot Topics in Medicinal Chemistry*

RADIATION EFFECTS ON EYE COMPONENTS

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The radiation damage of the most important water-soluble components of the vertebrate eye (lens proteins, aqueous humor, vitreous, hyaluronic acid, ascorbic acid) has been investigated by various methods of physical biochemistry. The impact of X-rays and UV light resulted in several significant changes of their structure. The nature of the primary damages is similar, differences depending on the component under analysis and the nature of the radiation used. For example, the main effects of X-irradiation of α-crystallins are aggregation, whereas β-crystallins, exhibit dissociation and fragmentation; the γ-crystallins turn out to be rather insensitive. UV light seems to cause large aggregates as well as dissociation products and fragments.

UV absorption and fluorescence spectroscopy, in addition to circular dichroism studies, unveiled changes of the chromophores/fluorophores of the constituent biopolymers and low-molecular components, together with alterations of the helix content and the occurrence of aggregation. SEC, analytical ultracentrifugation, densimetry, viscometry and light scattering experiments monitored changes of the global structure of proteins and polysaccharides involved. Electrophoreses allowed conclusions on fragmentation, unfolding and cross-linking. Analytical methods provided information regarding the integrity of groups of special concern (SH, SS).

By means of various measures and additives, manifold modifications of the impact of both ionizing and nonionizing radiation may be achieved. Caused by differences in the primary reactions, eye polymers are protected efficaciously by typical ·OH radical scavengers against X-irradiation, whereas compounds which exhibit absorption behavior in the UV range turn out to act as potent protectives ('chemical filters') against UV light. A few substances, such as ascorbate, are able to provide protection against both sorts of radiation and are even able to exhibit a slight chemical repair of already damaged particles.

If compared to other proteins, crystallins show an extraordinary stability against different types of noxious effects [1, 2]. The extreme stability of crystallins against radiation is achieved *in vivo* by favorable conditions: extremely high packing density of the crystallins in the lens, suppression of aggregation caused by the chaperone function of the α-crystallins, permanent presence of radioprotectives (thiols, ascorbate and other reductants) in the lens and the defense system in front of the lens (tear film, aqueous humor of the anterior chamber), and UV-absorbing behavior provided by the cornea. The results obtained are of importance for understanding pathological alterations of the eye (loss of transparency, cataractogenesis) and for developing new strategies for protection and repair of eye components.

Keywords: Effects of ionizing and nonionizing radiation, reactive oxygen species, damages of biomolecules, protection and repair strategies, antioxidants.

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SL-123

Track: *Anti-Cancer Discovery & Therapy*

THE EFFECT OF 5-FLUOROURACIL ON THE LONG TERM SURVIVAL AND PROLIFERATION OF CELLS IN THE RAT HIPPOCAMPUS

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Chemotherapy has been reported to produce cognitive impairments in a significant number of cancer patients. These deficits frequently involve aspects of spatial or declarative memory which can persist for up to several years after completion of the treatment. We have recently shown that 5-fluorouracil (5-FU), a commonly used chemotherapy drug, induces cognitive impairment and a reduction in hippocampal neurogenesis using a rat model of chemotherapy. The present study examines the effects of two weeks of 5-FU treatment on cell proliferation in the sub granular zone (SGZ) of the dentate gyrus and the survival of newly dividing cells over a six week period after the end of treatment. Cell proliferation at each time point was quantified by staining for the cell proliferation marker Ki67 while the survival of cells, dividing at the start of treatment, was determined by quantification of BrdU positive cell numbers after pulse labelling with BrdU at the start of drug treatment. The results show that 2 weeks of 5-FU treatment did not significantly reduce cell proliferation in the SGZ immediately after treatment. However cell proliferation was significantly reduced, compared to saline treated controls, two weeks after the end of treatment and remained significantly reduced at 6 weeks. The survival of cells, dividing at the start of treatment, was significantly reduced when quantified immediately after the end of treatment and continued to decline compared with control animals over the following 2 weeks but no further change occurred at 6 weeks. Quantification of COX-2 positive cell numbers in the hippocampus did not correlate with the reduction in cell proliferation or survival suggesting that inflammation is not responsible for these changes. These results demonstrate that 5-FU has delayed and prolonged effects on hippocampal neurogenesis after the end of chemotherapy treatment. This correlates with patient reports of continued cognitive impairment after treatment and indicates that changes in neurogenesis may underlie these effects.

SL-33

Track: *Drug Discovery in Preclinical Research*

PROTECTION AGAINST LPS-INDUCED INFLAMMATION AND OXIDATIVE STRESS BY L-ARGININE IN EXPERIMENTAL ANIMALS

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Objectives: This study was undertaken to investigate the possible beneficial effects of L-arginine in protection against the inflammation and oxidative stress induced by LPS in rats, and also to explore the mechanism by which L-arginine might exert its actions.

Materials and Methods: Thirty two male Sprague-Dawley rats were divided into 5 equal groups. The control group injected i.p. with saline; the induction group injected with LPS (4 mg/kg b.w.); the treatment group injected with LPS (4mg/kg b.w.), followed by 10 mg/kg b.w. L-arginine; the inhibition group injected with the iNOS inhibitor, L-NAME (10 mg/kg b.w.), followed by 10 mg/kg b.w. LPS then with 4 mg/kg b.w. L-arginine; the protection group injected with 10 mg/kg b.w. L-arginine for one week before injection with 4 mg/kg b.w. LPS on the day of sacrifice. All animals were sacrificed after 12 h of the last injection. For all groups, levels of TBARS, GSH, NO, IL-6, IL-1β, TNF-α, creatinine, urea and activity of SOD, ALT and AST was measured in plasma. Expression of TNF-α was performed by RT-PCR.

Results: Administration of LPS resulted in increased plasma markers of inflammation (IL-1β, IL-6, and TNF-α levels), oxidative stress (TBARS, NO, and GSH levels; and SOD activity), renal function (creatinine, urea levels), liver function (ALT and AST activity), as well as increased expression of TNF-α in the induction group. However, administration of L-arginine, either before or after LPS, in the protection and treatment groups has significantly decreased all previous parameters, except NO that was significantly increased, compared to the induction group. The inclusion of L-NAME in the inhibition group prevented the effects seen in the treatment group, suggesting the NO-NOS pathway for L-arginine action that results in increased production of NO.

Conclusions: This study shows that L-arginine supplementation, either before or after LPS injection into experimental animals, has a protective effect against oxidative damage of tissues and inflammation. This protective effect is most likely to occur through NO-NOS pathway through increased production of NO.

Keywords: LPS, Inflammatory cytokines, Oxidative stress, L-arginine, L-NAME.

SL-23

Track: *Diabetes and Obesity Drug Discovery & Therapy*

LIPID PATTERN IN SERUM OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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The most common pattern of diabetic dyslipidemia is elevated triglycerides levels and decreased high density lipoprotein cholesterol (HDL-C) levels. Type 2 diabetic patients may have elevated levels of non-high density lipoprotein cholesterol (non-HDL-C). The concentration of low density lipoproteins cholesterol (LDL-C) was reported to be not significantly different from non-diabetic individuals. Recently it has been reported that the measurement of LDL-C as well as triglycerides may not be fully standardized in many clinical laboratories. The present study is designed to compare the serum lipid pattern of type 2 diabetes mellitus patients with non-diabetic individuals and the LDL-C was determined by a direct method. Fasting blood samples were collected from 94 subjects (47 diabetic and 47 non-diabetic). In the present study diabetic samples showed, significantly higher levels of total cholesterol, TC (175.34 mg/dl ± 30.7), LDL-C (112.68 mg/dl ± 27.9), non-HDL-C (136.06 mg/dl ± 28.9) and TG (144.04 mg/dl ± 55.7), than non-diabetic samples, TC (150.26 mg/dl ± 24.7), LDL-C (90.74 mg/dl ± 22.1), non-HDL-C (104.54 mg/dl ± 24.2) and TG (97.6 mg/dl ± 33.8), with p values of $p< 0.0004$, $p< 0.0001$, $p< 0.00001$, $p< 0.00001$, respectively.

Diabetic serum samples showed significantly lower HDL-C levels, (39.53 mg/dl ± 9.2) than that of non-diabetic samples, (43.94 mg/dl ± 9.8), with p value of $p< 0.03$.

Conclusion: Diabetic patients had a high TC, TG, LDL-C and non-HDL-C levels than the non-diabetic individuals, which may indicate that diabetic patients are more susceptible to cardiovascular disease than the non-diabetic individuals.

SL-34

Track: *Chemistry*

BIOACTIVE NATURAL PRODUCTS OF PLANT ORIGIN IN DRUG DISCOVERY

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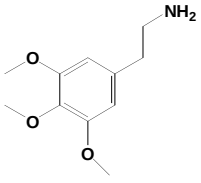
The talk will cover our recent characterization of bioactive naturally occurring compounds from traditional medicinal plants. The traditional uses of 61 species collected from Sinai desert (from 29 families of Egyptian plants) were documented and their biological activity was investigated using a cytotoxicity assay against human lymphoma U-937 GTB. The most potent extracts were those from *Asclepias sinaica*, *U. maritima*, *Nerium oleander* and *Catharanthus roseus*, followed by those from *Cichorium endivia*, *Pulicaria undulate* and *Melia azedarach* (El-Seedi *et al*., 2013a).

The second topic will reflect our discovery of mescaline (1) from peyote. The isolated compound displayed psychotropic properties and peyote samples appear to be the oldest plant drug ever to yield a major bioactive compound i.e. as long as 5700 years ago (Bruhn *et al*. 2002).

Then the recent change of chemosystematic significance will be introduced demonstrating the isolation of cyclopeptide alkaloid (2) from *Heisteria nitida* (El-Seedi *et al*., 2005b). It was discovered in the family Olacaceae for the first time (El-Seedi *et al*., 2007).

Finally we will be closing up by discussing the possible applications including anti-microbial, anti-schistosomiasis and anti-inflammatory activities. For instance, new aryl coumarin glucoside (3) from *Asphodelus microcarpus*, showed potent anti-microbial activity (El-Seedi, 2007). Furthermore, triterpene glycoside (4) from the Egyptian medicinal plant *Asparagus stipularis* was recently evaluated as anti-schistosomiasis agent. It resulted in a retardation of worm growth and inhibition of locomotion at the first day and showed a significant activity of egg-laying suppression at 200 µg/mL concentration (El-Seedi *et al*., 2012). Moreover, anti-inflammatory activity of sesterterpene (5) was investigated from *Alphitonia zizyphoides* (El-Seedi *et al*., 2013a)**.** Subsequently, another bioactive bufadienolide was shown to be proscillaridin A (6) as isolated from *U. Maritime* (El-Seedi *et al*., 2013a).



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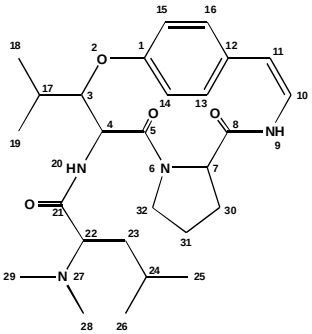

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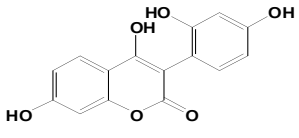

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SL-17

Track: *Diabetes and Obesity Drug Discovery & Therapy*

NOVEL ORAL VACCINE FOR TYPE 1 DIABETES BASED ON LIVE ATTENUATED *SALMONELLA*

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Type 1 diabetes (T1D) is a metabolic disease that is initiated by the autoimmune destruction of pancreatic insulin-producing beta cells that is accompanied by the development of antigen-specific antibodies and cytotoxic T lymphocytes (CTLs). Several studies have shown that vaccination with diabetic autoantigens provides some protection against this process. In this report we describe a new oral vaccine that utilizes attenuated *Salmonella* for delivery of autoantigens as well as immunomodulatory cytokine genes to immune cells in the gut mucosa. This novel strategy was tested by fusion of preproinsulin with SseF effector protein of *Salmonella* pathogenicity island-2 (SPI2) for translocation into the host cell cytosol and co-delivery of *Salmonella* carrying the gene for transforming factor beta (TGFβ) for host cell expression. Co-vaccination of non-obese diabetic (NOD) mice significantly reduced the development of diabetes and improved the response to glucose challenge. The combination therapy of autoantigen and TGFβ also resulted in increased circulating levels of tolerance-associated cytokines such as IL10, IL2, IFNγ, and IL4, but without significant effect on proinflammatory cytokines IL6 and IL12, indicating a shift toward a tolerogenic response. In conclusion, *Salmonella*-based oral vaccines expressing autoantigens combined with tolerogenic cytokines appears to be a promising therapy for prevention of T1D.

SL-5

Track: *Diabetes and Obesity Drug Discovery & Therapy*

A NOVEL OPPORTUNITY FOR DIABETES MELLITUS: TREATMENT BY POLYCLONAL ANTIBODIES IN RELEASE ACTIVE FORM

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According to WHO estimates (2013) more than 347 million people worldwide suffer from diabetes mellitus. Development of drugs and innovative approaches for its effective and safe treatment remains a topical issue. The use of the release-activity phenomenon (Epstein O.I., 2013) consisting of the modifying action exerted by specifically processed ultrahigh dilutions of the starting substance could lay the foundation for one of those innovative methods. Subetta is a combination drug containing release-active dilutions of antibodies to beta-subunit of insulin receptor and antibodies to endothelial NO synthase. In two animal models of diabetes mellitus, streptozotocin-induced diabetes and Goto Kakizaki rats with spontaneous diabetes type 2, subetta showed antidiabetic activity similar to that of rosiglitazone. The drug improves blood glucose control and prevented the age-related spontaneous deterioration of glucose tolerance. Results of in vitro studies revealed that subetta significantly stimulates adiponectin production by mature human adipocytes in the absence of insulin. Taken together, the above-mentioned results provides much evidence that subetta acts as an insulin-sensitizing agent through modulating the activity of beta-subunit of the insulin receptor**.**

SL-119

Track: *Recent Advances in Spectroscopy*

DISTINGUISHING BETWEEN POLYMORPHIC FORMS OF CHIRAL ACTIVE PHARMACEUTICAL INGREDIENTS BY SOLID-STATE CIRCULAR DICHROISM

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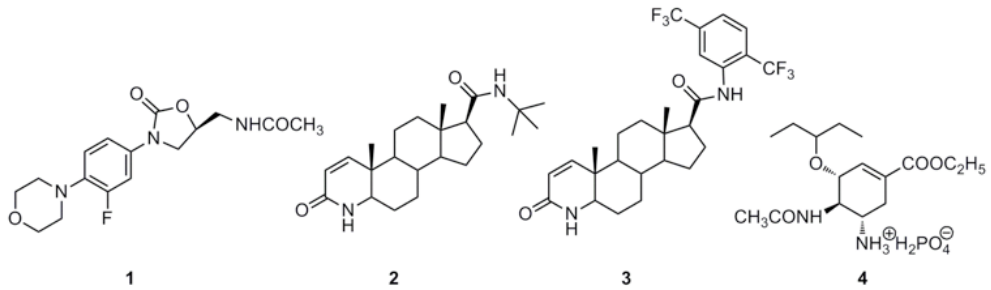
Recent progress in equipment enabled the development of reliable measurement methodology of the electronic and vibrational circular dichroism (ECD & VCD) spectra in solid-phase. However, among commonly used methods distinguishing polymorphic forms of APIs the use of chiroptical methods is very limited or even non-existed in the broader sense. To supplement this deficiency we undertook studies on the efficient utilization of chiral spectroscopy for this purpose.

Linezolid (1), finasteride (2), dutasteride (3) and oseltamivir phosphate (4) were selected as model compounds for studying polymorphic phenomena by circular dichroism (CD) spectroscopy (Fig. **1**). These substances were chosen due to their different conformational lability, well-known ability to form conformational polymorphs and important uses as therapeutic agents.

In the present work, we wish to demonstrate the potential of combined use of ECD and VCD spectroscopy in solid-state as a tool for distinguishing between polymorphic forms of APIs. To support the experimental results time-dependent density functional theory (TD-DFT) calculations were performed to provide theoretical backgrounds for ECD phenomenon in solid-state.

The results of these studies allow the effective and broad application of CD spectroscopy in exploring other APIs possessing polymorphic forms, providing these APIs are chiral.

Acknowledgement: The authors acknowledge a Grant Preludium no. UMO-2011/03/N/ST4/02426 from National Science Centre, and Grant No. G34-15 for computational time at the Warsaw Supercomputing Centre (ICM).



SL-27

Track: *Drug Discovery in Preclinical Research*

PROTEINKINASE C ALPHA CONTRIBUTES TO IMPAIRMENT OF RENAL BLOOD FLOW AND INFLAMMATION IN HYPOXIA INDUCED RENAL ISCHEMIA REPERFUSION INJURY (IRI)

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Background – Renal ischemia reperfusion injury (IRI) leads to acute kidney injury (AKI) after major cardiac surgery and contributes to increased post-operative morbidity and mortality. In this study we analyzed the role of PKC-α in hypoxia induced impairment of renal blood flow (RBF) and inflammation in PKC-α deficient mice compared to wild type littermates.

Methods – Renal IRI was induced in WT or PKC-α knock out mice by transient unilateral clamping of the right renal pedicle for 35 min. Functional contrast free magnetic resonance imaging (MRI) was performed at d1 to measure renal

blood flow (RBF), edema formation and cell infiltration. Histological, renal morphology and inflammatory cell infiltration were investigated. CTGF expression as profibrotic marker was evaluated by qPCR.

Results – PKC-α knock out mice had significantly better survival and less s-creatinine elevation than WT mice. By MRI techniques IRI induced renal perfusion impairment was markedly reduced in PKC-α knock out mice compared to WT. Acute kidney injury (AKI) and inflammatory cell infiltration was significantly reduced in the PKC-α knock out mice and up-regulation of CTGF expression was abolished pointing towards impaired TGF-β signalling in this model.

Conclusion – Our study proves that PKC-α deficiency attenuated hypoxia induced renal IRI by blocking TGF-β up-regulation. Thus PKC-α inhibition might be a promising therapeutic option to reduce hypoxia induced IRI in after major surgeries.

SL-138

Track: *Clinical Trials & Regulatory Affairs*

FUTURE OF CLINICAL TRIALS AND REGULATIONS IN ALGERIA

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The past few years have witnessed a significant increase toward geographic expansion in conducting clinical trials. It has become routine to target countries in E. Europe, Asia and Africa and very recently the MENA region. Algeria is one of these locations and although very nascent in the field of clinical trials, it has shown an amazing potential for patient recruitment. Additionally, the local regulatory agencies are committed to develop the frame work to conduct these studies within the established good practices and regulations. Algeria is not a country to dismiss as a clinical trial destination. Within the MENA region, it is one of the two largest economies and investors in healthcare with S. Arabia. It has a large population, the advantage of closeness to the West, and will allow the recruitment of significant patient populations that are no longer available elsewhere. For clinical and regulatory research teams, these opportunities require the understanding of the country with its cultural and regulatory environment while adhering to good clinical practice guidelines.

SL-19

Track: *Anti-Cancer Drug Discovery & Therapy*

MALIGNANCIES IN PRIMARY IMMUNODEFICIENCY DISORDERS

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Primary immunodeficiencies (PIDs) are inherited disorders of the immune system. These disorders are categorized into defects of the innate immune system, phagocytes and complements, and defects of the adaptive immune system (cellular, humoral and combined cellular and humoral defects).

PIDs predispose the affected individuals to increased risk of infection and immune dysregulation that can present in either increased risk of autoimmunity, malignancy or both. Development of advanced techniques to diagnose infections, immunoglobulin replacement and supportive care led to reduced early morbidity and mortality from infection. However, malignancies continue to be a significant cause of premature death in those patients.

Increased risk of malignancy in PIDs is possibly due to increased susceptibility to infections with oncogenic viruses leading to a severe inflammatory status that promotes cell survival and proliferation. As well, there is an impaired immune surveillance against premalignant and malignant cells allowing those cells to survive and metastatize in the body of patients with PIDs.

The presentation will focus on some of these rare diseases, exposing critical insights into the mechanisms controlling host antiviral and antitumor immunity.

SL-24

Track: *Hot Topics in Natural Products*

NATURAL PRODUCTS FOR JOINT HEALTH: ANCIENT ROOTS TO MODERN MEDICINE

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Objective: Interleukin-1β (IL-1β) is present in osteoarthritic joints at high levels and causes an increase in many catabolic enzymes and inflammatory mediators through activation of NF-kB pathway. In the present study we investigated the mechanism of NF-kB inhibition by a polyphenol rich Pomegranate extract (PE) by determining its effect on the activation of the kinases upstream of IkB in primary human chondrocytes.

Research Methods & Procedures: OA chondrocytes were pretreated with PE followed by stimulation with IL-1β for different time points. Activation of NF-kB p65 was determined by specific ELISA-based DNA binding assay. Total protein levels and phosphorylated forms of different kinases were determined by Western immunoblotting. mRNA levels were determined by real time PCR. Total intracellular ROS was determined by DCF assay.

Results: PE inhibited IL-1β induced DNA binding activity of NF-kB p65, degradation of IkB and phosphorylation of NIK. PE also inhibited the phosphorylation of IKKβ as well as down-regulated the expression of IKKb mRNA and protein. Moreover, PE strongly inhibited IL-1β-induced increase in intracellular ROS concentration in human chondrocytes.

Conclusions: Taken together the data presented here suggest a novel mechanism of NF-kB inhibition by PE acting at multiple levels. These results may help to develop pharmacological inhibitors of NF-kB derived from PE for the effective management of osteoarthritis.

SL-115

Track: *Drug Delivery and Targeting*

IN VITRO AND *IN VIVO* EVALUATION OF A SELF-MICROEMULSIFYING DRUG DELIVERY SYSTEM (SMEDDS) FOR PEPTIDE DRUGS

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The aim of the study was to investigate a permeation enhancing self-microemulsifying drug delivery system as carrier for the model peptide drug leuprorelin (leuprolide acetate) which prevents the sensitive drug from enzymatic degradation in order to achieve improved *in vivo* bioavailability. To enable incorporation of the commercially available acetate salt of the drug into lipophilic SMEDDS the nonapeptide was modified by hydrophobic ion paring to obtain the more lipophilic leuprolide oleate. To facilitate drug uptake a SMEDDS formulation containing permeation enhancing lipids was chosen (30% Cremophor EL, 30% Capmul MCM, 10% propylenglycol and 30% captex 355).

It could be shown that the microemulsion prevents the peptide drug from enzymatic degradation by trypsin and α-chymotrypsin. The leuprolide acetate control solution showed complete degradation after 1h. In contrast, leuprolide oleate incorporated in lipid phase of the microemulsion resulted in a significant lower degree of degradation, after 2h 70 % of initial leuprolide in the formulation was still undegraded after treatment with trypsin. A significant improvement of bioavailability of leuprolide administered as oral SMEDDS formulation compared to the control solution was detected. A more then 10-fold increase of the absolute bioavailability could be demonstrated.

SL-57

Track: *Traditional Chinese Medicine*

THE ESTABLISHMENT OF MATHEMATICAL MODEL AND PARAMETER DETERMINATION OF NETWORK PHARMACODYNAMICS FOR CHINESE MATERIA MEDICA FORMULA

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It had been established a new mathematical model and determination method of network pharmacodynamics for Chinese Materia Medica Formula (CMMF). By network pharmacokinetic principle, combining with the Laplace transform, as well as linear algebra, the general solution for equation of network pharmacodynamics were obtained and their parameters were analyzed. The CMMF network pharmacodynamic model was a polynomial with e power. The equilibrium constants of each nodals in network were obtained by solving linear equation established with AUC (equilibrium concentration) and initiate quantum (intravenous drip velocity) for their. The equilibrium constants calculated in oral administration was similar with in injection, only supernumerary of the absorption equilibrium constants. That suggested the network pharmacodynamics for dose-ratios, dose-chrono and dose-effect of the CMMF was carried out; There is network biologic principle of conservation that the initiate value (intravenous drip velocity) for each nodals in network is equal to the summation of producet quilibrium constant versus AUC (quilibrium concentration).

SL-65

Track: *CNS Drug Discovery & Therapy*

REMOTE ISCHEMIC CONDITIONING: WILL IT TRANSLATE INTO A PROMISING TREATMENT FOR ACUTE STROKE

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Approximately 15 million people suffer stroke worldwide. It is the 3rd leading cause of adult morbidity and number one cause of disability. Due to associated risk of hemorrhage, the FDA approves IV-tPA within 3 hrs post-stroke, which benefits only 3 – 5% of sufferers. In >30 years of stroke research, all other pharmacological trials failed except IV-tPA which is quite discouraging for both, clinicians and pharma industries. STAIR recommends development of therapies, which can be used with and without IV-tPA and in pre-hospital settings.

Our remedies oft in ourselves *do lie- Shakespeare.* Therefore, we propose remote ischemic conditioning (RIC), a sub-lethal ischemia using BP instrument and cuff on a remote resistant organ like limb, as a novel and ideal approach for the treatment of acute stroke via modulation of endogenous mechanism. RIC increases cerebral blood flow (CBF) and survival mechanism, and reduces infarction with and without IV-tPA in a partially humanized novel embolic stroke model developed by us. RIC prevented the post-thrombolysis edema, hemorrhage and associated mortality. It improves short- and long-term motor and cognitive deficits in mice. In human subjects within 14 days post-stroke, RIC increased CBF as measured by ASL with a persistent diffusion-perfusion mismatch. We developed a software program and a non-invasive programmable ischemic conditioner for rodents and human. We are in communication with FDA for a possible clinical trial in future. We are also exploring the possible humoral mechanism of increased microvascular perfusion and reduced no-reflow by RIC via AMPK-eNOS-HSP90 pathway, using conditional knock out mouse models and plasma of conditioned animals.

SL-41

Track: *Drug Delivery and Targeting*

OCULAR OFLOXACIN MICROSPHERES LOADED *IN SITU* GELLING SYSTEMS: PREPARATION, CHARACTERIZATION AND *IN VIVO* EVALUATION

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Topical application of ophthalmic drugs is the method of choice for treatment of ophthalmic disorders. Microparticulate delivery systems and in situ gelling systems were developed to increase the bioavailability of ophthalmic drugs.

The aims of this work were to prepare biodegradable ofloxacin-loaded PLGA microspheres and to evaluate the effects of process parameters on encapsulation efficacy, release, size, and surface morphology were evaluated. In addition the optimized formulation was subjected to *in-vivo* study compared with marketed Ocuflox® eye drops using an animal model.

It was found that by using O/O method and a mixture of acetonitile, methyl alcohol and methylene chloride in ratio 6:4:1 as internal phase, high surfactant and polymer concentrations led to a more appropriate encapsulation efficiency, low burst effect and desirable release pattern. Ocuflox® achieved the therapeutic level of ofloxacin only during the first hour after instillation. While the microspheres incorporated in Gelrite *in situ* gel showed longest duration of action more than 8 hrs after instillation.

In conclusion, ofloxacin microspheres loaded in situ gelling systems could be considered a successful novel controlled release formulation for ocular deliver.

Keyword: Ofloxacin, microspheres, *in situ* gel, ocular, bioavailability.

SL-107

Track: *Pulmonary Drug Discovery & Therapy*

BIODEGRADABLE POLYMER MICRO/NANOPARTICLES AS CARRIER FOR PULMONARY DELIVERY OF DRUGS

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Polymers are playing an integral role in the advancement of drug delivery technology and biodegradable polymers have led to the development of various novel drug delivery systems. The controlled surface and bulk physical properties of polymers aid in engineering of polymers for novel controlled drug delivery system. Dry powder inhaler (DPI) formulations, where micronized (<5 μm) drugs mixed with conventional lactose microcarriers are delivered into deep lungs using a suitable device. Currently available lactose carrier is not performing well due to the difficulty associated with lactose carrier particles such as controlling the size, shape and surface roughness. These factors, in turn, affect the dispersion of drug from DPI formulations. The use of polymer micro/nanoparticles in the pulmonary drug delivery system is in its infancy and their use as carriers in DPIs has not been well studied. The aim of our work involved in investigating the engineered biodegradable polymer micro/nanparticles of polycaprolactone (PCL), polylactide-co-glycolide (PLGA), and chitosan with reproducible surfaces, as an alternative carrier to lactose for deep lung delivery of drugs. We achieved a better understanding on the polymer micro/nanocarriers for the development of DPI formulations for efficient lung delivery of drugs.

SL-121

Track: *Advances in Neuroscience Technique Useful for Drug Discovery and Therapy*

NEUROTOXIN 1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE (MPTP)-INDUCED MICE MODEL FOR PARKINSON'S DISEASE

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Parkinson's disease (PD) is a common neurodegenerative disorder characterized by a slowly progressive motor dysfunction and loss of dopaminergic neurons located in the substantia nigra innervating to the striatum, causing depletion of dopamine to which leads a hyper-activation of the striatal medial spiny neurons. To understand the pathophysiological details of PD and for developing and screening the novel therapeutic and/or neuroprotective substances, animal models for PD induced by neurotoxins have been developed. Among them, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is the most commonly used as a PD model because it has a lot of merits compared to other models with well satisfying the face, constructive and predictive validities of human PD. As a facial validity, bilateral motor dysfunctions related to extrapyramidal syndrome have been well reproduced, and many behavioral tasks for animal models have been developed. As constructive validities, following characteristics observed in human PD are well reproduced: specific cell death of nigro-striatal dopaminergic neurons; decrease of the striatal dopamine and its metabolites; activation of astrocytes and microglia; oxidative stress caused both by mitochondrial dysfunction and activated glial cells; inflammatory reactions. As a predictive validity, many of the drugs in clinical use for PD are also effective in MPTP model. I have been using MPTP-induced PD model of mice and evaluating some possible compounds for PD. In this symposium, I first overview the characteristics of the MPTP-treated mice with its practical experimental methods including behavioral, biochemical, immunohistochemical and molecular examinations, and then show actual data of some compounds evaluated in this model with discussing its molecular mechanisms of action.

SL-16

Track: *Chemistry*

TETRACYCLIC HETEROAROMATIC SYSTEMS-SYNTHESIS OF ETHOXYCARBONYL-PHENYL-PYRIDO[3',2':5,6]THIOPYRANOQUINOLINES

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7-benzylideneamino-5H-thiochromeno[2,3-b]pyridin-5-ones and 9-benzylideneamino-5H-thiochromeno[2,3-b]pyridin-5-ones, on reaction with ethyl pyruvate to afford 1-ethoxycarbonyl-3-phenyl-12H-pyrido[3',2':5,6] thiopyrano[3,2-f]quinoline-12-ones and 4-ethoxycarbonyl-2-phenyl-7H-pyrido[3',2': 5,6]thio-pyrano[3,2-h]quinoline -7-ones respectively by the two different methods. These products were precipitated by addition of ethanol, water (1:1), were purified by recrystalizing from appropriate solvents, and were characterized from their IR, 1H-NMR and mass spectral data.

SL-31

Track: *Anti-Cancer Discovery & Therapy*

ECONOMIC BURDEN OF CANCER PATIENTS IN MOLECULAR TARGET THERAPY

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Purpose: It is to find the actual situation of cancer patient's copayment, especially when high-cost molecular target treatment is necessary and to investigate rational measures for reduction of the burden.

Method: An investigation was conducted in 42 core institutions in cancer care in Japan. Clinical information was also got from doctors and both data were linked.

Results: The average annual out-of-pocket expenses (including indirect expenses) of the whole patients with solid tumor (n=2,114) and those of patients who received the molecular target therapy were US $6,600 and $12,200 respectively. The annual sum of co-payment by molecular target drug were as follows; $10,000 in rituximab (n=131), $11,000 in trastuzumab (n=158), $11,500 in gefitinib (n=45), $12,000 in imatinib (n= 135) and $16,500 in bevacizumab (n=70).

Conclusion: It was revealed that the economic burden of the patient who received the molecular target therapy was considerably serious. It is indispensable to reduce the burden in order to send the remarkable technical progress to all patients with cancer.

SL-136

Track: *Advances in Neuroscience Technique Useful for Drug Discovery and Therapy*

PREVENTING THE DEVELOPMENT OF EPILEPSY BY INHIBITING NKCC1 TRANSPORTER

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Epilepsy is a neurodevelopmental disorder which is often accompanied by the formation of aberrant neural circuits during development. Specifically, in the hippocampus of patients with temporal lobe epilepsy (TLE) and its animal models, it has been suggested that abnormally located dentate granule cells provide aberrant excitatory networks in the dentate gyrus. However, cellular and molecular mechanisms that induce the emergence of ectopic granule cells remained unclear. Using a rat model of complex febrile seizures, which are thought to be a precipitating insult of TLE later in life, we found that aberrant migration of neonatally generated granule cells results in granule cell ectopia that persists into adulthood. Febrile seizures induced an upregulation of $GABA_A$ receptors ($GABA_A$-Rs) in neonatally generated granule cells, and hyperactivation of excitatory $GABA_A$-Rs caused a reversal in the direction of granule cell migration. This abnormal migration was prevented by RNAi-mediated knockdown of the $Na^+K^+2Cl^-$ co-transporter (NKCC1), which regulates the excitatory action of GABA. NKCC1 inhibition with a widely used diuretic, bumetanide, after febrile seizures rescued the granule cell ectopia, susceptibility to limbic seizures and development of epilepsy. We further found that the bumetanide application improved memory performances that was adversely affected by early-life febrile seizures, likely through preventing the emergence of ectopic granule cells. Thus, our study identifies a previously unknown pathogenic role of excitatory $GABA_A$-R signaling and highlights NKCC1 as a potential therapeutic target for preventing granule cell ectopia and the development of epilepsy after febrile seizures.

SL-35

Track: *Drug Delivery and Targeting*

A NOVEL COLLOIDAL SYSTEM BASED GEL FOR EFFECTIVE DELIVERY OF KETOROLAC TROMETHAMINE

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The gastric ulcerogenic effect of water soluble ketorolac tromethamine renders it a suitable candidate for transdermal delivery. Solubility studies in propylene glycol, PEG 400 and Tween 80 were carried out and solubility was found to be highest in propylene glycol (60 mg/g). The gel formulation was prepared with a colloidal solution of drug and surfactants to which carbopol gel was added. The preparation was completely dispersed within the gel using a high speed homogenizer (Remi, India). Cloud point was determined visually by noting the average temperature at which turbidity is observed and disappeared. Release studies were performed in Franz diffusion cell in phosphate buffer at pH 7.4. The developed formulations were easily washable, smooth to feel and showed no clogging, which indicated superior texture of the system. Formulations prepared with decreasing polysorbate 80 ranged in size from 217.7-293.3 nm with polydispersity index between 0.233-0.360. They showed greater spreadability and high drug diffusion rate when compared to gels made with increasing concentrations of pluronic F 127. Drug content of gel formulations were in the range of 90-94%. The pH of the formulations ranged between 5.0 and 6.5, reflecting less risk of skin irritation. Propylene glycol and TPGS enhanced the spreadability of the gel by increasing viscosity. *Ex vivo* skin permeation studies for the optimized formulation showed 55.34% drug release, which is significantly greater than the release observed with the market preparation (34.37%) over a period of 24 h. The prepared optimized formulation was found to be stable without any significant changes at room temperature.

SL-134

Track: *Diabetes and Obesity Drug Discovery & Therapy*

DIABETES TREATMENT DURING RAMADAN FASTING: CAN WE GET IT RIGHT?

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Fasting during the Holy Month of Ramadan is practice by Muslims worldwide. The fast entails abstinence from eating and drinking between dawn and sunset. Traditionally, the fast is broken by some sweet food. The iftar is often rich in carbohydrates. There are no restrictions to eating or drinking between sunset and the dawn.

Although the sick are exempt from this practice, many patients with diabetes opt to fast for cultural, social, personal as well as religious reasons. This may put the patients at risk of hypo- and hyperglycaemia. Indeed, epidaemiological studies such as the EPIDIAR, have demonstrated an increased risk of hyperglycaemia (7.5 fold) and hypoglycaemia (4.7 fold). Guidelines, including those published and updated by the American Diabetes Association, have categorized patients to different risk groups.

Our own continuous glucose monitoring study of patients during Ramadan fasting has shed further light on glucose fluctuations among patients with diabetes on various medication groups. A major problem is the post-iftar glucose rise which may be due to the constitution of the food consumed, but inappropriate dosing and timing of medication may be other contributing factors to this excursion which is almost universal to all patients. We have highlighted the effect of prior glycaemic control and medication category on glucose excursions during Ramadan fasting. We have also been able to arrive at a simple predicting index to help the patient and the clinician decide on how safe the Ramadan fast may be for the individual patient.

It is apparent that patients on insulin and sulfonylureas may be at particular risk of deteriorating control, whereas those on no medication, metformin, gliptins, or glitazones are generally at lower risk. Clearly, not all insulin regimens are the same and treatment has to be individualized. Experience and also recent evidence indicates that we are not achieving acceptable control. The lecture will address some of the common and uncommon, but more serious problems encountered by the fasting patients and attempt formulate solutions to help get things right.

SL-95

Track: *Traditional Chinese Medicine*

KAEMPFEROL FROM *DRYNARIA FORTUNEI* PROMOTES THE PROLIFERATION OF KIDNEY TUBULAR-CELL AND THE SECRETION OF BGF

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Six compounds were isolated and identified to be naringin, neoeriocitrin, Kaempferol, naringenin-7-O-β-D-glucoside, kaempferol-3-O-β-D-glucopyranoside- 7-O-α-L-arabinofuranoside and kaempferol-3-O-α-L-rhamnosyl-7-O-β-D-glucoside were isolated from *Drynaria fortunei.* The activity of the components was examined by studying the proliferation and bio-function of Opossum Kidney (OK), osteoblast (MC3T3 E1) and human fibroblast cells. Kaempferol was found to be active in promoting OK cell growth which increased by 16-30% and 11.6% respectively in the absence or presence of gentamicin. Kaempferol promoted neither MC3T3 E1 nor HF cell proliferation. OK cell-conditioned culture medium (OKM) increased MC3T3 E1 growth by 198%. MC3T3E1 cell growth additionally increased by 127% in comparison to control OKM. The results of OKM promoted osteoblast proliferation indicate that the kidney cell secretes BGF. Kaempferol stimulates kidney cells proliferation and increases secretion of BGF. The data suggest that patients with CKD associated with bone deficiency, may have a lower level of BGF. Kaempferol may serve to stimulate kidney repair and up-regulate bone formation and may be useful in treating CKD and osteoporosis.

SL-69

Track: *Traditional Chinese Medicine*

RESEARCH ON MECHANISMS AND PRINCIPLES OF WARM-UNBLOCK AND WARM-TONIC EFFECTS ON MOXIBUSTION

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Based on the research of principles and mechanism of warm-unblock and warm-tonic effects induced by moxibustion, the study aims to explore the mechanism of warm-unblock and warm-tonic effects, the relation between these two effects and the characteristics of effects rules. The preliminary results showed that the mechanism of warm-unblock and warm-tonic effects could be modulation the neural-endocrine-immune pathway and also the function of *Zangfu* organs, and promotion the circulation of *Qi* and blood by activating the related acupoints. They also indicated that the relations of effects would be presented as following: warm-effect would promote unblock-effect and generate tonic-effect; unblock-effect would enhance tonic-effect, and *vice versa*. Moreover, they pointed out the characteristics of effect principles might be unblock- and tonic-effect features, particularity, conditionality, extent, diversity and sustainability.

SL-75

Track: *Traditional Chinese Medicine*

THE CENTRAL MECHANISM OF PUNCTURING AT ACUPOINTS ALONG SHAOYANG MERIDIANS FOR MIGRAINEURS: AN FMRI STUDY

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Objective: To explore the central mechanism of acupuncture analgesia.

Method: Fourty-one migraineurs without aura were randomized into acupoints along shaoyang meridians group (RA), sham acupoints group (SA) and waiting list group (WL). Migraineurs in the RA and SA were received 20 times acupuncture within 4 weeks and those in WL were observed for 4 weeks without treatment. Clinical evaluation and functional Magnetic Resonance Imaging (fMRI) data were collected pre- and after-treatment.

Results: Comparing pre-treatment to after-treatment, cerebral responses of migraineurs mainly located in brain stem, limbic system and PFC, and HD improvement positively correlated with changes of middle brain and OFC in WL; cerebral changes mainly in the right Parahippo and PFC, and HD improvement positively correlated with changes of Parahippo in RA. Related brain areas extensively located in bilateral limbic cortices and PFC in SA.

Conclusion: The central mechanism of acupuncture may relate to the targeting modulation of the function of stem-limbic-prefrontal cortices.

SL-127

Track: *Cardiovascular Drug Discovery & Therapy*

STUDY ON PHARMACOLOGICAL FUNCTION PROPERTIES, FORMULA PRINCIPLES, CORE BIOACTIVE COMPONENTS, EFFICACY TARGETS AND MECHANISMS OF A TRADITIONAL CHINESE HERBAL FORMULA FOR CARDIOVASCULAR DISEASES COMPOUND XUESHUANTONG CAPSULE (CXC)

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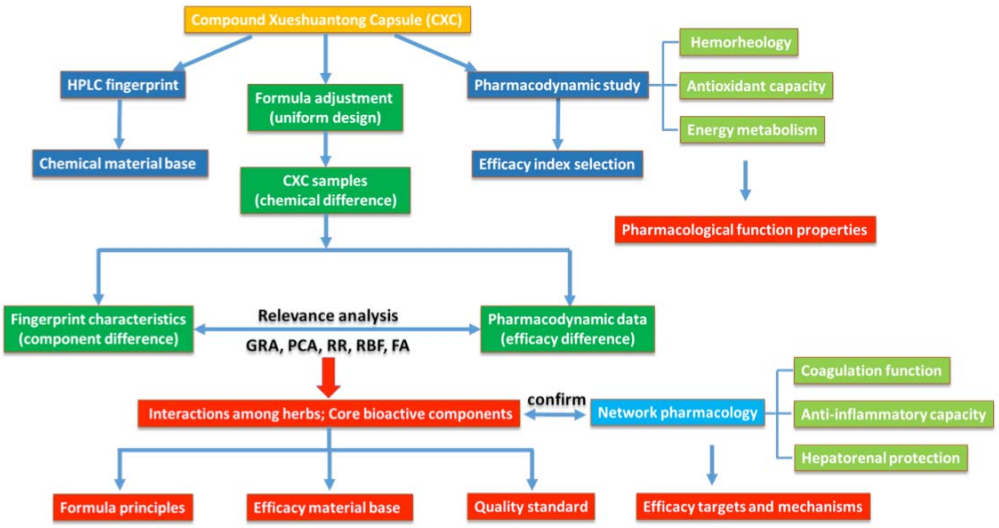
Compound Xueshuantong Capsule (CXC) is a traditional Chinese herbal formula performing excellent effects on promoting blood circulation. CXC is comprised of *Panax notoginseng*, *Radix astragali*, *Salvia miltiorrhizae*, and *Radix scrophulariae*. Taking CXC as the research carrier, the present study was thus designed to explore pharmacological function properties, illustrate formula principles, identify core bioactive components, improve quality control, and reveal underlying efficacy targets and mechanisms based on the combination of HPLC fingerprint, experimental pharmacology, statistical analysis, and network pharmacology.

The results demonstrated that: CXC can perform multiple effects on hemorheology, oxidative stress, energy metabolism, inflammation, and hepatorenal function; *Panax notoginseng* has the highest efficacy contribution and can significantly regulate red blood cell (RBC) deformability and blood clotting activity to improve microcirculation disturbance, while *Radix astragali*, *Salvia miltiorrhizae*, and *Radix scrophulariae* can significantly reduce RBC aggregation to prevent blood hypercoagulability; Ginsenoside Rb_1 (RBC aggregation), panaxytriol (RBC aggregation), angoroside C (platelet aggregation), protocatechualdehyde (intrinsic clotting activity), ginsenoside Rd (RBC deformability), and calycosin-7-O-β-D-glucoside (extrinsic clotting activity) are core bioactive components in CXC; Among 115 thrombosis disease-related targets, 41 may be affected by CXC, therein, F2, PDE5A, ACE, FDP, FIB, AT_{III}, iNOS, vWF, etc. are further experimentally confirmed to be the key efficacy targets.

The graphic abstract is depicted below



SL-34

Track: *Innovative Drug Discovery and Nanotechnology*

THE PHOSPHOLIPID ENZYME CTP:PHOSPHOETHANOLAMINE CYTIDYLYLTRANS-FERASE (Pcyt2) IS A NEW TARGET FOR OXIDATIVE STRESS THERAPY AND ISCHEMIA

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It is well-known that is beneficial to transiently block respiration during ischemia/reperfusion; however there is an unmet clinical need for discovering new compounds and targets that can inhibit the respiration. We established that the 'over-the-counter' anti-histaminergic drug Meclizine could inhibit mitochondrial respiration (uncoupling the OXPHOS) by elevating the levels of phosphoethanolamine, an intracellular metabolite in phospholipid biosynthesis and the exclusive substrate of Pcyt2. That phosphoethanolamine was the only elevated intermediate (35-fold) during the inhibition of respiration with Meclizine strongly directed towards Pcyt2 as the drug target. The extensive metabolic studies as well as studies on recombinant Pcyt2 protein provided strong evidence for direct inhibition of Pcyt2 with Meclizine. The impact of our discovery is not only how to expand the future use of Meclizine but also to offer the first inhibitor for the CDP-ethanolamine Kennedy pathway, to continue to investigate the regulation of the membrane phospholipid synthesis and the basic function of Pcyt2. This is the first time to be demonstrated that the membrane biogenesis impacts mitochondrial OXPHOS and that the inhibition of the CDP ethanolamine pathway at the level of Pcyt2 is protective under pathological conditions of oxidative stress and ischemia.

SL-66

Track: *Biologics*

NEUROCARDIOVASCULAR DISEASES-NOVEL THERAPEUTICAL ASPECTS OF THE OLD ISSUES

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Dynamic environmental changes contrasting basic functional needs of the organism dramatically challenge the neural cardiovascular adaptive mechanisms. Neurocardiovascular diseases are the syndromes where autonomic nervous system (ANS) dysfunction plays a dominant etiological role. Neurocardiovascular disorders can be classified as sympathetic *vs.* vagally mediated disorders, though in many disorders both systems are dysfunctional. Target molecules for therapeutical intervention can be found all along the signalling pathways of ANS, though due to the plasticity of ANS their relative contribution to the pathological phenotype is different between different populations. When joined parasympathetic and sympathetic nervous system disequilibrium is considered, the focus of research should be on molecules providing the cross-talk between the two systems: on intracellular and intercellular level and on the level of the signalling process integration (1). Proposed therapeutical strategies are gene, pharmacologic and behavioural modulation of ANS.

SL-92

Track: *Anti-Infectives*

ON THE ROLE OF GENOMIC ISLANDS IN BACTERIAL PATHOGENICITY AND ANTIMICROBIAL RESISTANCE

Doaa Safwat Mohammad

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Transfer of virulence and antimicrobial resistance genes among different bacterial strains is one of the main causes of antimicrobials use failure. Genomic islands (GEIs) play a crucial role in this genetic

transfer. They are discrete DNA segments which contain virulence, antimicrobial resistance and other types of genes. They can excise from a host chromosome, transfer to other bacterial strains and integrate into the chromosome of a new host. GEIs transfer horizontally between different species by transformation, conjugation and transduction. This genetic transfer causes virulent strains to be more virulent and the nonpathogenic strains to be pathogenic which contributes in bacterial evolution to great extent. GEIs are originally symbiotic to enable bacteria to adapt their surrounding environment, but after environmental changes and acquisition of different genes they become pathogenic which means that pathogenicity is due to a combination of events. Bacteria can be diagnosed through detection of GEIs as they are species-specific in some strains. The most well known GEIs include the locus of enterocyte effacement (LEE) PAIs of Enteropathogenic *E. coli* (EPEC), the cytotoxin-associated gene (cag) and tfs4 GEIs of *H. pylori*, *Stapylococcus* PAIs encoding toxic shock syndrome toxin (TSST), Salmonella genomic island 1(SGI1) of *Salmonella typhimurium* and the AbaR and Tn6167 GEIs of *A. baumannii*. Clustered regularly interspaced short palindromic repeats (CRISPRs) and their associated (Cas) proteins are targeting DNA, causing genomic alterations and resulting in bacterial evolution and pathogenicity. Variation in genomic signature from host chromosome is used for GEIs detection.

Keywords: Antimicrobials, evolution, horizontally, islands, pathogenicity, resistance, symbiotic.

SL-131

Track: *Advances in Neuroscience Technique Useful for Drug Discovery and Therapy*

IN VIVO AUTOMATED INTRACELLULAR RECORDING FROM MULTIPLE NEURONS

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Although multiple *in vivo* intracellular recording is a useful technique for understanding how neurons and neural circuits function, this is formidable tasks for researchers. In order to overcome this difficulty, we developed an automated intracellular recording (AIR) system. This AIR system can automatically move an electrode in the brain, find a neuron, activate a brief high frequency current to penetrate the neuron and inject the optimal negative current to recovery from the penetration damage. We evaluated the performance of the AIR system in anesthetized head-restrained mice. The success rate for one electrode was 63 % (n=11 electrodes). The average stable recording time was 56 min, and a maximum time was 193 min. After stable intracellular recording from one neuron was finished, this system could continuously find another neuron and achieve the intracellular recording from it without changing the electrode. We could record from up to 4 neurons using 1 electrode. For multiple *in vivo* intracellular recording, we run 6 AIR systems in parallel and succeeded in simultaneous recording from 4 neurons; 2 neurons from the primary somatosensory and 2 neurons from the secondary motor area. This system will enable us to record from neurons that are synaptically connected and help us to understand the mechanism of the synaptic transmission *in vivo*.

SL-72

Track: *Translational Medicine*

OLD PROBLEMS, NEW SOLUTIONS: VARIABILITY AND NONLINEARITY IN BIOPHARMACEUTICAL PROCESSES AND MATHEMATICAL MODEL-BASED PROBLEM SOLVING

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In the drug development arena, the rapid accumulation of new quantitative methodologies and tools pushed the emergence of systemic and mechanistic studies of pharmacology that drive the drug R&D. Particularly, tools based on modeling and simulation (M&S) gained a large popularity in the milieu considering the increasing number of success stories involving M&S. The efficient use of these tools heavily relies on advanced mathematical methodologies and their appropriateness to the problem at hand.

Dose-exposure-effect relationship involves physiological and drug related variability as well as nonlinearity in therapeutic outcomes, which are at the centre of our methodological developments. In this talk, I will discuss how these

phenomena can be tackled within a probabilistic framework. To illustrate, I will report on the experience the team has developed in the area of biopharmaceutical research, fully supported by mathematical proof of concepts, with projects ranging from patient compliance, optimal design of drug regimens, limited sampling strategies as well as new insights in drug disposition.

Dr. J. Li is the main collaborator. Other team members contributing to this research program are: O. Barrière, S. Sarem, G. Bonnefois, M. Craig, L. Kheibarshekan and X.T. Wu.

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SL-74

Track: *Anti-Infectives*

HIDDEN ANTIBIOTICS IN ALLIUM HIRTIFOLIUM

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Allium hirtifolium which is known as Persian shallot (locally called Mooser), is used as traditional medicine in Iran for the treatment of rheumatic and inflammatory disorders, gout, arthritis, diarrhea, stomach pain, psoriasis and hemorrhoid. We investigated the antimicrobial activity against clinical important drug resistant pathogen with special focus on methicillin resistant *Staphylococcus aureus* (MRSA). The semi-purified dichloromethane (DCM) fraction of the crude methanol extract was assessed for antibacterial activity by disc diffusion test, minimum inhibitory concentration (MIC) and time kill study. Persian shallot exerted inhibitory activities against MRSA) with different staphylococcal cassette chromosomes *mec* (SCC*mec*), methicillin susceptible *Staphylococcus aureus* (MSSA), *Staphylococcus epidermidis, Streptococcus pyogenes, Proteus vulgaris, Escherichia coli, Bacillus subtilis,* and *Acinetobacter baumannii.* MICs ranging from 1.6 to 4.0 mg/ml for different MRSA strains. All MRSA strains were killed completely within 20 minutes at the MIC. Gram staining and electron microscopy documented a clear detrimental effect on bacterial cell morphology. All these data gives indication that Persian shallot contain potent antibiotics with clear antibacterial activity. We are currently working on isolation, purification and identification of potential bioactive compounds and the drug targets in bacteria.

SL-126

Track: *Advances in Neuroscience Technique Useful for Drug Discovery and Therapy*

RHOA/RHO KINASE PATHWAY IS NEW TARGET FOR TREATMENT OF NEUROPATHIC PAIN

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Neuropathic pain is a common symptom in several diseases such as nerve-injury, cancer, and diabetes mellitus. The progression of neuropathic pain causes serious problems in daily life and may affect the

prognosis of these diseases. Neuropathic pain is resistant for opioid analgesics, and new curatives are required. Several intracellular signaling molecules have been considered to participate in neuropathic pain. Activation of protein kinase C in the spinal cord has been reported to play a central role in the pathogenesis of neuropathic pain. We recently found that small molecular G-protein RhoA in the spinal cord is also involved in the development and/or maintenance of neuropathic pain. Indeed, pharmacological inhibition of Rho-associated kinase (ROCK), which is activated by RhoA, also attenuates the hyperalgesia. Simvastatin, which inhibits RhoA activation though the inhibition of protein isoprenylation, attenuated the hyperalgesia in diabetic and nerve-injured mice. Since ROCK was co-localized with astroglial marker GFAP in the spinal cord, astrocyte might be main target of simvastatin. Interestingly, simvastatin and ROCK inhibitor attenuated the increased expression of GFAP in the dorsal horn of spinal cord of nerve-ligated mice. Moreover, simvastatin treatment attenuated the phosphorylation of myristoylated alanine-rich protein kinase C substrate (MARCK), which modulates the neurotransmitter release and is suggested to be involved in hyperalgesia, in nerve-ligated mice. Inhibition of ROCK also attenuates the MARCKS protein phosphorylation in the spinal cord, suggesting that increased phosphorylation of spinal MARCKS in nerve-ligated mice is caused by the activation of spinal astroglial ROCK. These results indicated that RhoA/ROCK signaling inhibitors are attractive candidate for the treatment of neuropathic pain. It is also possible that substances that modulate astroglial function ameliorate the symptoms of neuropathic pain.

SL-47

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

CHEMICAL STRUCTURES ACCOUNT FOR HALF OF RHABDOMYOLYSIS CAUSING DRUGS

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We have extracted 16 basic active structures (BASs) for rhabdomyolysis. The base data was JAPIC2012 database containing labels of 1187 drugs on Japanese market. Chemical structure mining has identified BASs characteristic to 92 drugs with rhabdomyolysis side reaction. The results contain biphenyls, fluorine compounds, and those characteristic to ARBs and statins. They cover nearly half toxic compounds.

We have provided a new database to verify the usability of the BASs. It consists of drugs in JAPIC (2008 to 2013) and DrugBank. Drugs in the categories of *approved* and *withdrawn* were employed from DrugBank. The integrated database contains 2002 drugs, in which 702 drugs appear in both databases. Rhabdomyolysis appeared 74 times in JAPIC labels, while it was only 6 by DrugBank toxicity retrieval. Therefore we employed SIDER2 descriptions (higher than *post-marketing*) to judge the occurrence of the side effect. The application of the BASs to 767 drugs not sold in Japan resulted in the contingency table at the right. The BASs explain more than half of the drugs with the side effect, and the probability of rhabdomyolysis raises more than 5 times when a drug has a BAS. The p-value by Fisher's exact test is 0.001. The same tendency was observed in the analysis of agranulocytosis.

DrBk only		BAS		sum
		cover	uncover	
Rhab	y	5	4	9
	n	76	682	758
sum		81	686	767

SL-44

Track: *Medical Imaging*

EVALUATION OF THE HEALTH/DRUG INFORMATION-SEEKING BEHAVIOR OF THE HEALTH PRACTITIONERS AT THE POINT OF CARE AT A TERTIARY HOSPITAL IN SOUTH WEST NIGERIA

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This study aimed at evaluating the health/drug information-seeking behaviour of healthcare professionals including physicians, pharmacists and nurses at the point of care at the University College Hospital (UCH), Ibadan, Nigeria. A total number of 594 questionnaires were administered by stratified random sampling and 445, corresponding to 75% response were returned. Data analysis was carried out using SPSS Version 11.5 for windows; simple percentage was done to describe the information resources used by all the practitioners. Chi-square analysis and ANOVA were used for the responses of the health professionals. Three hundred and eighty three (86.1%) respondents were computer literate while 337 (75.7%) had access to computers. Two hundred and seventy-three (61.4%) used the internet for health drug information seeking, 84 (18.9%) used internet for e-mail purposes and 26 (5.8%) used internet for other purposes while 62 (13.9%) did not use the internet. Sources of health/drug information used included textbooks 181(40.1%), journals 7(1.6%), other professionals 97(21.8%) and others such as medical representatives 163(36.6%). The frequency of search for information needs differed significantly ($p<0.05$). The nurse professionals 96(61.0%) were the least in the health/drug information seeking behavior compared with the physician's 235(100%) and pharmacists 52(100%). Access to the computer was least among the nurses 50(31.7%).

Education and training of health professionals will enhance their clinical practices regarding the use of available internet for the information seeking behavior at the point of care.

Keywords: Physicians, pharmacists, nurses, health and drug.

SL-12

Track: *Hot Topics in Natural Products*

SEMI-SYNTHESIS AND BIOLOGICAL EVALUATION OF URSOLIC ACID AND ITS DERIVATIVES

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Mimusops caffra provided sufficient Ursolic acid (UA) (**1**) which was used as a template for the semi-synthesis of the bioactive compounds. Sequential solvent extraction of the leaves of this plant, it was found that ethyl acetate was the best solvent for the extraction since it gave more extract (3.1% recovery yield) and direct solvent extraction gave 9% recovery yield. Defattening the crude extract by simple pre-purification, semi-pure extract was obtained. This study confirmed the report from literature that UA is always accompanied by its isomer Oleanolic acid (OA) (**2**) which makes it hard to be isolated by simple chromatographic methods since both isomers have the same R_f value of 0.49 on the Thin Layer Chromatography(TLC) plate, the closeness on their structures is also confirmed by Nuclear Magnetic Resonance (NMR) methods. The separation of UA from OA by acetylation was achieved to give acetate of UA(0.75;62%) and acetate of OA (0.58;18%) respectively followed by UA (Rf 0.49; 90%) and OA (Rf 0.49; 89%).

This research entails the Structure Activity Relationship (SAR) where three more C3 and C28 modified-analogues of UA were successfully synthesized in good yields; 3-Acetyl-UA-28-methylate (**3**) (70%), 3-Acetyl-UA-28-benzylate (**4**) (52%) and 3-Acetyl-UA-28-cinnamate (**5**) (48%). The biological evaluation of the all these compounds as anticancer, anti-inflammatory and anti-hypertensive agents are hereby discussed.

SL-91

Track: *Nutraceutical Drug Discovery & Therapy*

SYSTEMS MEDICINE, APPLYING SYSTEMS BIOLOGY APPROACHES FOR MULTIPLE SCLEROSIS TREATMENT BY THE USE OF SPECIFIC STRUCTURED MOLECULES AND ANTIOXIDANT VITAMINS: THE PLP10 NOVEL INTERVENTION PARADIGM

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Background: For many years, the role of polyunsaturated fatty acids (PUFA) in the pathophysiology and development of neurodegenerative diseases and specifically multiple sclerosis has been a subject of considerable discussion and research but without proof of efficacy. We aimed to assess whether our novel intervention, formulated based on systems medicine concept, comprising specific fatty acids and vitamins within a specific ratio, quantity, quality, and structural form reduce disease activity in patients with relapsing remitting multiple sclerosis who were either treated with disease modifying treatment or untreated.

Design: A 30-month randomised, double-blind, placebo-controlled, parallel design, phase II proof-of-concept clinical study.

Settings: Cyprus Institute of Neurology and Genetics.

Participants: 80 participants were randomised into four groups of 20 each. A total of 41 (51%) patients completed the 30-month trial. The eligibility criteria were an age of 18–65; a diagnosis of relapsing–remitting MS according to the McDonald criteria; a score of 0.0–5.5 on the Expanded Disability Status Scale (EDSS); MRI showing lesions consistent with MS; at least one documented clinical relapse and either receiving or not a disease-modifying treatment within the 24-month period before enrolment in the study. Patients were excluded because of a recent (<30 days) relapse, prior immunosuppressant or monoclonal antibody therapy, pregnancy or nursing, other severe disease compromising organ function, progressive MS, history of recent drug or alcohol abuse, use of any additional food supplements, vitamins or any form of polyunsaturated fatty acids, and a history of severe allergic or anaphylactic reactions or known specific nutritional hypersensitivity.

Interventions: The first intervention (A) was composed of Ω-3 and Ω-6 polyunsaturated fatty acids at 1:1 wt/wt. Specifically, the Ω-3 fatty acids were docosahexaenoic acid and eicosapentaenoic acid at 3:1 wt/wt, and the Ω-6 fatty acids were linoleic acid and γ-linolenic acid at 2:1 wt/wt. This intervention also included minor quantities of other specific polyunsaturated, monounsaturated and saturated fatty acids as well as vitamin A and vitamin E (α-tocopherol). The second intervention (B, PLP10) was a combination of A and γ-tocopherol. The third intervention (C) was γ-tocopherol alone. The fourth group of 20 participants received placebo. The interventions were administered per os once daily, 30 min before dinner for 30 months.

Main outcome measures: The primary end point was the annualised relapse rate (ARR) of the three interventions versus the placebo at 2 years. The secondary end point was the time to confirmed disability progression at 2 years.

Results: A total of 41 (51%) patients completed the 30-month trial. Overall, for the per-protocol analysis of the 2-year primary end point, eight relapses were recorded in the PLP10 group (n=10; 0.40 ARR) versus 25 relapses in the placebo group (n=12; 1.04 ARR), representing a 64% adjusted relative rate reduction for the PLP10 group (RRR 0.36, 95% CI 0.15 to 0.87, p=0.024). In a subgroup analysis that excluded patients on monoclonal antibody (natalizumab) treatment, the observed adjusted RRR became stronger (72%) over the 2 years (RRR 0.28, 95% CI 0.10 to 0.79, p=0.016). The per-protocol analysis for the secondary outcome at 2 years, the time to disability progression, was significantly longer only for PLP10. The cumulative probability of disability progression at 2 years was 10% in the PLP10 group and 58% in the placebo group (unadjusted log-rank p=0.019). In a subgroup analysis that excluded patients on natalizumab, the cumulative probability of progression was 10% for the 10 patients in the PLP10 group and 70% for the 12 patients in the placebo group, representing a relative 86% decrease in the risk of the sustained progression of disability in the PLP10 group (unadjusted log-rank p=0.006; adjusted HR, 0.11; 95% CI 0.01 to 0.97, p=0.047). No adverse events were reported. Interventions A and C showed no significant efficacy.

Interpretation: PLP10 treatment significantly reduced the ARR, and the risk of sustained disability progression without any adverse or significant side effects. This is the first clinical study of systems medicine approach medical nutrient formula that holds strong promise as an effective treatment for relapsing remitting multiple sclerosis.

Trial registration: International Standard Randomised Controlled Trial, number ISRCTN87818535.

SL-39

Track: *Regenerative Medicine*

GDNF AND ITS MODIFICATIONS AS STIMULATOR OF NEURAL DIFFERENTIATION OF PROGENITOR CELLS- POSSIBLE APPLICATIONS

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GDNF therapy is effective against disorders associated with the degeneration of dopaminergic neurons, such as Parkinson's disease. This treatment not only increases the dopaminergic synaptic neurotransmission in the corpus striatum but also decelerates the degenerative processes in the nigrostriatal projections. We have created a modified GDNF to stimulate neural differentiation of progenitor cells. Effect of the transgenic cell secreted modified GDNF on the growth of neural sprouts was studied in the spinal ganglia of 14 day rat embryos. Media conditioned by the transgenic cells secreting modified GDNF were used to culture the spinal ganglia attached to the bottom of the plate. The spinal ganglia has demonstrated active growth of neural sprouts which are immunopositive for neuronal marker, beta-3-tubulin, as early as on the fourth day of culturing. The ganglia cultured in control medium without modified GDNF had no neural sprouts even after 10 days of culturing. Thus the modified GDNF is an effective stimulator of neural differentiation. *In vivo* permanent over-expression of this transgenic factor could induce many disorders, including cancer. Therefore, transplantation of the transgenic cells secreting modified GDNF requires its regulated expression.

We have explored temperature regulated hsp70 promoter of Drosophila for the temporary expression of gdnf inside the cells. Surprisingly that it is possible to activate hsp70 promoter of Drosophila in the mammalian cells. The temperature range of activation has been determined. The copy number of Heat Shock Elements within hsp70 promoter up-stream region effects the activation. The cells transgenic with gdnf under control hsp70 promoter had been transplanted into a local focus of cerebral ischemia of the mice brain, and it has been shown the expression of gdnf during 7-10 days.

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SL-93

Track: *Chemistry*

SYNTHESIS OF NOVEL 1'-(4-(2H-CHROMEN-3-YL)THIAZOL-2-YL)-3',5-DIMETHYL-2-PHENYL-1'H,2H-3,4'-BIPYRAZOL-5'-OL DERIVATIVES

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Heterocycles are widely used in the development of modern pharmaceuticals, this being one of the reasons why continuous efforts are placed towards the design of amenable synthetic approaches for the synthesis of new heterocyclic systems. The pyrazole nucleus represents a very attractive scaffold for obtaining novel molecules endowed with diverse biological activity, including anti-inflammatory, antidepressant, anticonvulsant, anticancer, analgesic, anthelmintic, antioxidant and herbicidal properties. Thiazole ring systems are known to possess various pharmacological properties such as anti-tubercular, antifungal, analgesic and anti-cancer activity. In this work, 1'-(4-(2H-chromen-3-yl)thiazol-2-yl)-3',5-dimethyl-2-phenyl-1'H,2H-3,4'-bipyrazol-5'-ol derivatives have been synthesized by the reaction of 3-(2-bromoacetyl)-2H-chromen-2-one, thiosemicarbazide with 3-acetyl-4-hydroxy-6-methyl-2H-pyran-2-one refluxed in ethanol afforded 3-(2-(2-(1-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)ethylidene) hydrazino)thiazol-4-yl)-chromen-2-one. To this reaction mixture 2 drops of HCl was added and heated about 2 h afforded 1-{5-Hydroxy-3-methyl-1-[4-(2-oxo-2H-chromen-3-yl)-thiazol-2-yl]-1H-pyrazol-4-yl}-butane-1,3-dione derivatives. This product was isolated and treated with phenyl hydrazine afforded the title products in good to excellent yields. All the synthesized compounds were characterized by their analytical and spectral data. The screening of these compounds for anticancer activity is in progress.

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SL-50

Track: *Recent Advances in Patient Treatment and Care*

ABOUT THE LACK OF EFFICACIOUS DRUG THERAPY TOWARD MEDICAL TREATMENT OF ALCOHOLISM

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In the very beginning of his profession, the author as a rural doctor did not have the preparedness for alcohol-related health problems. However, within several years, his everyday experiences, together with the results of his own epidemiological studies drew his attention to these problems. In 1978, he made a survey of alcohol infectedness of his district-population in Bácsbokod, and he found that it was 17%. After that he performed a follow-up reaserch on alcohol-related morbidity and mortality until 1986 in Bácsbokod. He conducted similar research in Felsőszentiván from 1987 until now. Currently, his research is focused on the relationship between alcohol-related and cancer mortality. As one of his most important results, he obsreved that more than half of the cancer mortality was alcohol-related in his practice during the past 25 years. By reason of more decennial own experiences, the author concluded that the alcoholism is one of the most important public health problem. At the same time he refers to statistics data of the international literature that alcoholism is one of the biggest world problem and alcoholism itself is a disease like diabetes mellitus. Because of the lack of efficiacious drug therapy the efficiacious medical treatment of alcoholism is practically impossible, the author as family physician with special degree in addictology asks the drug-researchers when such drug(s) will be expected.

SL-51

Track: *Cardiovascular Drug Discovery & Therapy*

THE CHANGING DYNAMICS OF DRUG DISCOVERY: USING BIG DATA TO ACCELERATE THE PATHWAY FROM BENCH TO BEDSIDE

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As industry pressures increasingly force companies to look at the ROI and value of the medicines they produce, the dynamics of successful drug discovery are changing. There is a growing trend to focus on niche markets such as rare diseases and targeted sub-populations of larger cancer indications where the barriers to entry can be lower and value can be easier to demonstrate. Strategies such as repositioning are also being employed to cut development costs and accelerate the pathway to market. With the ever expanding volume of data available in the public domain on the targets and pathways implicated in diseases, big data methods of information interpretation are being employed to accelerate the drug development process. In this presentation we introduce novel strategies being employed by companies to develop a more efficient, cost effective way to conduct pharmaceutical R&D.

SL-64

Track: *Pharmaceutical Research & Development*

ACHIEVEMENTS AND LIMITS ON THE CONTROLLED RELEASE OF A DRUG FROM THE SURFACE OF A TEXTILE FABRIC TO DERMIS

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The paper presents the overall results of theoretical realizations and experimental details when designing a material for a textile fabric/implant, which releases a drug for a specific pathology. It presents the conclusions of the researches on the development of textile support as an anti-allergic, anti-fungal and anti-psoriasis type, but also on toxicological, biocompatibility and therapeutic issues for establishing the amount of drug needed for the *trans*-dermal diffusion. This paper estimates the possibility of applying on a textile surface of a cyclodextrine polymer/composite which form temporary reservoirs by complexing and subsequent releasing the drug under the action of coetaneous stimuli. One refers to the achievements of authors, and works submitted by other research groups in the area of textile substrates used as implant or underwear worn next to the skin. The results are analyzed both as a scientific communication, and the potential application for a potential current industrial processing.

SL-30

Track: *Hot Topics in Natural Products*

PROTECTIVE ROLE OF THYMOQUINONE AGAINST CYCLOPHOSPHAMIDE TOXICITY ON SPERM ATTACHMENT TO OOCYTE AND FERTILIZATION IN MICE

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Thymoquinone is one of the major active ingredients of *Nigella sativa*, a medicinal herb known as 'Habatus-sawdah', that has been found to be capable of reducing the adverse effects of conventional chemotherapy. Cyclophosphamide is an anti-cancer drug clinically used to treat a variety of cancers. The aim of this study was to investigate the possible chemoprotective effects of thymoquinone on possible cyclophosphamide-induced reproductive toxicity affecting attachment of sperm to oocyte and fertilization rates. Experiments were performed using BALB/c mice, 12-14 weeks of age weighing 25-30 g each. The animals were divided into four groups and all treatments were administered by intraperitoneal injections. The control group was administered normal saline solution while mice in the cyclophosphamide group received a single dose of the alkylating agent at a dose of 200 mg/kg. In the thymoquinone group, mice were injected with 10 mg/kg of thymoquinone on alternate days for 38 days. Similarly, in the combination treatment, 10 mg/kg of thymoquinone was administered on alternate days up until day 38 following a single injection of 200 mg/kg cyclophosphamide. At the end of the study period, epididymis was excised and sperm was obtained for sperm analysis, sperm attachment and *in-vitro* fertilization observations. Inverted phase contrast microscopy revealed a decreased number of sperm attachment to oocytes and non-fertilization for the group treated with cyclophosphamide alone. The combination of thymoquinone and cyclophosphamide resulted in an increment in sperm motility, sperm count, sperm attachment to oocyte and fertilization rates. Similarly, thymoquinone on its own significantly increased sperm attachment to oocyte and the rates of fertilization as compared to that following treatment by cyclophosphamide alone. A reduction in the number of sperm produced was however observed following the treatment with thymoquinone alone but overall sperm quality and sperm parameters appeared to be improved and the process of sperm attachment to oocyte including fertilization rates seemed to be protected against effects of the anticancer drug.

SL-98

Track: *Anti-Infectives*

DISCOVERY OF NOVEL DRUG-LIKE COMPOUNDS FOR CONTROLLING AMPLIFIED INFLAMMATORY RESPONSES MEDIATING THROUGH TOLL-LIKE RECEPTOR/ MYELOID DIFFERENTIATION PROTEIN2 HYPER ACTIVATION

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Toll-like receptor 4 (TLR4) recognises endotoxic lipopolysaccharide (LPS) present in the outer membrane of Gram-negative bacteria and triggers innate immune responses. Upon recognition of LPS, TLR4/myeloid differentiation protein 2 (MD2) complex undergoes homodimerisation leading to inflammatory responses, mediated through either MyD88-dependent and MyD-88 independent pathways. Hyper activation of TLR4/MD2 in response to LPS causes uncontrolled amplification of inflammatory responses, leading to fatal septicaemia. Therefore, identification of selective modulators of TLR4/MD2 activity inhibiting only one pathway such that some activation remains to stimulate protective immunity would an ideal strategy to control the amplified inflammatory responses.

In our research, we have utilised various computational modelling techniques such as docking, pharmacophore, molecular dynamics *etc*., to identify and design the potential compounds that selectively inhibit TLR4/MD2 activation. Identified compounds were obtained from commercial vendors and designed compounds were synthesised in our laboratory. We have tested the activity and efficacy of the compounds in various experimental models, *viz*., LPS induced TLR-4 activation in HEK-Blue^{TM}hTLR4 cells to identify TLR4 agonists, partial agonists and antagonists; Greiss assay for nitric oxide production in RAW 264.7 cells, and the results were confirmed through western blotting of TLR4/MD2 downstream signaling proteins in RAW 264.7 and HEK-Blue^{TM}hTLR4 cells.

We have discovered few novel compounds that are selectively modulating the TLR4/MD2 activity.

SL-100

Track: *Anti-Cancer Drug Discovery & Therapy*

HPMA-BASED COPOLYMER CONJUGATES OF DOXORUBICIN BOUND THROUGH AN AMIDE OR HYDRAZON BOND: SYNERGISTIC ACTION IN TREATMENT OF SOLID TUMORS

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The cytostatic effects of polymeric conjugates based on *N*-(2-hydroxypropyl)methacrylamide copolymers (HPMA) and containing doxorubicin bound through amide (DOX^{AM}) and hydrazone (DOX^{HYD}) bonds (mixed conjugates) were compared with the cytostatic effects of monoconjugates containing drug bound through an amide or hydrazone bond only. One group of mixed conjugates was formed from two (DOX^{AM} and DOX^{HYD}) comonomers. A second group was formed from two different interconnected HPMA copolymers, one containing DOX^{AM} and the other DOX^{HYD}, forming a high-molecular-weight branched structure. The third system was a simple mixture of monoconjugates DOX^{AM}-HPMA and DOX^{HYD}- HPMA. *In vivo* antitumor activity proved a significant synergism between DOX^{AM} and DOX^{HYD} derivatives. Remarkably, old mice (56-week-old) respond to the treatment better that young ones (8-week-old).

Recently, concept of immunogenic cancer cell death (ICD) characterized by stimulation of the anti-cancer immune response is considered as important factor significantly contributing to the chemotherapy. We have seen repeatedly that primary treatment with HPMA-based polymeric doxorubicin stimulates therapy-dependent cancer resistance which follows a basic rule: the more effective therapy induces the lower cancer resistance and *vice versa*. The explanation may lie in availability of immune response stimulating antigen, i.e. cancer cells. More aggressive treatment which facilitates

very rapid elimination of tumor cells induces low tumor resistance whereas a slower eradication of tumor mass induces tumor resistance that is strong enough and could protect up to 100% of cancer-bearing animals against a second tumor attack. This confirms a significant contribution of anti-cancer immune response to the final outcome of the therapy.

SL-36

Track: *Anti-Infectives*

DEVELOPMENT OF NEW TREATMENT FOR CUTANEOUS LEISHMANIASIS BASED ON PHOTODYNAMIC THERAPY WITH HYPERICIN: STUDIES *IN VITRO* AND *IN VIVO*

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Very few drugs are available for treatment of leishmaniasis and all of them are highly toxic, costly, and their efficacy is becoming lower. Therefore, new drugs are needed. Hypericin is the main component of Hypericum perforatum and it has traditionally been used throughout the history of folk medicine. Studies report several biological activities. Hypericin is also considered one of the most powerful type II photosensitizer found in nature, which is useful to photodynamic therapy as an alternative treatment for cutaneous leishmaniasis (CL). Here, Hypericin was evaluated for its anti-leishmanial properties. *In vitro* studies showed that hypericin is highly active against Leishmania amastigotes with EC values of 0.9 + 0.14 μM. On the other hand, topical treatment of hamsters with CL after experimental infection with *L. amazonensis* in the dorsal skin (6 applications of hypericin in presence of light, twice a week) produced complete cure in 4 of 5 animals. The last hamster showed a decrease in the lesion size of 79,8%. In absence of light cure was observed only in 2 of 5 animals. No toxicity associated to dose was observed with Hypericin. These results suggest that hypericin has a great potential as drug candidate against CL.

SL-68

Track: *Anti-Infectives*

EXPERIMENTAL CUTANEOUS LEISHMANIASIS IN HAMSTERS INFECTED IN THE DORSAL SKIN: AN USEFUL MODEL FOR *IN VIVO* SCREENING OF ANTILEISHMANIAL DRUGS

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New a better drugs to treat cutaneous leishmaniasis (CL) are needed. Here, the hamster model for CL was optimized by inoculation in the dorsal skin. In this model of infection the therapeutic response of the lesion is easily determined by comparing the size of the lesion before and after the treatment and the clinical response in terms of cure is followed according to the re-epithelialization of the lesion site. Previous anesthesia, golden hamsters (male and females) was inoculated intradermally at the dorsal skin with 10 to 50 million promastigotes of different Leishmania species. Animals were treated after development of typical skin lesions. Compounds were applied topically or orally daily during 10 to 20 days. The effectiveness of each treatment was assessed comparing the lesion sizes prior to and after treatments every 2 weeks during 3 months. This approach has proven its versatility and easiness but also its correlation with therapeutic potential of new alternatives to treat CL. By using this method the quality of animal life regarding locomotion, search for food and water, play and social activities is also preserved.

SL-92

Track: *Inflammation and Immunology*

SIGNALING OF INNATE-IMMUNE RECEPTOR DECTIN-1 AND ITS MOLECULAR MODELING AND DOCKING WITH PKCΛ: A NOVEL GATEWAY IN DRUG DISCOVERY TO CONTROL INFLAMMATORY AND IMMUNE DISEASES

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Human Dectin-1 receptor, a type of Pattern Recognition Receptor (PRR), express in dendritic cells, monocytes, macrophages and a subset of T-Cells. It comprises of an extracellular C-type lectin domain (CTLD), transmembrane region and ITAM motif containing cytoplasmic domain. Stimulation of CTLD by fungal β-glucans initiates various cellular pro-inflammatory responses and host defense that are controlled by downstream signaling components (Syk and Src kinases and PKCδ) of Dectin-1 receptor. Syk and Src association with Cytopalsmic Domain of Dectin-1 Receptor (CDDR) is dependent on PKCδ expression and activity that directly bind with the Tyr-15 of ITAM motif, this molecular complex is a unique target for drug design.

In the present study, homology modeling of human cytoplasmic domain of Dectin-1 receptor (CDDR), transmembrane region and CTLD was carried out separately. pGenTHEADER, a fold recognition method, identified *Pseudomonas sp.* L-aspartate beta-decarboxylase (pdb id; 2ZY2) as a structural homlogue of human CDDR. The templates for transmembrane and CTLD of human Dectin1 were recognized typically using Psi-BLAST tool as rat membrane protein-2 (pdb id; 3HD7) and murine Dectin 1 receptor (pdb id; 2CL8), respectively. All the constructed models were reliable and very close to their respective templates. The overall fold of CDDR homology model was found to consist of three beta strands stacked together as mixed beta-sheet and the location of Immunoreceptor Tyrosine-based Activation Motif (ITAM) was observed between first two beta-strands of CDDR homology model. Whereas, CTLD fold comprises of two antiparallel beta sheets flanked by two α-helices and transmembrane region folds into a single α-helix. However, CDDR and PKCδ interaction analysis through protein-protein docking strategy using HADDOCK web-server delineates the protein-protein interface to be comparatively more hydrophobic with only few ioinc bonds.The availibility of the 3D structure of CTLD can be implicated in strcuture-based drug designing in order to discover its potential inhibitors. On the other hand, interaction analysis of CDDR and PKCδ will be a milestone in drug discovery programs for introducing various protein inhibitors that can either interfere with various inflammatory responses or can augment the host defense regulating intracellular production of NADPH oxidase-dependent superoxide anion and phagocytosis during fungal and bacterial infections. Additionally, CDDR structure based drugs will provide new insight in the intervention of atherosclerosis and chronic granulomatous disease.

SL-137

Track: *Cardiovascular Drug Discovery & Therapy*

PREVENTIVE ROLE OF GREEN TEA CATECHINS AGAINST OBESITY AND RELATED DISORDERS ESPECIALLY HYPERCHOLESTROLEMIA AND HYPERGLYCEMIA

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The core objective of current research is to explore nutraceutical worth of locally grown green tea variety (Qi-Men) against lifestyle related disorders. For the purpose, green tea catechins and epigallocatechin gallate (EGCG) were isolated, characterized and the functional drinks containing these active components were assessed in experimental rats modeling. Based on diets, four studies were conducted i.e. study I (normal diet), study II (high cholesterol diet), study III (high sucrose diet) and study IV (high cholesterol + high sucrose diet). Functional drinks caused significant reduction in body weight and maximum lowering effect was observed in study II and III i.e. 10.73 to 8.49 % and 10.12 to 10.49%, respectively. Likewise, cholesterol and LDL were substantially reduced by 14.42% and 30.43% in study IV and study II, respectively. The serum glucose and insulin levels were also lowered considerably. It is concluded that drinks supplemented with catechins and EGCG are effective against obesity, hypercholesterolemia and hyperglycemia.

Keywords: Epigallocatechin, gallate (EGCG); catechins; hypercholesterolemia; obesity; hyperglycemia.

SL-87

Track: *Inflammation & Immunology*

THE IMMUNOMODULATORY EFFECT OF COMBRETUM HERERoense AND CANTHIUM MUNDIANUM ON INTERLEUKIN 6 PRODUCTION AND EXPRESSION

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Interleukin 6 (IL-6) is a multifunctional cytokine that plays important roles in host defense, acute phase reactions, immune responses, and hematopoiesis. Interleukin 6 performs a prominent role during disease and has been described as both a pro- and anti-inflammatory cytokine. Therefore, the modulation of IL6 could be useful in the control of infections particularly at this era of HIV and AIDS. Medicinal plants have been used for years by different cultures throughout the world and many of them have been used to modulate immune response.

In the present study, peripheral blood mononuclear cells were isolated by centrifugation gradient method from different volunteers donors based selected based on gender and health status and were maintained in culture for three days at 37ºC under 5% CO_2. The effects of Combretum Hereroense and Cathium mundianum water extracts on the production and expression of interleukin 6 was also evaluated form cell culture supernatant by solid-phase sandwich ELISA kit. RNAesy mini kit from Qiagen was used to extract total RNA from cultured. Reverse transcriptase real time polymerase chain reaction was used for the evaluation of PHA inducible gene mRNA expression levels.

IL6 production and expression was determined in HIV negative and HIV positive donors. Activity index of interleukin 6 in dose dependent manner from HIV negative donors was inhibited in four different concentrations (C1=300µg/ml, C2=50µg/ml, C3=20g/ml and C4= 1µg/ml) of Combretum hereroense and Cathium mundianum extracts. The production of interleukin 6 from HIV negative donors was also increased in one concentration (300µg/ml) of Combretum hereroense and in four difference concentration of Cathium mundianum. The higher concentration yield low production and the lower concentration produce high cytokine expression.

Overall our study indicates that donors that had no diseases showed no production of interleukin 6, while those that were HIV positive and have other diseases showed high levels of interleukin 6. This study will help traditional healers and department of health with information on the evaluation of immunomodulatory system with regards the use of Combretum Hereroense and Cathium mundianum in traditional medicine. This also provides information for further studies on both plants**.**

SL-76

Track: *Pharmaceutical Research & Development*

ANTIBACTERIAL, WOUND HEALING ACTIVITY AND MECHANISMS OF ACTION OF PROTEIN FROM THE EASTERN DIAMONDBACK RATTLE SNAKE

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The skin diseases caused by the pathogenic bacterium *Staphylococcus aureus*, is a major health concern. *S. aureus* becomes multi-drug resistant (MDR) due to the over use of antibiotics. In order to overcome these challenging clinical issues, we need to search for new agents that combat to pathogens and are free from side-effects to human. In this study, we identify and characterize new classes of small molecules from the venom of the eastern diamondback rattlesnake. The *Crotalus adamanteus* toxin-II (CaTx-II) induced bactericidal effects (7.8 µg/ml) on *S. aureus*, while *on B. pseudomallei* and *E. aerogenes* were killed at 15.6 µg/ml. The molecules target the key regulator of membrane damage and pore formation on the bacterial wall. CaTx-II was not cytotoxic on lung (MRC-5), skin fibroblast (HEPK) cells and in mice. CaTx-II-treated mice showed significant wound closure and complete healing by 16 days compared to untreated controls ($P<0.01$). Histological examination revealed enhanced collagen synthesis and neovascularization after treatment with CaTx-II versus 2% Fusidic Acid Ointment treated controls. Measurement of tissue cytokines revealed that IL-1β

expression in CaTx-II treated mice was significantly suppressed versus untreated controls. In contrast, cytokines involved in wound healing and cell migration (i.e., MCP-1, FGF-basic, KC, GM-CSF) were significantly enhanced in CaTx-II treated mice, but not in the controls. CaTx-II modulates nuclear factor-kappa B (NF-kB) activation during skin wound healing. The CaTx-II protein highlights distinct snake proteins as a potential source of novel antimicrobial agents with significant therapeutic application for bacterial skin infections.

SL-71

Track: *Drug Delivery and Targeting*

DESIGN AND CHARACTERIZATION OF DIOSMIN-CYCLODEXTRIN COMPLEX AS A NOVEL TRANSDERMAL GEL

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Diosmin (DSN), a naturally occurring flavonoid, has been used for its phlebotonic properties as a vascular protector for the treatment of hemorrhoids, varicose vein, and venous leg ulcers. Unfortunately, DSN suffers poor oral absorption and high inter-subject variation due to its scantly solubility and poor permeability. Topical administration of flavonoid has met with considerable interest due to their good high vasoprotective activity and anti-inflammatory activity. The most important problem for topical application of DSN is its low penetration through the skin, due to its unfavorable physicochemical properties.

Cyclodextrins (CyDs) have attracted interest for topical use as penetration enhancers due to their ability to affect absorption by influencing physicochemical properties of the drugs and/or the biomembrane permeability. Nevertheless, impact of complexation with CYD on enhancing dissolution and permeation characteristics of DSN has not so far been investigated.

Therefore, this work investigated the potential of DSN-HP-β-CyD complex to improve topical delivery characteristics of diosmin. Differential scanning colorimetry (DSC), infrared spectroscopy (IR), and X-ray diffractrometry studies indicate successful complex formation. Prepared gels were subjected to physical evaluation for its viscosity, pH and drug content. *In vitro* drug release and *in vitro* drug permeation experiments were carried out on Franz diffusion cell using cellophane membrane and animal skin respectively. The release rates when compared were found to be highest with gel containing inclusion complex than the gels containing pure drug and physical mixture.

In conclusion, transdermal gel of DSN-CyD complex could be used as a novel topical delivery system to improve DSN dissolution and permeation.

Keyword: Transdermal gel, cyclodextrin, diosmin, preameation.

SL-15

Track: *Drug Discovery in Preclinical Research*

PROTECTIVE EFFECT OF CAESALPINIA BONDUCELLA (LINN.) SEED KERNEL EXTRACT IN STZ-INDUCED DYSLIPIDAEMIA AND β-CELL DAMAGE IN RATS

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India continues to be the 'Diabetic Capital' of the world with 50.8 million diabetics. Diabetes is associated with markedly increased risk of atherosclerosis and cardiovascular diseases. Cardiovascular disease is the leading cause of mortality in patients with diabetes. Herbal treatments are becoming increasingly popular, as the herbal preparations have no or least side effects than synthetic hypoglycemic drugs. In Ayurveda, *Caesalpinia bonducella* has been acknowledged to treat various diseases and disorders, including diabetes. Present study was undertaken to evaluate the effect of *Caesalpinia bonducella* seed kernel extract, on hyperglycemia, dyslipidaemia and oxidative damage in streptozotocin

diabetic rats. Experimental diabetes was induced by single *i.v*. injection of streptozotocin (40mg/kg). *Caesalpinia bonducella* extract (200, 400 and 600 mg/kg) was administered orally to diabetic rats for 21 days. Blood glucose, lipid profile, tissue glutathione and TBARS levels in pancreas were estimated. The microscopic structure of pancreas and cardiac muscles were examined in both controlled and treated animals.

A significant ($p<0.05$) increase in glucose level, total cholesterol, VLDL and LDL cholesterol level, with reduction in HDL cholesterol level was observed in STZ diabetic rats. *C. bonducella* produced a significant ($p<0.001$) hypoglycaemic effect in a dose dependent manner. Administration of *C. bonducella* reduced the levels of these cholesterol and increased the HDL cholesterol level in diabetic animals. Marked improvement in the morphology of pancreas and heart of animals treated with extract of *C. bonducella* was revealed by histopathological examination. Further studies are warranted to isolate active principle and to find out its exact mechanism of action.

SL-11

Track: *Diabetes and Obesity Drug Discovery & Therapy*

ANTHRAQUINONE DERIVATIVES FROM THE FUNGUS ALTERNARIA SP. (XZSBG-1) ISOLATED FROM SALT LAKE SEDIMENTS AS A BIOLOGICAL EQUIVALENT OF THE MARINE ENVIRONMENT

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Seven secondary metabolites including three new anthraquinone and tetrahy-droanthraquinone derivatives (1-3) along with four known compounds (4, 5, 6, 7) were obtained from extracts of fungus strain Alternaria sp. XZSBG-1 from sediments of the Salt Lake, Tibet, as an equivalent of the marine environment. Their structures were established on the basis of one- and two-dimensional NMR spectroscopy, UV, CD, and mass spectrometry. Compound 2 is a new tetrahydroanthraquinone with a rare epoxy ether bond between C-4a and C-9a, exhibiting a considerable cytotoxicity against human MCF-7/ADR breast cancer cells with an IC50 value of 18.48 μM. Compound 3 is the first macrosporin dimer with a C-5, 5' linkage. The known 4 showed strong inhibitory effect against α-glucosidase with an IC50 value of 7.2 μM, displaying a stronger inhibition than genistein, used as positive control; it may be a promising lead for the development of potent α-glucosidase inhibitors.

SL-38

Track: *CNS Drug Discovery & Therapy*

TREATMENT AND SOCIAL IMPACT OF CEPHALIC HYPERSENSITIVITY SYNDROME RELATING TO MIGRAINE

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Objectives: In this cohort study, we will report that pertinent use of triptan agents reduce risk of incidence of Cephalic Hypersenseitivity (Supersensitivity) Syndrome (CHS or CSS), which has been disseminated concept of CHS in Japan lately.

Methods: In this study, observation items are: 1) demographics of subjects, 2) medical magnificence by electroencephalogram and laboratory test for detection of reactivation of varicella-zoster virus, 3) treatment status. The ethic committee at Tokyo Women's Medical University was performed for approval of the study beforehand.

Results: Of 1000 subjects, the proportion of female in analyzable subjects (n=964) whose mean age are 46.3±16.0 yrs, were approximately 73.3%.

To identify factors relating to migraine onset, we performed multivariate analysis. Gender, age pre-photophobia and tinnitus were suggested onset of migraine attack. Anti-epileptics are effective in 80% of patient with this condition.

Conclusions: Our study suggested that mistaken methods of treatment of migraine from childhood may exacerbate hypersensitivity of the brain and cause the development of dizziness, tinnitus, or cephalic ringing, and that prophylactic agents against migraine such as anti-epileptics are effective for treating this condition. An appropriate triptan use during the past migraine attacks was expected to reduce risk of onset of CHS.

SL-77

Track: *Proteomics & Bioinformatics*

FLUOROQUINOLONES: THE ANTI HCV DRUGS OF THE FUTURE?

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HCV is responsible for about 200 million infections worldwide. The current therapy against HCV has adverse effects, and is too costly for patients in developing countries. Hence, there is a need to develop new therapeutic agents against HCV. Recent studies have identified NS3 as a potential inhibitory target for fluoroquinolone drugs. In the present study, we assessed the efficacy of two-fluoroquinolone combinations against NS3 in *in vitro* helicase assay. Computational analysis was also performed on fluoroquinolone-NS3 complexes to explore the functional groups of fluoroquinolones and NS3 amino acids involved in their mutual interactions. For the combinatorial assay, the reaction was prepared by mixing the double-stranded substrate withNS3 helicase, buffer, ATP, SYBR Green I and two fluoroquinolones in different concentrations. The *FlexX* docking software was used to dock the drugs onto the NS3 protein, and the interactions between the drug and helicase were analyzed. *In vitro* experiments showed that the combinations of Balofloxacin with Enrofloxacin; Balofloxacin with Sparfloxacin; andBalofloxacin with Lomefloxacin exhibited greater inhibition of helicase activity than the individual drugs. Docking analysis established that each of these drugs interacted strongly with different amino acids in the active site of NS3. These docking results were independently confirmed by two different software tools. This study shows that the combinations of fluoroquinolone drugs may have enhanced inhibitory action on NS3 than the individual dugs. This study will provide the basis for designing new fluoroquinolones derivatives that have the combined properties of pre-existing drugs, and hence a higher potency against HCV.

SL-135

Track: *CNS Drug Discovery & Therapy*

ANTIGEN-SPECIFIC THERAPY OF MULTIPLE SCLEROSIS *VIA* MYELIN IMMUNODOMINANT EPITOPE

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The presence of anti-myelin antibodies in patients with early multiple sclerosis (MS) and in MS animal models led to renewed interest in a role for B cells, plasma cells and their products in the pathogenesis of the disease. Here we propose a novel strategy based on engineered filamentous phage in which its major coat protein was fused to the immunodominant epitope derived from the myelin oligodendrocyte glycoprotein (MOG 37-44). Filamentous phages are well-studied, both structurally and genetically. Their shape as a long fiber, 1000nm long and 6nm wide, enables penetration to the central nervous system via nasal administration. Experimental autoimmune encephalomyelitis (EAE) diseased mice (as a model of MS) intranasally treated with phage-MOG showed: improved clinical scores; reduction of antibodies against MOG; reduced proinflammatory cytokines, in particular monocyte chemoattractant protein 1 (MCP-1) interferon γ (IFN-γ) and IL-6; and prevented demyelinization, compared to untreated animals. Brain delivery of MOG *via* filamentous phages suggests that the improved clinical effects obtained in EAE mice may be due to depletion of MOG autoantibodies *in situ* and/or stimulation of immune mechanisms towards induced tolerance in the periphery, indicating that the humoral immune system in MS would be a reasonable therapeutic option.

SL-106

Track: *Anti-Cancer Discovery & Therapy*

NOVEL IN SILICO-DESIGNED SPINDLE DISRUPTORS EXHIBIT ANTI-CANCER PROPERTIES *IN VITRO* AND *IN VIVO*

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In the design of anti-cancer therapeutics, it is not merely a matter of demonstrating that the proposed compounds kill cells. Required is information on the mode, mechanism and signalling pathways of the cell death(s) induced, the molecule's anti-proliferative effects, reduction in malignant cell migratory capacity, inhibition of neoplastic cell invasion and anti-angiogenic effects. 2-Ethyl-3-O-sulphamoyl-estra-1,3,5(10)15-tetraene-3-ol-17one (ESE-15-one) and 2-ethyl-3-O-sulphamoyl-estra-1,3,5(10)16-tetraene (ESE-16) are novel, sulphamoylated 2-methoxyestradiol analogues designed and synthesized by our research team with the aim of improving the potency and pharmacokinetic constraints of the parent compound's anti-cancer properties [1]. After synthesis of the compounds they were assessed for effectively on five cells lines, including a multidrug resistant PgP overexpressing line. Microscopic and flow cytometric techniques demonstrated that the compounds induce apoptosis and autophagy in exposed cells [2]. The hypothesis that ESE-15-one and ESE-16 disrupt microtubule dynamics thereby causing metaphase block was confirmed by flow cytometric quantification of cyclin B1 and various fluorescent microscopic evaluations, the latter to gain insight into the temporal and mechanical mechanisms of the microtubule disruption and the cellular reaction. Signalling pathways were elucidated using Western blotting. Synergistic/antagonistic interactions with clinically approved chemotherapeutic agents were performed. Analysis of ESE-15-one and ESE-16 effects on motility, migration and invasion was conducted using wound healing and MADRIGELTM transwell assays. Chorioallantoic membrane assay with engrafted MDA-MB-231 breast cancer cells was used to determine the compounds' *in vivo* anti-tumoural, anti-angiogenic and anti-metastatic properties. Mice xenograft studies are envisaged as the next step to continue the evaluation of novel compounds on the effect on tumour progression and metastatic dissemination.

Keywords: Microtubules, apoptosis, autophagy, 2-methoxyestradiol analogues, anti-cancer, anti-angiogenic, mitotic block.

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SL-18

Track: *Hot Topics in Natural Products*

PROTECTIVE EFFECT OF ACAI BERRY EXTRACT ON GLYCEROL INDUCED ACUTE RENAL FAILURE IN RATS

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Mimusops caffra provided sufficient Ursolic acid (UA) (1) which was used as a template for the semi-Acute renal failure (ARF) is one of the most common problems encountered in hospitalized critically ill patients. In recent years great effort has been focused on the introduction of herbal medicine as a novel therapeutic agent for prevention of ARF. Hence, the current study was designed to investigate the effect of Acai Berry Extract (ABE) on glycerol induced ARF in rats. Results of the present study showed that rat groups that received oral ABE in a dose of 100mg/kg/day and 200mg/kg/day for 7days before induction of ARF by a single i.m. glycerol injection reported a significant improvement in kidney functions tests (decrease in serum urea, serum creatinine, and blood urea nitrogen) when compared to the ARF model group. Moreover, there was significant amelioration in renal oxidative stress markers (renal catalase, renal reduced glutathione) and renal histopathological changes in the ABE treated groups when compared to ARF model group. The most significant improvement was reported in the group where ABE was

administered in a dose 200/mg/kg/day for 7 days before induction of ARF. These results indicate that ABE has a potential role in ameliorating renal damage involved in ARF.

SL-42

Track: *Anti-Infectives*

ANFOLEISH (3% AMPHOTERICIN B CREAM), A NEW TOPICAL TREATMENT IN DEVELOPMENT FOR CUTANEOUS LEISHMANIASIS: REPORT OF CASES

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Looking for new therapies for cutaneous leishmaniasis (CL), the PECET, University of Antioquia has established a Public Private Partnership leading to the discovery, preclinical studies (*in vitro* and using the hamster as animal model) and clinical trials. In collaboration with Humax pharmaceutical (Medellin-Colombia) PECET have developed Anfoleish a cream with 3% amphotericin B. In preclinical evaluations this formulation showed to be safe and effective therefore, it was selected by DNDi as a leader product to determine safety and efficacy in randomized clinical trials. In a non-randomized, open label clinical observation this formulation was used in 19 patients from 3 to 69 years old. All had parasitological diagnosis of CL. Three patients presented co morbidities in which standard treatment with antimonials was not indicated: preeclampsia, hypertension and cardiomyopathy. The number of lesions ranged between 1 and 9. Patients received the cream 3 times per day during 20 or 28 days and were followed-up for 6-24 months. Cure was observed in all lesions, except for one located in the right ear. Complete cure was observed between the end of treatment and 6 weeks after. No relapses or severe adverse events were found. The studies encourage the development of clinical trials.

SL-132

Track: *Cardiovascular Drug Discovery*

HEME CATABOLIC PATHWAY AS A POTENTIAL THERAPEUTIC TARGET FOR CARDIOVASCULAR DISEASES

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Serum bilirubin has been consistently demonstrated to be negatively related to cardiovascular diseases (CVD) with similar prognostic value as HDL cholesterol. Each micromolar decrease of serum bilirubin is associated with marked increase in CVD risk. Additionally, recent studies also proved serum bilirubin to be associated with CVD-related diseases and risk factors, such as arterial hypertension, diabetes, metabolic syndrome, and body mass index.

Bilirubin is the major product of heme catabolism in the intravascular compartment originating predominantly from hemoglobin of senescent erythrocytes. Its production is dependent on several key metabolic steps. The first one is the heme breakdown catalyzed by heme oxygenase (HMOX), HMOX1 isoform being the most inducible enzyme in the human body. The other clinically important step is the conjugation of bilirubin with glucuronic acid in the liver by bilirubin UDP-glucuronosyl transferase (UGT1A1). UGT1A1 is partially deficient in subjects with Gilbert syndrome known to have substantially lower prevalence and incidence of CVD.

Based on this data, pharmacologic, non-pharmacologic, and genetic interventions have been attempted to increase serum bilirubin levels to protect from CVD development. These attempts have included drugs or nutraceuticals to induce HMOX1 and/or partially inhibit UGT1A1, or use the molecules resembling in their structure that of bilirubin including plant and algal tetrapyrollic compounds, such as phycocyanobilin or even chlorophyll. It is worthy to note, that pulverized bovine gallstones containing substantial amounts of bilirubin have been used for centuries in China to treat a large number of diseases including CVD.

SL-101

Track: *Traditional Chinese Medicine*

CHARACTERISTICS OF TRADITIONAL CHINESE MEDICINE (TCM) IN THE PREVENTION AND TREATING OF HIV/AIDS INFECTION

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This paper mainly discusses the characteristics and advantages of Traditional Chinese Medicine (TCM) in preventing and treating HIV/AIDS. The latest research developments and literatures study about TCM treating HIV/AIDS infection were collected to be summarized in this lecture. The main features of TCM for HIV/AIDS prevention and treatment includes three phases. The first phase is that Chinese medicine early interferes with virus replication when the patients suffered from HIV/AIDS with no significant symptoms, which is known as asymptomatic period called "preventive treatment of disease" in TCM term. The second phase is that TCM can cope with varied clinical features in HIV/AIDS period to alleviate the systemic symptom, reduce opportunistic infections and improve patients' life qualities. The third phase is that TCM can combine the complex clinical signs and symptoms in the complications period, and also can regulate holism that reflects the "holism" theory of TCM. Prevention and treatment of HIV/AIDS by TCM plays an irreplaceable role right now in China and has a great development potential in the future.

SL-73

Track: *Hot Topics in Medicinal Chemistry*

NOVEL PLATINUM COMPOSITES WITH THERANOSTIC POTENTIAL FOR CANCER TREATMENT

Xiaoyong Wang

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Platinum anticancer drugs such as cisplatin are vital for the chemotherapy of various cancers. However, indiscriminate body distribution or poor cellular uptake of these drugs has resulted in some severe side effects and drug resistance. Therefore, to improve the tumor selectivity or cellular accumulation of the drugs has become a major task in the development of platinum anticancer agents. On the other hand, the distribution and accumulation of platinum drugs *in vivo* are largely unknown. Lack of such information would badly hinder the rational design of new platinum drugs and retard the revelation about the tumor resistance mechanism. Theranostic agents are newly emerging multifunctional compounds capable of simultaneous diagnosis and therapy for diseases. These agents allow a large degree of real-time control over the therapeutic efficacy during the clinical treatment. Magnetic nanoparticles (MNPs) have attracted much attention as targeted drug carriers because they could guide drugs to the biological target through external magnetic field and hence reduce the damage to normal tissues. The intrinsic properties of MNPs also endow them with diagnostic ability as magnetic resonance imaging (MRI) contrast agents. Recently, we developed a series of theranostic platinum agents through combining platinum pharmacophore with MNPs. In these nanocomposites, surface-modified superparamagnetic magnetite or maghemite nanoparticles perform the diagnostic and/or targeted transporting functions, while platinum moieties play the therapeutic role. In addition, gadolinium contrast agents were also chosen to accomplish a similar purpose. Our attempts have produced some interesting results. For example, rhodamine-embedded maghemite nanoparticles can convey and trace platinum anticancer drugs *in vitro* and *in vivo*; they are highly cytotoxic against cisplatin-resistant cells, thus show a potential for overcoming the resistance to cisplatin. On the whole, these multifunctional composites have successfully fulfilled the basic mission of a "theranostic agent" and may provide an alternative approach to the "see and treat" ideal for cancer treatment in the future.

SL-25

Track: *Anti-Cancer Drug Discovery & Therapy*

USING RADIATION AS SYSTEMIC THERAPY

James W. Welsh

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With the recent success of checkpoint inhibitors and other immune-stimulating agents, there has been renewed interest in the combination of such agents with radiation. The biological premise behind such a strategy is that the tumor antigen release achieved by localized radiation will promote specific adaptive immune system targeting, which can be augmented further by systemic immune-stimulating agents. In this manner, clinicians hope to induce a phenomenon known as the abscopal effect, where localized radiation results in immune-mediated tumor regression in disease sites well outside of the radiation field. We present a critical review of the early clinical and pre-clinical evidence behind this approach, with special attention to the treatment of non-small cell lung cancer.

SL-63

Track: *Traditional Chinese Medicine*

STUDIES ON PREPARATION AND EVALUATION OF ALUM-BORNEOL NANOEMULSION

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It had been established a new mathematical model and determination method of network pharmacodynamics for Chinese Materia Medica Formula (CMMF). By network pharmacokinetic principle, combining with the Laplace transform, as well as linear algebra, the general solution for equation of network pharmacodynamics were obtained and their parameters were analyzed. The CMMF network pharmacodynamic model was a polynomial with e power. The equilibrium constants of each nodals in network were obtained by solving linear equation established with AUC (equilibrium concentration) and initiate quantum (intravenous drip velocity) for their. The equilibrium constants calculated in oral administration was similar with in injection, only supernumerary of the absorption equilibrium constants. That suggested the network pharmacodynamics for dose-ratios, dose-chrono and dose-effect of the CMMF was carried out; There is network biologic principle of conservation that the initiate value (intravenous drip velocity) for each nodals in network is equal to the summation of producet quilibrium constant versus AUC (quilibrium concentration).

SL-89

Track: *Traditional Chinese Medicine*

A NOVEL STRATEGY FOR SCREENING BIOACTIVE EQUIVALENT COMBINATORIAL COMPONENTS FROM CARDIOTONIC PILL

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Cardiotonic Pill (CP) is a widely used Chinese herbal formulation for cardiac diseases prepared from Radix Salviae Miltiorrhizae and Radix Notoginseng. Clinical observations and pharmacological effects on CP have been well investigated. The exact composition of effective components, however, is often elusive due to the complexity of the chemical constituents and the lack of adequate screening methodology. In this work, we developed a bioactive equivalence oriented stepwise screening strategy consisting of (1) chemical profiling of CP by high perfermance liquid chromatography (HPLC) combined with quadrupole time-of-flight mass spectrometry (QTOF MS); (2) determining candidate bioactive equivalent combinatorial components (BECCs) from CP; (3) preparing candidate BECCs by real-

time components trapping and combining system, and (4) assessment of bioactive equivalence between candidate BECCs and original CP. Using this strategy, we have identified a combination BECCs of 18 compounds as BECCs, which could represent the therapeutic efficacy of original CP against myocardial infarction (MI). This work provides a universal approach for discovering BECCs from herbal medicines and answers "which are real bioactive components for the Chinese herbal medicines that have been used in clinic for long years".

SL-45

Track: *Regenerative Medicine*

SYNTHESIS, CHARACTERIZATION AND CYTOCOMPATIBILITY OF POLY (DIOL-CO-TRICARBALLYLATE) BIODEGRADABLE MATRICES FOR USE IN TISSUE ENGINEERING AND OTHER BIOMEDICAL APPLICATIONS

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Purpose: To investigate the synthesis and *in vitro* characterization of a novel family of thermoset biodegradable poly (diol-co-tricarballylate) (PDT) elastomeric polymers for the purpose of their use in implantable drug delivery and tissue engineering applications.

Methods: PDT prepolymers were first synthesized via polycondensation reaction of tricarballylic acid with alkylene diols of varying chain lengths at 140 ^{o}C for two hours under vacuum. After purification, the formed prepolymers were further crosslinked under vacuum at 120 ^{o}C for 18 hours to form PDT elastomers. The prepared prepolymers were characterized using Proton Nuclear Magnetic Resonance (^{1}H-NMR), Fourier Transform Infrared analysis (FT-IR) and Differential Scanning Calorimetry (DSC). PDT elastomeric films were subjected to cytocompatibility studies to assess the potential of elastomer films to support the adhesion and growth of human mesenchymal stem cells (MSCs). Cell Viability Assay was used to assess cell viability & proliferation.

Results: ^{1}H-NMR and FT- IR analysis confirmed the chemical structure and the purity of the PDT prepolymers. The obtained elastomers were stretchable and rubbery and swell rather than dissolve in most of organic solvents. Mechanical properties were found to be dependent on the number of methylene groups in the chain of precursor diol and the crosslinking density of the elastomeric matrices. Adhesion studies showed that MSCs extensively attached to films sterilized with ethanol and coated with fibronectin. Cells were healthy and expanded by day 7 as indicated by cell viability assay as indication of the cytocompatibility of these ne elastomers.

Conclusions: Biodegradable, polyester elastomeric matrices were successfully prepared and characterized. The family of thermally crosslinked PDT biodegradable polyesters has promising use in drug delivery and other biomedical applications including tissue engineering.

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SL-70

Track: *Pharmaceutical Research & Development*

SYNERGISTIC EFFECT OF VALPROIC ACID CO-ADMINISTRATION WITH CURCUMIN IN HEPATIC REGENERATION OF CCL_4-INDUCED FIBROSIS

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Background: Liver regeneration is a complex process regulated by group of genetic and epigenetic factors. Histone deacetylases (HDACs) are exciting compounds with altering gene expression properties that induce

chromatin remodeling, cell survival, proliferation, differentiation and apoptosis by deacetylating histones as well as many non-histone proteins. Safety evaluation studies indicated that curcumin (cur) is well tolerated at very high dose without producing any toxic effect. Recent studies have highlighted the anti-fibrotic properties of valproic acid (VPA) in nephropathy and liver fibrosis models. This study investigated whether treatment with valproic acid co-administration with curcumin would prevent and/or reverse hepatic fibrosis.

Methods: We explored the anti-fibrotic effects of curcumin at a dose of 450mg/kg in combination with 200mg/kg valproic acid on liver regeneration using histological analysis and alterations in pro- versus antifibrotic genes expression represented by CTGF, MMP-2 by qRT-PCR and NF-κB complex dissociation level by western blotting. It also addresses the possible involvement of the multifunctional protein APE1 and Sirt-2 expressions in this mechanism.

Results: Our results indicate that using curcumin-valproic acid combination inhibited NF-κB p105 complex dissociation when added either for protection or treatment. Curcumin administration with valproic acid for 4 weeks revered hepatic fibrosis by 50% and induced hepatic regeneration, with marked induction of APE1 (1.6 fold) and p53 expressions. Moreover, this treatment combination exerted hepato-protective effect against CCl_4 by modulating levels of pro- versus anti-fibrogenic markers represented by 0.2 fold reduction in CTGF level and inducing 3 folds increase in MMP-2 expression, reducing oxidative stress by increasing total antioxidant capacity and GSH levels as well as maintaining high level of APE1 expression compared to fibrosis-induced group. In addition to, total acetylated proteins were increased significantly (120 fold) in the rats treated with VPA and cur compared to cur-alone treated rats (60 fold). Results indicated also significant elevation of Sirt-2 expression during fibrogenesis that is inhibited by cur and/or VPA treatment.

Conclusions: The HDAC inhibitor, VPA in combination with Cur, attenuated the hepatic fibrosis and improved hepatic structure and function, possibly by suppressing inflammation. Control of hepatic histone or non-histone protein acetylation is a potential therapeutic approach for preventing hepatic remodeling.

Keywords: Valproic acid (VPA), Curcumin (Cur), Apurinic/Apyrimidinic endonuclease1 (APE1).

POSTERS

PO-31

Track: *Regenerative Medicine*

PREPARATION AND CHARACTERIZATION OF 3D ELECTROSPUN BIODEGRADABLE NANOFIBERS FOR WOUND DRESSING AND OTHER TISSUE ENGINEERING APPLICATIONS

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Background: The use of electrospinning technology (ET) in fabrication of three-dimensional biodegradable electrospun nanofibers scaffolds (BENS) has recently gained considerable attention in tissue engineering. BENS are superior to other existing scaffolds in tissue regeneration as they provide high surface area-to-volume ratio, possess high porosity, and offer a biomimetic environment in a nanometer scale.

Objectives: To fabricate & characterize BENS using polyethylene glycol 35000 (PEG35000) as a biodegradable polymer loaded with Amoxicillin Trihydrate (AT) for use as a wound dressing.

Method: Solutions of PEG35000 in chloroform of varying concentrations were used to fabricate BENS using ET. Blank & 10% w/v AT loaded BENS was fabricated & further characterized. Morphology, size and diameter of BENS were assessed using Scanning electron microscopy (SEM). Fourier Transform Infrared (FTIR) Spectroscopy was used to identify the interaction between PEG35000 and AT. Differential Scanning Calorimetry (DSC) was used to access the crystallinity and thermal behavior of the prepared BENS.

Results: Blank & AT loaded 35% w/v PEG3500 solutions produced the most homogenous and intact nanofibers. Major bands of AT in FTIR were clearly observed in the spectrum of AT with PEG3500 post electrospinning. Moreover, DSC thermograms indicated that AT existed in it amorphous dissolved state within PEG supported by the disappearance of its melting peak at 133 °C and confirmed by absence of AT crystals under SEM.

Conclusion: BENS using PEG35000 loaded with AT were successfully fabricated and characterized. Our findings show that this dressing has features that make it a promising product for wound healing applications.

PO-108

ROLE OF BIOTECHNOLOGY IN DIAGNOSIS OF BRUCELLOSIS

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Brucellosis is a true zoonotic disease caused by either one of the 4 types of Brucella namely *B. abortus*, *B. melitensis*, *B. Sui* and *B. canis*; transmittable to humans that shows a high degree of morbidity, both for animals and humans. This disease is not only of veterinary importance but also have a major impact on the health and economic prosperity of the developing world. An appropriate diagnosis is the key for eradication and control of this disease.

Recent advances in our understanding of brucellosis and new development provide new opportunities for biotechnical companies in developing countries to make an essential contribution to the control of this disease.

PO-104

Track: *Pharmaceutical Research & Development*

SELF-NANOEMULSIFYING DRUG-DELIVERY SYSTEM FOR IMPROVED ORAL BIOAVAILABILITY OF ROSUVASTATIN USING NATURAL OIL HAS ANTIHYPERLIPDEMIC EFFECT

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Rosuvastatin Calcium (Rs) is the most effective statin drug has antihyperlipidemic effect. It has relatively low absolute oral bioavailability attributed to its low solubility.

Aim: The aim of the present study is to improve the bioavailability of Rs through improving its solubility using self nanoemulsifying drug delivery system (SNEDDS) containing natural oil full of unsaturated fatty acid and omega 3.

Methods: A 7*32 full factorial design was adopted for the optimization of oil ratio, Surfactant: Cosurfactant (S: CoS) ratio and oil: S/CoS ratio. Ternary phase diagrams were constructed for optimizing the system with different drug loading. The optimized SNEDD systems were evaluated according to their droplet size, zeta potential (ZP), physical robustness to dilution in different media and ratio, cloud-point measurement and transmission electron microscopy evaluation. Percent drug dissolved at first 10 min was determined. Furthermore, anti-hyperlipidemic efficacy of SNEDDS was compared with commercially marketed product and the pure drug suspension.

The results: The system containing (Tween 80 : PEG 400) 3:1 and olive oil : garlic oil (1:1) as an oily phase has droplet size less than 100 nm, ZP (+ 13.43± 2.58 mV), PDI (< 0.02), and cloud point (>90°C). *In vitro* drug release studies showed remarkable enhancement of the Rs release from Rs-SNEDDS compared to a drug suspension (>80% within 10 minutes). The antihyperlipidemic effect of Rs-SNEDDS is greater than that of the commercial tablets and pure drug.

Conclusion: Rs-SNEDDS is a promising drug delivery system for improving the drug solubility, bioavailability and antihyperlipidemic effect using natural oil like (olive oil and garlic oil).

Keywords: Rosuvastatin calcium, Self nanoemulsifing drug delivery system, natural oil, antihyperlipidemia.

PO-5

Track: *Anti-Cancer Drug Discovery & Therapy*

SYNTHESIS OF NOVEL PYRAZOLONE NUCLEOSIDES AS ANTIMICROBIAL AGENTS

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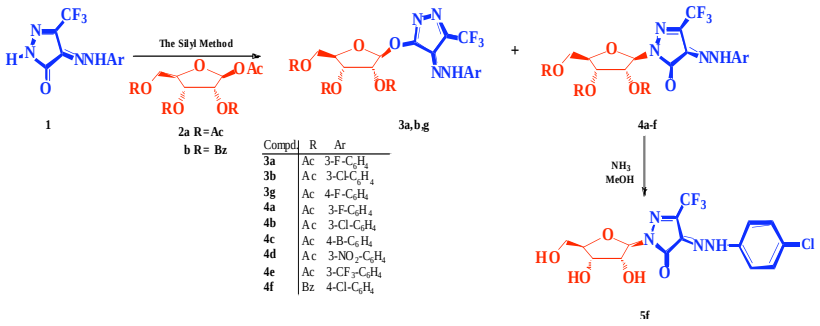
Nucleosides and their analogues are known to be one of the most important classes of compounds due to their intersting properities and wide applications in pharmacological and medicinal fields. A new series of pyrazolone nucleosides **3-5** was designed and synthesized as potential biologically active agents. The silyl method was used to produce two isomeric products **3**, **4**. Isomer **3** was charachterized as *O*-nucleoside while isomer **4** was found to be *N*-nucleoside. Both of the two isolated stereoisomers were found to be as *β*-configration.

Ammonolysis of selected isomeric product **4f** furnished the free nucleoside **5f** in a quantitative yield. Compounds **3$_a$**, **4$_{a, d, f}$** were evaluated for their antibacterial activity. The newly synthsized nucleosides showed higher *in-vitro* growth inhibition compared to the known antibiotic Ceftriatone CEF.



Compd	R	Ar
3a	Ac	3-F-C_6H_4
3b	Ac	3-Cl-C_6H_4
3g	Ac	4-F-C_6H_4
4a	Ac	3-F-C_6H_4
4b	Ac	3-Cl-C_6H_4
4c	Ac	4-B-C_6H_4
4d	Ac	3-NO_2-C_6H_4
4e	Ac	3-CF_3-C_6H_4
4f	Bz	4-Cl-C_6H_4

Scheme 1. Synthetic scheme of compounds **3-5**.

PO-57

Track: *CNS Treatment*

LEUKAPHARESIS-DERIVED MSCs CAN BE INDUCED INTO DOPAMINERGIC NEURONS, USING 2 STEPS LIQUID CULTURE WITH ASCORBIC ACID

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Introduction: Parkinson disease (PD) is the most common neurodegenerative movement disorder, and is accused as the most common cause of chronic progressive parkinsonism; it is also called (primary parkinsonism) or (idiopathic parkinsonism). Many interrelated hypothesis have been postulated about the death of dopaminergic neurons. Dopamine replacement with levodopa is standard and initial therapy for PD associated with great improvement in motor function, , however, long term use of levodopa causes excessive spasmodic movement. Cell replacement showed limited ability for differentiation to DA neurons.

Embryonic stem cells (ESCs) and autologous embryonic stem cells (generated through therapeutic cloning) have been proposed as promising candidates for future. Adult Mesenchymal stem cells (MSCs) are another important source of cell preparation for compensatory therapy. However, the use of BM as a source for MSCs is limited because of the invasive collection procedure as well as the decrease in cell number, proliferation, and differentiation capacity in vitro with the age of the culture and alternatively, the autologous peripheral blood can be an important source of MSCs for cell based therapy, since they have been proven to be mobilized along with hemopoeitic stem cells in standard mobilization regimens.

Objective: The aim of this study was to explore the *in-vitro* ability of leukapharesis-derived human adult mesenchymal stem cells to differentiate into dopaminergic neurons using ascorbic acid (AA).

Subjects and Method: Peripheral blood mononuclear (MNCs) were obtained from 10 leukapharesis-derived samples from donors undergoing stem cell mobilization by apharesis, MSCs separated, and culture in humid CO_2 incubator. Differentiation of MSCs into dopaminergic neurons was done using combined ascorbic Acid (AA) and nerve growth factor in polyornithine coated tissue culture plates. Evaluation of transdifferentiation was done using morphological, immunophenotypic and immunohistochemical patterns. Immunohistochemical staining was done using neurofilament (NF) and antityrosine hydroxylase (TH) antibodies.

Results: MSCs were verified by: morphology, culture characters, immunophenotyping, and trilineage differentiation capacity to adipocytes, osteoblasts, chondrocytes. Cytospin preparations from culture specimen's immunostained with antineurofilament (NF) and antityrosine hydroxylase (TH) antibodies showed scattered immunopositive cells (brown Deposit). The percentage of cells stained for NF was 15.38 ± 3.84, the percentage of cells stained for TH was 5.94 ± 0.65.

Conclusion: Leukapharesis-derived MSCs can be isolated, expanded and transdifferentiated to dopamine-producing nerve cells.

Keywords: Mesenchymal stem cells, Stem cell mobilization, Ascorbic Acid, Nerve growth factor, DA neurons.

PO-33

Track: *Anti-Infectives*

GENOTYPING OF BACTERIA ISOLATED FROM POULTRY FARMS IN GHANA USING ERIC-2 PCR

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Enterobacterial repetitive intergenic concensus sequence polymerase chain reaction (ERIC-PCR) arose out of a number of studies which show that bacteria belonging to the enterobacteriaceae family have highly conserved non-coding regions. These regions, usually 126 base pairs in length, are often repetitive. A number of primers have been designed

for these non-coding regions and when a PCR is performed, a unique pattern is obtained depending on the orientation, location and frequency of these regions in any bacteria [1]. Identical bacteria species produce identical band patterns when subjected to the same reaction conditions. Transmission of genetic material from one organism to another and transfer of bacteria from animals to farm hands, especially in the area of antibiotic resistance, has received considerable interest [2].

Aim: To determine the genotypic patterns of *Escherichia coli* and *Staphylococcus aureus* isolated from poultry litter and farm hands in the Ashanti region of Ghana.

Method: ERIC-PCR was performed on a total of 179 *E. coli* and 189 *S. aureus* isolates. Stored suspensions of the isolates were streaked on LB agar and incubated at 37^{o}C for 18-24 h. pure colonies were suspended into 50uL Tris EDTA buffer. DNA was prepared by lysing the cells at 95^{o}C for 10 min on cooling ice. The suspension was then centrifuged at 8000 rpm for 1 min. Two microliters of the supernatant was used as the DNA template for the PCR amplification. PCR amplification made at 94^{o}C for 1 min, denatured at 94^{o}C for 30 s, annealed at 50^{o}C for 1 min, elongated at 65^{o}C for 8 min and after 35 cycles, a final extension at 65^{o}C for 10 min. The amplified PCR products were run on a 2% agarose gel containing gel red stain and normalized with 1 kb plus ladder. Gels were run at 75V for 4 h.

Results: Isolates with 80-100% identical band patterns or sharing more than 4 identical bands were considered identical. Two percent of *E. coli* isolates from the same farm had identical band patterns between poultry and farm hand whiles *S. aureus* was 7%. Both human-liter and litter-litter identical patterns from different farms were higher among *E. coli* isolates (28 and 21%) than were among *S. aureus* isolates (14 and 11%, respectively). Humans from different farms shared identical band patterns among *S. aureus* isolates (11%) than among *E. coli* (6%). With non-matching band patterns, over half of the *S. aureus* isolates (59%) had their own unique patterns whiles 43% of the *E. coli* isolates had non-matching patterns.

Conclusion: The above findings indicate that there is possibility of sharing of bacterial genetic materials from isolates of *E. coli* and *S. aureus* between poultry birds and farm hands.

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PO-34

Track: *Anti-Infectives*

ANTIMICROBIAL AND WOUND HEALING PROPERTIES OF MYRIANTHUS ARBOREUS AND ALCHORNEA CORDIFOLIA

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Introduction: *Myrianthus arboreus* P. Beauv. (Cecropiaceae) and *Alchornea cordifolia* Schumach & Thonn. (Euphorbiaceae) are tropical plants used for the treatment of ailments such as diarrhoea, malaria, boils, dysentery, wounds and skin infections [1, 2]. There are no scientific reports to support the above medicinal uses of these plants.

Aims: To investigate the antimicrobial, antioxidant and wound healing properties of methanol leaf extract of *M. arboreus* (MLMA), aqueous (ALAC) and ethanol leaf extracts (ELAC) of *A. cordifolia*.

Methods: The antimicrobial activity of the extracts was examined using the agar diffusion and micro-dilution methods [3] against *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 4853, *Staphylococcus aurous* ATCC 25923, *Bacillus subtilis* NTCC 10073 and clinical strains of *Streptoccocus pyogenes* and *Candida albicans.* Antioxidant property of the extracts was determined by DPPH method [4] and wound healing property of the extracts determined using excision wound model [5].

Results: MLMA showed exhibited activity against *S. aureus, B. subtilis, S. pyogenes, E. coli, P. aeruginosa, C. albicans* with MIC values of 8, 6, 8, 8, 6 and 6mg/mL respectively. ELAC showed a good antimicrobial activity against *S. aureus, B. subtilis, E. coli, P. aeruginosa, C. albicans* with MICs of 3, 4, 6, 4 and 4mg/mL respectively; and ALAC had MICs of 2.5, 3, 10, 4 and 3mg/mL respectively. The IC_{50} of MLMA, ELAC and ALAC were 2.68, 0.79, 0.78µg/mL respectively. The extracts (5% w/w extract aqueous creams) showed potent wound healing capacity with better wound closure ($p<0.05$), and tensile strength ($p<0.01$), improved wound tissue regeneration compared to untreated wounds at

day 9. Phytochemical screening of extracts revealed the presence of tannins, alkaloids, sterols, saponins, glycosides, terpenoids and flavonoids.

Conclusion: The biological activities of the extracts of the two plants may justify their uses in treatment for microbial infections and wounds.

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PO-30

Track: *Drug Delivery Systems*

ENHANCEMENT OF DISSOLUTION PROPERTIES OF TADALAFIL IN ORALLY DISINTEGRATING TABLET FORMULATIONS: PREPARATION AND IN VITRO EVALUATION

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Tadalafil is a phosphodiesterase-5 inhibitor indicated in the treatment of erectile dysfunction. However, it has very low aqueous solubility, leading to its poor dissolution in the gastrointestinal tract, resulting in variable bioavailability and delayed onset of action.

The aim of the present study was to enhance the dissolution behavior of tadalafil via solid dispersion technique, using polyvinylpyrollidone (PVP) as a hydrophilic carrier, to be further compressed intoorally disintegrating tablets which would expectedly increase its bioavailability & hasten its onset of action.

Tadalafil/PVP binary solid dispersions were prepared in different ratios;1:1; SD1,1:2; SD2,1:3; SD3 and 1:4; SD4, respectively using solvent evaporation -co precipitation technique.Tertiary solid dispersion of tadalafil/PVP/Avicel® (1:2:2, respectively; SD5) was also prepared.

Orally disintegrating tablets (ODTs) were prepared by direct compression of a homogenous mixture of SD5 (25 mg) & different concentrations of mannitol, croscarmellose & avicel® forming five different ODT formulations.

The prepared solid dispersions, in different ratios, were evaluated for dissolution properties in 0.1 N HCl containing 0.2% sodium lauryl sulphate (SLS) compared to those of pure tadalafil. The % yield of the prepared solid dispersions was also determined.

Fourier transform infrared spectroscopy (FTIR), X-ray powder diffractometry (XRPD), scanning electron microscopy (SEM) & differential scanning calorimetry (DSC) were used to characterize the solid state properties of the selected binary solid dispersion system.

SD2 exhibited the highest improvement in dissolution rate of tadalafil; Q10 =71% ±1.3, corresponding to 34% ±1.8 in case of pure drug. XRPD & DSC showed the loss of the crystalline properties of tadalafil, in the prepared SD2, that has been verified through the SE micrographs. FTIR spectrum showed hydrogen bonding between N-H group of the drug and C=O group of PVP.

Percentage yield of the binary SDs decreased by the increase of PVP concentration may be due to the high water absorbing ability of PVP thus decreasing the flow properties. So to improve % yield of the selected SD2 (70.14%), it was mixed with avicel®(SD5) which offers good flow properties. SD5 showed a % yield value of 94.22%. There was no significant difference in % tadalfil released in case of SD2&SD5 (student t-test, $p>0.05$). Therefore, SD5 was used for preparation of different ODT formulations (DC1-DC5).

The prepared tablets were characterized with respect to their drug content uniformity, weight variation, tablet breaking strength, % friability, wetting behavior & oral disintegration time. Dissolution behavior was tested for the selected ODT formulation.

The selected tadalafil ODT (DC3), containing 37% mannitol, 16% avicel® and 16% crosscarmellose, showed superior wetting time; 36 secs along with an excellent oral disintegration time; 20 secs with an accepted value of hardness; 3.6

Kg &% friability; 0.7. DC3 exhibited an improvement in the dissolution profile of tadalafil compared to that of pure drug.

In conclusion, ODT containing solid dispersion can be successfully used for enhancement of the dissolution of tadalafil, with a rapid onset of action.

Keywords: Tadalafil, PVP, oral disintegrating tablets, solid dispersions, solvent method, direct compression.

PO-48

Track: *Chemistry*

STABILITY OF ACONITINE IN ALCOHOLIC EXTRACTS

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Aconitine is a highly toxic norditerpenoid alkaloid isolated from different *Aconitum* species. Traditional Chinese Medicine (TCM) uses *Aconitum* in several formulations as an anti-inflammatory, cardio-tonic and in treatment of skin abscesses caused by *Staphylococcus aureus* infection, but only after processing, usually boiling and steaming in order to hydrolyse ester groups i.e. acetate and/or benzoate yielding a less toxic compounds. HPLC and HRMS with electrospray ionisation (ESI) were used to separate and identify some of the aconitine degradation products obtained on treatment with different alcohols. Phenomenex Luna 5µ PFP 15 x 4.5 mm column; mobile phase: 0.1% formic acid: acetonitrile [65:35 v/v], 1 mL/min; sample 20 µL, detection UV λ = 232 nm. Pyraconitine (586 Da), 14-*O*-benzoylaconine (604 Da) and aconitine (646 Da) and 8-*O*-alkylated-14-*O*-benzoylaconine derivatives were characterised. The alkylated derivatives eluted at Rt = 5.3 min in the case of MeOH and d_4-MeOH, and at Rt = 3.8 min in the case of EtOH and d_6-EtOH. Alcoholic solvents displace the C-8 acetyl group. Therefore such solvents should be avoided in any extraction procedure for the analysis of aconitine and other diester diterpenoid alkaloids (DDA).

ACKNOWLEDGEMENTS

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PO-6

Track: *Anti-Cancer Drug Discovery and Therapy*

POTENTIAL CANCER CHEMO-PREVENTIVE PROPERTY OF *MUCUNA PRURIENS* (MP) LEAVES

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Background: Most medicinal plants contain antioxidants: compounds that scavenge Reactive Oxygen Species (ROS). Some natural antioxidants in medicinal plants could be useful as anti- cancer agents because they induce D.N.A damage in the presence of transition metals. *Mucuna pruriens* (MP) leaves, are widely used as medicinal herbs, but have not been tested for potential anti-cancer effects.

AIM: To test for antioxidant effect of MP leaf extract (MPLE) against biological related ROS- superoxide ion ($O_2^{\cdot}$): To test for potential anti-cancer effect of MPLE.

Methods: Superoxide ion scavenging activity (SSA) was assessed in *vitro* using enzymatic and non enzymatic $.O_2$ generating systems. Anti-cancer potential was assessed as influence of copper ions ($Cu2^+$), on toxicity of MPLE in Human (EA.Hy926) endothelial cell lines.

Results and Conclusion: MPLE showed comparable SSA to Tempol (a synthetic superoxide ion dismutase mimetic). Safe concentrations of $Cu2^+$ significantly enhanced toxicity of MPLE in EA.Hy926 cells. Resveratrol a polyphenol and a natural antioxidant, causes D.N.A damage in the presence of $Cu^{2+;}$ and MPLE displayed similar effects. Therefore, our findings suggest, MPLE may contain resveratrol- like compound that may be useful for cancer chemo-preventive therapy.

PO-3

Track: *Anti-Cancer Drug Discovery & Therapy*

STUDIES ON COMBINATION OF PHYTOCHEMICALS IN THE HUMAN OVARIAN TUMOUR MODELS

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Background: Traditional chemotherapeutic agents act by killing cells that divide rapidly, one of the main properties of most cancer cells. And developing drug resistance is the major hurdles in cancer chemotherapy in all cancer types include ovarian cancer. One way of overcoming drug resistance is to employ combination of phytochemicals with different mechanism of action.

Aim of the Study: To use combination of phytochemicals with different mode of action (Paclitaxel and Colchicine are mitotic inhibitor**)** with (Curcumin, Epigallocatechin gallate (EGCG) and Resveratrol are antioxidant**)** using different sequence of administration.

Methods: Three ovarian cancer cell lines, parent (A2780) and resistance lines ($A2780^{CisR}$) and ($A2780^{ZD0473R}$) are treated with phytochemicals, individual and in binary combination using three sequences of administration. Individual treatment is done to determine the IC_{50} values (drug concentration required for 50% cell kill) of each compound. Cell viability is quantified using the MTT reduction assay. The analysis of combination results is based on the equation derived by Chou and Talalay (1984), the actual calculations are done using Calcusyn software.

Results: All of the selected phytochemicals are found to inhibit growth of both parent and resistant ovarian cell lines. And combination of phytochemicals showed sequence-dependent synergism.

Conclusion: Appropriate sequenced combination of phytochemical may provide a means of overcoming drug resistance.

PO-45

Track: *Chemistry*

MICROWAVE-ASSISTED SYNTHESIS OF CHALCONES, FLAVANONES AND 2-PYRAZOLINES: THEORETICAL AND EXPERIMENTAL STUDY

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Condensation of 2-acetyl-1-naphthol and 1-acetyl-2-naphthol with benzaldehydes under microwave irradiation gave chalcones or flavanones depending on the type of ketone. Also, 2-pyrazolines were synthesized by the condensation of chalcones with phenyl hydrazine under microwave irradiation in presence of dry acetic acid as a cyclizing agent. The results obtained indicated that, unlike classical heating, microwave irradiation resulted in higher yields, shorter reaction times and cleaner reactions. Chalcones, either natural or synthetic, are known to exhibit various biological activities [1] such as antioxidant [2], anti-inflammatory. Also, they are of high interest due to their usage as starting materials in synthesis of a series of heterocyclic compounds. 2-hydroxychalcones are considered as precursors in the synthesis and biosynthesis of several flavonoids, such as flavanones,The members of the flavanoid family are attracting increased attention due to their anticancer, antinflammatory, antimalarial and anti-AIDS [3] pharmacological activities.

Keywords: 2-Acetyl-1-naphthol, 1-Acetyl-2-naphthol, Chalcones, Flavanones, 2-Pyrazolines.

PO-105

Track: *Pharmaceutical Research & Development*

EFFECT OF LITHIUM SALTS ON SELECTED PARAMETERS TO STUDY ITS ANTOPSYCHOTIC ACTIVITY IN ALBINO MICE

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An experimental study was undertaken to study the possible antipsychotic action of the three lithium salts in albino mice using Skinner box; the mice are trained to avoid electric shock in response to auditory cue alone.The selected doses were lithium carbonate 250 mg/Kg, lithium chloride 500 mg/Kg, and lithium sulphate 500 mg/K (doses which did not produce any lethality and without obvious toxicity). The results showed that chlorpromazine hydrochloride in the small dose (1.5 mg/Kg) blocked the conditioned avoidance response in 38% of the mice but without statistical significance ($P>0.05$), while the higher dose (3 mg/Kg) produced block of the response in 88% of mice with a highly statistically significant effect ($P\leq0.0001$). Lithium (carbonate, chloride and sulphate) alone did not inhibit conditioned avoidance response significantly. The combination of lithium salts with the lower dose of chlorpromazine hydrochloride produced a highly statistically significant ($P\leq0.0001$) potentiation, in case of lithium carbonate combination (88%), and lithium chloride combination (63%) of the mice. However, the chlorpromazine combination with lithium sulphate did not produce any statistically significant effect in this response ($P>0.05$).

Keywords: Antipsychotic, lithium salts, Skinner box.

PO-132

CRYPTOSPORIDIUM INFECTION IN HOUSE HOLD DOGS

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Cryptosporidum, an enteric coceidian, is a common enteropathogen in birds and mammals including human particulary in immunocompromised individual. In this study rectal swabs from 191 dogs (101 household & 90 stray dogs) were collected from three aged groups (O-6 mounths, 6 mounths to 4 years and over 4 years). They selected from clinically normal dogs that refered to Small Animal Teaching Hoslital of Veterinary Faculty in Tehran. The samples were collected during winter and spring. Two smears were prepared from each swab sample. One smear underwent Flurescent Auramine and the other Modified Zeihl-Neelsen technique. Oocysts were detected by both staining methods in one male household dog with clinical signs of diarrhea (aged 4 months). Diarhea was recorded in in 5 household dogs. There was no significant difference between the household and the stray dogs.

Keywords: Cryptosporidium, Dog, Auramine, Modified Zeihl-Neelsen.

PO-78

TRANSFER WITH CLASSICAL APPROACH - BASED VALIDATION OF STABILITY INDICATING METHOD FOR ORIGINAL AND GENERIC OF DICLOFENAC SODIUM RELEASE AND ITS IMPURITIES IN ACID STAGE CONDITION

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The study aims to support the life cycle of analytical methods development for pharmaceutical quality control namely, validation and transfer of analytical method based on classical approaches for release determination and impurities profile of diclofenac sodium in gastric resistance condition (dissolution test) based on different approaches. The current study was performed in accredited laboratory as sending site. RP – HPLC method for impurities profile of diclofenac sodium in gastric resistance condition were validated based on classical approach namely Society French of

Pharmaceutical and Technical Sciences 1992 (SFPTS) at sending site. The validated method was transferred into receiver site. The classical approach and USP concept (1010) were used as tools to accept the transfer of analytical method. The results showed that the method was developed using classical approaches with procedure of transfer, as a decision tool which is better than the classical approach only. Receiving site guarantees that each of future results will be within the acceptance limits and it can implement the transfer of the method of analytical procedure and more important be able to obtain reliable results.

Keywords: Validation, transfer, analytical method, quality control, pharmaceutical product, statistical approaches.

PO-79

DEVELOPMENT OF METHODS FOR THE DETERMINATION OF BISPHENOL A AT TRACE CONCENTRATIONS IN BABY BOTTLES INCLUDING EXPERIMENTAL DESIGN FOR ITS EXTRACTION

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Different analytical methods for the determination of Bisphenol a (BPA) in baby bottles have been compared. In addition, the optimization of the BPA extraction based on experimental design namely *Box-Behnken design* that was carried out. A High performance liquid chromatography with fluorescent detector (HPLC – FD) for the direct measurement of BPA in baby bottles was validated. On the other hand, the HPLC – FD method was transferred into Ultra high performance liquid chromatography with tandem mass (UHPLC - MS/MS) and validated for the same purpose. Sensitivity of UHPLC MS/MS detector over HPLC – FD was evaluated by comparison of LOQ values of BPA for both methods. The results showed that HPLC- FD can significantly increase throughput with quality results for determination of BPA in baby bottles due to the BPA is sensible for FD more than MS/MS detector associated with extraction method by 4% acetic acid at 35 °C for 36 hr. Therefore, the HPLC – FD was applied for quality control of BPA in baby bottles of parallel market that contained this compound.

Keywords: Bisphenol A, experimental design, UHPLC - MS/MS, HPLC – FD, extraction, baby bottles.

PO-58

Track: *Chemistry*

DETERMINATION OF SELENIUM CONTENT IN SULFATED SELENINOPOLY-SACCHARIDE: A NEW CLASS OF CHEMICAL COMPOUND

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Polysaccharides, including sulfated polysaccharides, are the important polymers having very wide applications and roles in living organisms. Similarly, selenium is an essential element, showing the activities as an antioxidant and free radicals scavenger.

In this work a compounds belonging to class of seleninoorganic compounds, namely sulfated seleninopolysaccharides, have been synthesized and analyzed.

Polysaccharides involved in the synthesis, were obtained from the cress seeds (*Lepidium sativum L.*).

The synthesis of sulfated seleninopolysaccharides were performed by introducing the sulfate groups using chlorosulfonic acid and selenite groups using selenious acid in *N,N*-dimethylformamide into polysaccharides.

Sulfated seleninopolysaccharide were separated and purified from unwanted salts by the application of gel filtration technique using glass column chromatography with Sephadex G-25, and water as a mobile phase. The two obtained fractions were named as (SeSLS1 and SeSLS2) and two fractions obtained after H_2O_2 degradation of insoluble part named as (SeSLSa1, SeSLSa2).

By the exclusion chromatography using analytical Water steel Protein Pak column, SeSLS1 fraction was recognized as three sub-fractions with three different molecular mass, LS1I, LS1 II and LS1 III while the second fraction SeSLS2 was recognized as two sub-fractions, LS2 I and LS2 II. First degraded fraction SeSLSa1 was recognized as only one fraction LSa1 I while the SeSLSa2 fraction contain four sub-fractions with four different molecular mass LSa2 I, LSa2 II, LSa2 III, and LSa2 IV.

In the analytical part of this work, the aim was to determine of selenium content using graft furnace atomic absorption spectrometry. The highest detected in SeSLS1 was 6.43% while the lowest was 3.45% reported in SeSLSa2.

Selenite groups determined by HPLC-electrochemical technique and the highest selenite groups reported in SeSLS1fraction and it was 40.25 mmol per 100 gm of fraction while the lowest was 22.42 mmol. detected in SeSLSa1after treatment by H_2O_2.

Infrared spectroscopy provides an evidence of that all fractions separated contained both sulfate and selenite groups in their structure.

PO-43

Track: *Chemistry*

SYNTHESIS, MOLECULAR DOCKING, ANTIBACTERIAL EVALUATION OF VARIOUS QUINOLINESCHIFF BASES: LABELING&BIODISTRIBUTION OF 99MTC-2-(P-HYDROXYBENZYLIDENE)-(QUINOLIN-4-YL) HYDRAZINE

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A new series of 2-(substituted benzylidene) 1-(quinoline-4-yl) hydrazine was designed, synthesized and evaluated for their antimicrobial activity. A molecular docking study was performed against bacterial topoisomerase II (PDB code: 2XCT) by MOE 2012.10, Leadit 2.1 softwares. Compound 4a representing the remarkably active compound in this study was labelled with one of the most important radioactive isotopes (technethium-99m). 99mTc-4a complex showed higher labelling yield, stability and uptake in inflamed tissue (T/NT = 6.11 ± 0.5) than the commercially available 99mTc-ciprofloxacin (T/NT = 3.6 ± 0.4).

Keywords: Quinoline, Benzylidene, Molecular docking, Antimicrobial activity, technetium 99m.

PO-36

Track: *Anti-infectives*

NOVEL SEPTICEMIA BIOMARKER: HDL (HIGH DENSITY LIPOPROTEINS)

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Aims: Delay in diagnosis and initiation of antibiotics treatment have been shown to increase mortality. Biomarkers can play an important role in diagnosis and prognosis of sepsis. We aimed to evaluate the correlation between septicemia and high density lipoproteins (HDL) level in burned patients.

Methods: In our prospective study conducted at Al-Sadr teaching hospital, Maysan, Iraq, during period from April to September 2013. Blood samples were collected from patient every other day to measure the level of HDL (high density lipoproteins) and triglycerides. Other blood samples were collected in blood culture tubes for culturing to verify septicemia depending on the clinical evidences.

Results: 75 patients were admitted consecutively into burn unit, 35 of them (46%) developed septicemia about 11 patients of the 35 patients are died. All died patients were with HDL value (< 5 mg/dl) 1 or 2 days before dying since our blood samples were collected every 2 days. Also find that patients with high density lipoproteins (HDL) value < 15 mg/dl were with high risk of developing sepsis.

Conclusion: There was a strong correlation between high density lipoproteins (HDL) level and septicemia in burnt patient. HDL value is a good biomarker for sepsis, it decreases below normal level and continues to diminish and reach to immeasurable level at advance stage of septicemia.

Keywords: High density lipoproteins (HDL), septicemia, burns, biomarkers, triglycerides.

PO-83

Track: *Innovative Drug Discovery and Nanotechnology*

NOVEL CO-ENCAPSULATED NANO-LIPOSOME SYSTEM-BASED TWO HERBAL DRUGS OF SILIBININ & GLYCYRRHIZIC ACID (NANO-PHYTOSOME) FOR CO-DELIVERY TO LIVER CANCER CELLS

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Nano-phytosomes are Nano-liposome vesicles that formed due the interaction of hydrogen bonds between phospholipids of lipoid membrane and phyto-molecules for improving the delivery of therapeutic agents. This study is about two herbal drugs of Silibinin and Glycyrrhizic acid loaded Pegylated Nano-liposome system for delivery to liver cancer cells and increase stability of Silibinin in blood. Antitumor efficacy of Glycyrrhizic acid and Silibinin are attributing to inhibition of matrix of metalloproteases and primarily attributing to decrease N-nitrosodiethylamine in hepatocyte carcinoma cells. Preparation of Nano-liposomes by thin layer film hydration method with HEPES buffer and sonication at 25%, 40% and 60% Amplitude. Small uni-lamellar vesicles entrapping glycyrrhizic acid & Silibinin are prepared using DPPC: cholesterol: DSPE-mPEG2000 at 7:4:0.36 molar ratios. The fluorescent label (DIL) was incorporated in the lipid bilayer at 0.1 mol%. Results shown that Mean Nano-phytosome diameter decreased with increasing sonication amplitude. The formulation of pegylated nano-liposomes sonicated at 60% amplitude showed a narrow size distribution with an average diameter of 58.9 nm. The size and structure of Nano-phytosome was analyzed by SEM and TEM images. The zeta potential of the Co-encapsulated Nano-phytosome showed -23.25. The encapsulation efficiency for Silibinin and Glycyrrhizic acid were about 24.37% and 68.78%, respectively.

Keywords: Nano-liposome, Nano-phytosome, Silibinin, Glycyrrhizic acid, Encapsulation, Liver cancer.

PO-84

Track: *Innovative Drug Discovery and Nanotechnology*

TARGETING OF NANOLIPOSOMES FOR DRUG & GENE DELIVERY SYSTEMS TO CANCER CELLS

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Generally, tumor cells aberrantly express tumor associated antigens that can be utilized as appropriate target molecules. Targeted Nano-liposomes, when compared with non-targeted nanoparticles, have several potential advantages: the ability to partition more of the nanoparticles within target tissue, increased uptake into target cells, higher therapeutic efficacy and lower toxicity. Targeting ligands-Coupled Nano-Liposomes are included of: 1. Monoclonal antibodies: Monoclonal antibodies (mAbs) & artificially engineered mAbs have been the preferred class of targeting molecules for the last several decades. 2. Aptamers: Aptamers are small nucleic acid ligands that can bind to targets with high sensitivity and specificity. Aptamers fold by intra-molecular interaction into unique conformations with ligand binding characteristics. 3. Peptide-based targeting molecules: Peptides are an attractive alternative targeting molecule due to their smaller size, lower immunogenicity, higher stability and ease of manufacture. There are a handful of oligopeptides that are distinct in their characteristics. These include A-domain proteins, AdNectins, and affibodies. 4. Antibody fragments: Due the limitations and challenges of using mAbs discussed earlier, there is increasing interest in using antibody fragments as targeting molecules while retaining the high antigen binding specificity of antibodies. These

include the Fab fragments, single chain variable fragments (scFV), minibodies, diabodies and nanobodies. 5. Small molecules: One of the most extensively studied small molecule targeting moieties in targeted drug delivery is folic acid (folate). The high-affinity vitamin folate is a commonly used ligand for cancer targeting because folate receptors (FRs) are frequently overexpressed on tumor cells. Targeted nano-liposomes can deliver therapeutic drugs and gene to a specific target cell population.

Keywords: Targeting, Nano-Liposomes, Drug Delivery, Gene Delivery.

PO-85

Track: *Innovative Drug Discovery and Nanotechnology*

DENDRIMERS FOR NANO MEDICINE APPLICATIONS AND NOVEL DRUG DELIVERY SYSTEMS

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The first dendrimer synthesis was noted by an R&D-100 Award (1991) and the Leonardo da Vinci Prize (Paris, 1996). Copolymers in General Structure of dendrimers: A. segment-block dendrimer; B. layer-block dendrimer. Properties of dendrimers: 1. Monodispersity, 2. Nanoscale size and shape Polyvalency, 3. Physicochemical properties, 4. Biocompatibility, 5. Immunogenicity. Dendrimers are produced by synthesizing A. The divergent growth method, B. The convergent growth method. There are now more than fifty families of dendrimers that the important families are such as Chiral-dendrimer, Liquid crystalline-dendrimers, Tecto-dendrimer, Pamamos-dendrimer, Pamam-dendrimer, Ppi-dendrimer, Hybrid-dendrimers, Peptide-dendrimers, Amphiphilic-dendrimers, Micellar-dendrimers, Multilingual-dendrimers. Applications of dendrimers for medicine and drug delivery systems: A-Pharmaceutical applications of Dendrimers are involved: 1. ocular drug delivery, 2. pulmonary drug delivery, 3. transdermal drug delivery, 4. oral drug delivery, 5. targeted drug delivery such as The encapsulation of anticancer drugs methotraxate and 5-fluorouracil into PEGylated generation 3 and 4 PAMAM-dendrimers, 6. gene delivery, 7. Dendrimers for controlled release drug delivery, 8. Dendrimer as solubility enhancer, 9. Cellular delivery using dendrimer carrier. B-Therapeutic applications of Dendrimers are involved: 1. photodynamic Therapy, 2. Dendrimers for boron neutron capture therapy. C-Diagnostic applications of Dendrimers are involved: 1. Dendrimers as molecular probes, 2. Dendrimers as X-ray contrast agents, and 3. Dendrimers as MRI contrast agents. Diagnostic applications of Dendrimers such as MRI contrast agents.

Keywords: Dendrimers, Drug delivery, Anti-cancer drug, Applications, nano biotechnology.

PO-10

Track: *Inflammation and Immunology*

PHARMACOLOGICAL INVESTIGATIONS ON THE STEM BARK OF *CAREYA ARBOREA* AS A POTENTIAL ANTI-INFLAMMATORY AGENT IN CFA INDUCED CHRONIC INFLAMMATION

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The objective of the study was to explore the anti-inflammatory effect of methanolic extract of stem bark of *Careya arborea*, a plant used locally in India for various painful inflammatory conditions, using chronic inflammatory model of Complete Freund's Adjuvant (CFA) induced arthritis in rats. Arthritis was induced by injecting 0.1ml of CFA containing 5mg/ml of heat killed *Mycobacterium tuberculosis* into the sub plantar region of the left hind paw. Treatment with the extract (100 and 200mg/kg) and standard (Indomethacin 5mg/kg) started on the day of induction of inflamogens and continued up to 28 days. There was a significant reduction in score of arthritic index in *Careya arborea* treated animals. The changes in size of tibio-tarsal joint diameter in groups 4 and 5 which received methanolic extract and group 3 with indomethacin treatment decreased. At the end of experiment, paw tissues and blood samples were collected for Nitric Oxide (NO), Myeloperoxidase (MPO), Malondialdehyde (MDA), C-

reactive protein (CRP) and γ-glutamyl transferase (GGT) estimation. In group 2 (untreated rats), there was a significant rise in NO, MPO, MDA, CRP and GGT. However, the levels of NO, MPO, MDA, CRP and GGT were significantly lowered in animals administered with *Careya arborea*. The findings were further supported by the radiographic changes/studies.

Keywords: *Careya arborea*, Chronic Inflammation, Complete Freund's Adjuvant, Nitric Oxide, Myeloperoxidase, C-reactive protein, γ-glutamyl transferase.

PO-131

Track: *Protein and Peptide Sciences*

THE ASSESSMENT OF ANTIOXIDANT ACTIVITIES OF PEPTIDE FRACTIONS OBTAINED FROM FERMENTED BOVINE MILK BY *LACTOBACILLUS SP* ISOLATED FROM KEFIR

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Milk proteins harbor numerous biological activities that make them effective in improving human health and nutrition. The therapeutic effects of fermented dairy products and lactic acid bacteria in cancer, allergy, infection and gastrointestinal disorders were investigated. The aim of this study was to evaluate the antioxidant activities of peptide fractions obtained from fermented bovine milk by fermentation with Lactic Acid Bacteria (LAB) - *Lactobacillus* sp. The proteolytic activity of used LAB strain was determined by SDS-PAGE after 24h of fermentation at 37 °C and the antioxidant activity of proteolysates was measured using a 2, 2'-azino-bis (3- ethylenebenzothiazoline-6-sulfonic acid) based method and compared with hydrolysated obtained in the presence of pepsin and proteinase K. The results showed that the antioxidant activity is of peptidic origin and it could be explained by the higher accessibility of antioxidant amino acid residues after bacterial hydrolysis. The obtained results suggest the potential interest of use of *Lactobacillus sp.* for production of fermented dairy product with antioxidant properties.

Keywords: Lactobacillus, antioxidant activity, peptide-hydrolysis.

PO-20

Track: *Innovative Drug Discovery and Nanotechnology*

NEW RUSSIAN FIBRINOLYTIC TROMBOVAZIM® IN COMBINED THERAPY OF INTRAOCULAR INFLAMMATION AFTER CATARACT REMOVAL

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Background: Intraocular inflammation is an early complication of cataract surgery, the standard therapy of which includes antibiotics, anti-inflammatory drugs, mydriatics and fibrinolytics. In 2007 Siberian Center of Pharmacology and Biotechnology (Novosibirsk, RF) made the first "per oral" fibrinolytic Trombovazim® by means of a classic Nano-Bio Technology (AXIS®).

Aim: is to estimate the influence of Trombovazim® on the indexes of ocular inflammation after cataract surgery.

Methods: 71 patients with this complication were examined and treated. The main group of patients was treated with standard therapy plus Trombovazim® at dose 400 IU (2 tablets) 2 times per day for 5-7 days, while only routine treatment was used in the comparative group.

Results: At the end of the therapy the main group demonstrated more significant increase in visual acuity, anti-inflammatory factor (IL-4) concentration in the lacrimal fluid and more evident decrease in the pro-inflammatory markers levels (C-reactive protein, fibrinogen in blood, TNF-α in the lacrimal fluid) in contrast to the second group.

Conclusion: Anti-inflammatory effect of fibrinolytic Trombovazim® was revealed as additional, that's quite advisable to use this drug in combined therapy of postoperative intraocular inflammation.

Keywords: Cataract surgery, Trombovazim®, intraocular inflammation.

PO-114

Track: *Anti-Cancer Discovery & Therapy*

DEVELOPMENT AND VALIDATION OF CLINICALLY PREDICTIVE MODELS FOR ANTI-CANCER DRUG DEVELOPMENT

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Clinically predictive preclinical cancer models are urgently needed for drug development. We propose an optimal strategy for efficacy testing of drug candidates for prostate cancer using well characterized and validated research models. In this strategy, a compound library is first screened for efficacy to inhibit proliferation of prostate cancer cells using an automated platform. Efficacy is confirmed by extensive testing *in vitro*, allowing reliable calculation of IC50 values. Compounds with confirmed efficacy are tested for their maximal tolerated dose *in vivo* to find optimal dose ranges. Efficacy is then tested *in vivo* using xenografts produced by the same cell lines whose proliferation the compounds were earlier demonstrated to inhibit effectively *in vitro*. Xenograft studies are started using orthotopic models, where primary tumors develop in prostate in close interaction with prostatic stroma and metastasize into local lymph nodes. Because most prostate cancer patients die due to bone metastases it is also important to demonstrate efficacy of the compounds on tumor growth in bone using intratibial models, and spreading of the cancer cells to bone and development of bone metastases using intracardiac models. This strategy is not limited to prostate cancer; it can be exploited widely in anti-cancer drug development.

PO-23

Track: *Chemistry (Asymmetric Synthesis)*

STEREOSELECTIVE SYNTHESIS OF *β*- AND *γ*-AMINO ETHERS, MORPHOLINES, AND 2-IMINOTHIAZOLIDINES VIA S_N2-TYPE RING-OPENING OF *N*-ACTIVATED AZIRIDINSES

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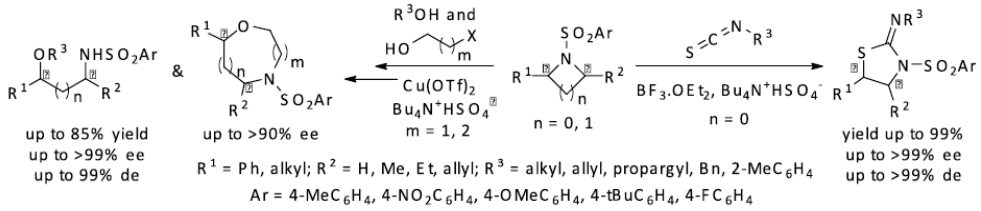

The small ring aza-heterocycles like aziridines and azetidines are vulnerable to a wide array of nucleophiles and thereby they can produce a number of valuable synthetic intermediates and end products of immense chemical and biological importance. We have established the reaction mechanism of Lewis acid catalyzed highly regioselective ring-opening of *N*-activated aziridines and azetidines as an S_N2-type pathway and we have effectively controlled the partial racemization of the starting substrate by using quaternary ammonium salts. The stratagem has been successfully applied for the synthesis of the nonracemic *β*- and *γ*-amino ethers, morpholines and their higher homologues using alcohols and haloalcohols as the nucleophiles, respectively, with excellent enantio- and diastereospecificity (ee up to >99%, de up to 99%). Some of the synthesized *β*- and *γ*-amino ethers have been found to possess anti-tuberculosis activity. Very recently, we have synthesized highly functionalized 2-iminothiazolidines in excellent yields (up to 99%) with excellent enantio- and diastereospecificity (ee up to >99%, de up to >99%) via a highly regioselective domino ring-opening cyclization (DROC) of substituted and *N*-activated aziridines with aryl- and alkyl isothiocyanates.

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PO-77

IDENTIFYING PATIENTS IN NEED FOR PROPHYLACTIC RENAL PROTECTIVE TREATMENT AFTER CARDIAC SURGERY

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Background: Renal dysfunction after cardiac surgery is seen in 30% of patients. This study aims to compare changes in renal function in coronary artery bypass grafting (CABG) and Aortic valve replacement (AVR) postoperatively in order to identify which group is at largest risk for renal dysfunction, and thus in need for prophylactic treatment.

Methods: A retrospective single centre study was performed including 6 953 CABG and AVR patients. Patients were followed up for a period of up to 9.5 years using a Cox proportional hazard. Renal outcome was measured as change in estimated Glomerular Filtration Rate (eGFR) Model.

Results: A total 5696 patients underwent CABG, 637 AVR. For the patients that underwent CABG, eGFR before surgery was 83.7 ± 23.7, at highest creatinine 72.8 ± 25.7 ($p<0.001$), and at discharge 83.7 ± 23.7 ($p<0.001$). For the patients that underwent AVR, eGFR before surgery was 80.0 ± 24.3, at highest creatinine 71.4 ± 28.7 ($p<0.001$), and at discharge 85.1 ± 30.2 ($p<0.001$).

Discussion: At discharge, patients who underwent CABG had 1.0% decrease in eGFR; patients who underwent AVR had 6.4% increases in eGFR. It seems as if CABG patients have persistent decline in renal function, whereas AVR patients have a full recovery during the hospital stay. Therefore, pharmacological intervention should be targeted to CABG patients rather than AVR patients.

Keywords: Cardiac Surgery, Renal function, CABG, AVR, Prophylaxis.

PO-13

CONSTRUCTION OF PACLITAXEL-LOADED STAR-SHAPED CHOLIC ACID-CORE PLGA-TPGS COPOLYMER NANOPARTICLES DELIVERY SYSTEM AND EVALUATION OF ITS ANTICANCER ACTIVITY

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Background: Nanoparticles are good drug carriers because of their good biocompatibility and biodegradability, and can be readily modified. This study was to develop a novel formulation of paclitaxel (PTX) that would improve its anticancer therapeutic index.

Methods: We developed a system of polymer–PTX drug conjugate with a concept of polymeric micelle drug delivery to form novel free PTX-loaded star-shaped cholic acid–core PLGA-TPGS conjugate nanoparticles (NPs) for breast cancer treatment. The structural properties and thermal stability of the copolymer was measured and confirmed by Fourier transform infrared spectroscopy, nuclear magnetic resonance, and thermogravimetric analysis. And the paclitaxel-loaded CA-PLGA-TPGS NPs efficiency as a new molecular biomaterial for drug delivery was evaluated by measurement of the anticancer activity of the paclitaxel-loaded CA-PLGA-TPGS NPs for breast cancer MCF-7 cells *in vivo* and *in vitro*.

Results: A system of novel nanoparticles (NPs) of star-shaped cholic acid–core PLGA-TPGS block copolymer for paclitaxel delivery for breast cancer treatment was developed, which demonstrated superior *in vitro* and *in vivo* performance in comparison with the paclitaxel-loaded PLGA NPs and the linear PLGA-TPGS copolymer NPs. The

paclitaxel- or coumarin 6-loaded NPs were prepared by a modified nanoprecipitation method and then characterized in terms of size, surface charge, surface morphology, drug encapsulation efficiency, *in vitro* release profile and physical state of the encapsulated drug. The CA-PLGA-TPGS NPs were found to have the highest cellular uptake efficiency, the highest antitumor efficacy compared with PLGA-TPGS NPs and PLGA NPs *in vivo* and *in vitro*.

Conclusion: The results suggest that such a star-shaped copolymer CA-PLGA-TPGS NPs is promising a new molecular biomaterial for drug delivery of high efficiency. This system can passively target cancer tissue and release drugs in a controllable manner, as determined by the pH value of the area in which the drug accumulates.

Keywords: Antitumor activity, Nanoparticles, Drug delivery, Star-shaped copolymer.

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PO-28

Track: *Drug Delivery & Targeting*

WITHAFERIN A: EVALUATION OF ANTILEISHMANIAL AND IMMUNOMODULATORY EFFECTS AND IN-SILICO DOCKING WITH TRYPANOTHIONE REDUCTASE

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Withaferin A, a major steroidal lactone present in *Withania somnifera* leaves and roots, has been attributed to many pharmacological activites like anti-cancer including antileishmanial [1] recently. It was shown to inhibit the growth of *L. donovani* promastigotes *in vitro*. We have also shown that withaferin A was able to inhibit the growth of intracellular amastigotes both in *in vitro* and *ex vivo*. IL-10, a key Th2 cytokine in *Leishmania* infection [2] is suppresed by withaferin A in dose dependent manner. A theoretical docking study was done with withaferin A and trypanothione reductase, a validated drug target enzyme of the *Leishmania* parasite. Withaferin A was found to bind at the active site of *L. infantum* Try R with lowest binding energy and RMSD values of -9.51 Kcal/mol and 0.294 Å respectively. Docking analysis of Try R with ligand enabled us to identify specific residues *viz.*, Lys-61, Val-103, Isoleu-106, Tyr-110, Leu-334, Cys-364, Ala-365 within the Try R binding pocket to play an important role in ligand binding. This study contributes towards understanding the mechanism of antileshmanial effect of the withaferin A on *L. donovani* parasite. Thus, on the basis of our *in vitro* and *in silico* studies, we hypothesize that withaferin A exhibits inhibitory effect against *L. donovani* parasites.

Keywords: Autodock, Trypanothione reductase, Withaferin A, *Leishmania infantum*, antileishmanial activity, *Leishmania donovani.*

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PO-15

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

IDENTIFICATION AND CHARACTERIZATION OF PHYTOTOXIC CONSTITUENTS FROM *PILEOSTEGIA VIBURNOIDES VAR. GLABRESCENS*

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Pileostegia viburnoides Hook. f. et Thoms. Var. glabrescens (C.C.Yang) S.M. Hwang is a traditional Chinese medicinal plant used for treating traumatic injury and fractures. Preliminary separation of *P. viburnoides var. glabrescens* was conducted at Hunan University of Traditional Medicine, Changsha, China and evaluations for antifungal and phytotoxic activity were completed at the USDA ARS, Oxford, MS in 2012. The n-butanol extract from *P. viburnoides var. glabrescens* was shown to be active at higher concentrations against *Agrostis* (monocot) and less active against *Lettuce* (dicot). Four compounds were separated by chromatography from the n-butanol extract of *P. viburnoides var. glabrescens*. Six compounds were identified, umbelliferone (1), skimmin (2), fraxin (3), n-Butyl-β-D-fructopyranoside (4),7-O-β-D-glucopyranosyl-8-methoxybenzo pyranone (5) and Syringin (6), which demonstrated the phytotoxic activity at different degrees aganist *Iceberg lettuce* and *Agrostis* seeds. Umbelliferone (1) and skimmin (2) possessed high phytotoxicity against the monocot and moderate phytotoxicity against the dicot. 7-O-β-D-glucopyranosyl-8-methoxybenzopyranone (5) produced the highest seed germination inhibiton in Agrostis.

PO-116

Track: *Anti-Cancer Drug Discovery & Therapy*

DIRECT *IN VIVO* INJECTION OF ^{131}I-GMS AND ITS DISTRIBUTION AND EXCRETION IN RABBIT

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After the ^{131}I labeled gelatin microspheres (^{131}I -GMSs) had been implanted in rabbit liver (41.336±5.106 MBq for each rabbit), the radioactivity distribution and metabolism *in vivo* were examined using single photon emission computed tomography (SPECT) and by blood and urine radioactivity counting. The nuclide was concentrated in the hepatic area until day 48 after ^{131}I-GMSs administration and radiography could be seen in thyroid areas in SPECT on days 4, 8, 16 and 24. The liver function was damaged but recovered rapidly. Eight days after ^{131}I-GMSs administration, the levels of free triiodothyronine and free thyroxin were reduced, which restored to normal levels on day 16. Histological examination showed that the microspheres were degraded to different degrees at 24, 32 and 48 d after ^{131}I-GMSs administration. Direct in vivo injection of ^{131}I-GMSs is safe in rabbits. It may be a promising method for treatment of malignant tumors.

PO-117

Track: *Anti-Cancer Drug Discovery & Therapy*

EFFECT OF 131I GELATIN MICROSPHERES ON HEPATOCELLULAR CARCINOMA IN NUDE MICE, AND ITS DISTRIBUTION FOLLOWING INTRATUMORAL INJECTION

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In this study, we investigated the effect of ^{131}I gelatin microspheres (^{131}I -GMSs) on human hepatocellular carcinoma cells (HepG2) in nude mice (Balb/c) and the biodistribution of 131I-GMSs following intratumoral injection. 131I-GMSs produced a pronounced reduction in HepG2 tumor volume, and the overall survival was 73.3% in the treatment group and only 13.3% in the control group ($P < 0.001$). Tissue radioactivity concentration measurements and SPECT demonstrated that the injected ^{131}I-GMSs mainly accumulated within the tumors. The concentration of FT4 was stable during the observation period. The microspheres could be observed by histological methods on day 32.^{131}I-GMSs suppressed the growth of HepG2 in nude mice and were retained in the tumor for a long period after injection. Direct intratumoral injection of ^{131}I-GMSs offers a promising modality for the treatment of hepatocellular carcinoma.

PO-90

Track: *Inflammation and Immunology*

DOLIROSIDE A ATTENUATES GOUT ARTHRITIS IN MONOSODIUM URATE CRYSTALS-TREATED RATS

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Dolichos falcata Klein (DF) as a Chinese Dai ethnic medicine has been widely used for the treatment of fracture and beriberoid disease for a long time in China. Our previous study has been demonstrated that DF ameliorated the gouty arthritis induced by monosodium urate (MSU) crystals and one of the active components, doliroside A, contributed to the anti-gouty arthritis effect of DF according to the *in vitro* study. However, there is still little known about the potential beneficial effects and possible mechanisms of doliroside A on gouty arthritis. Here, we investigated the underlying anti-inflammatory effects of doliroside A *in vivo*. Doliroside A at the doses of 10, 20 and 40 mg/kg were administered to the rats treated by MSU crystals. The results demonstrated that doliroside A (10, 20 and 40 mg/kg) significantly ameliorated the symptoms of gouty arthritis including decreasing pain threshold value, reducing the joint swelling degree and attenuating the inflammatory cell infiltration of articular tissue. Doliroside A also significantly decreased the levels of multiple pro-inflammatory cytokines in MSU crystals-treated rats. Furthermore, doliroside A obviously inhibited the expressions of caspase-1 and pro-IL-1β proteins in MSU crystals-treated rats. These findings indicate that doliroside A exhibits a prominent effect on ameliorating gouty arthritis induced by MSU crystals, which maybe through inhibiting the inflammatory activation of NALP3/caspase-1/ pro-IL-1β signaling pathway.

Keywords: Doliroside A, gouty arthritis, interleukin-1β, monosodium urate crystals, inflammation.

PO-59

QUANTITATIVE STRUCTURE RELATIVE VOLATILITY RELATIONSHIP MODEL FOR EXTRACTIVE DISTILLATION OF ETHYLBENZENE/P-XYLENE MIXTURES: APPLICATION TO BINARY AND TERNARY MIXTURES AS EXTRACTIVE AGENTS

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Although EB and PX are important raw materials in industrial process, the separation of EB and PX is a difficult process because the differences in boiling points between EB and PX are very small. The authors have been working to identify extractive agents for EB and PX separation through experimental methods. Among identified extractive agents, most of the halogenated compounds regarded as excellent extractive agents have several toxicities and safety hazards in Material Safety Data Sheet (MSDS) and they also badly damage many columns in distillation processes. From environmental toxicology, experiments using these hazard chemicals should be reduced in the future. The development of quantitative structure relative volatility relationships (QSRVR) is one of the good solutions for finding more efficient chemicals as extractive agents without many of the risks. For this reason, we introduce QSRVR models for binary and ternary extractive agents, with each model having two or three descriptors. In the case of binary extractive agents, the QSRVR model showed excellent accuracy of the mixture data. The ternary QSRVR model provides much potential on development of QSRVR model for several mixtures.

PO-11

IRIDOID GLYCOSIDE EXTRACTED FROM FRUCTUS GARDENIAE SUPPRESSES INFLUENZA-VIRUS-INDUCED PRO-INFLAMMATORY CYTOKINES BY INHIBITING THE ACTIVATION OF MAPKS AND NF-κB IN HUMAN A549 CELLS

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Background: Influenza virus infection can cause severe pneumonia and death. During replication Influenza virus activates the Raf/MEK/ERK-cascade and the transcription factor NF-κB. Both result in virus supportive and anti-viral effects by inducing expression of pro-inflammatory cytokines. Iridoid glycoside is the main active component of Fructus Gardeniae with antivirus and anti-inflammatory characteristics. However, no studies have been undertaken to investigate whether Iridoid Glycoside inhibits the inflammatory activity of activated human lung epithelial cell. The aim of this study was to examine whether Iridoid Glycoside modulates inflammatory reactions using human lung epithelial cell line A549.

Methods: A549 cells were infected with influenza virus strain PR/8/34. The inhibitory effect of Iridoid Glycoside on pro-inflammatory cytokine gene expression and production by stimulated A549 cells was measured by quantitative RT-PCR, and cytokine-specific ELISA assays, respectively. Western blotting was used to analyze the effect of Iridoid Glycoside on the activation of ERK in influenza-virus stimulated A549 cells. Effect on the activity of NF-κB was measured with an ELISA based highthroughput screening system. Significance of differences from control values were analyzed by means of standard statistical methods.

Results: Iridoid Glycoside significantly decreased influenza-virus stimulated inflammatory gene expression and production of IFN-beta, MCP-1 and interleukin (IL)-6 in A549 cells. The inhibitory effect of Iridoid Glycoside on the pro-inflammatory cytokines was ERK dependent. In addition, Iridoid Glycoside suppressed the NF-κB activation induced by influenza-virus in human lung epithelial cells.

Conclusion: This novel pharmacological actions of Iridoid Glycoside provide new suggestion that Iridoid Glycoside extracted from Fructus Gardeniae may be of therapeutic use for the treatment of influenza-virus induced inflammatory diseases by suppressing ERK and NF-κB activation.

PO-69

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

A NEW TOOL TO FIGHT ALZHEIMER'S DISEASE - ANACARDIC ACID DERIVATIVES AS POTENTIAL ACETYLCHOLINESTERASE INHIBITORS

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Alzheimer's disease is the leading cause of dementia among people over 65 years of age. Although its etiology is not fully known, the decrease of acetylcholine level has been linked to the pathophysiology of the disease. The cholinergic hypothesis is a line of therapy based on increasing the level of acetylcholine by reversible inhibition of the enzyme acetylcholinesterase (AChE) therefore promoting an improvement in the patient's cognitive profile. This work aims to propose possible candidates to AChE inhibitors, designed from the lipid phenolic derivatives of cashew nut. More specifically, we apply molecular modelling in the context of quantum mechanics to several anacardic acid derivatives. In total, twenty molecular structures with different functional groups were designed taking into account the possible interactions between these functional groups and enzyme active sites. For each molecule, a conformational analysis was carried out, in such a way to identify the more stable conformers. The geometries were first optimized by semi-empirical method and then optimized again, for greater accuracy, by using the hybrid functional B3LYP and basis set 6-311+G (2d, p). A single point was taken for the equilibrium geometry for each compound and several electronic properties important for the molecular recognition by the enzyme, like HOMO, HOMO-1, LUMO, LUMO+1, GAP and atomic charges, were calculated for the compounds studied. Geometric and lipophilicity properties were also determined for each compound using quantitative structure activity relationship. The principal components analysis (PCA) reveals that some of these compounds are correlated to donepezil, a drug with known biological activity, for a specific group of molecular descriptors. This correlation is shown more expressive when a solvating model, in this case the polarizable continuum model (PCM), is included in the ab initio calculations.

Keywords: Ache inhibitors, molecular modeling, Alzheimer's Disease.

PO-18

Track: *Innovative Drug Discovery and Nanotechnology*

STUDYING THE EFFECT OF 5-FLUROURACIL LOADED ON POLYMER NANOPARTICLES AND EXPOSED TO ULTRASONIC WAVES IN IMPROVING THE TUMORICIDAL EFFECT IN HEPATOCELLULAR CARCINOMA IN MICE

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Bovine serum albumin (BSA) has great potential as a nanocarrier. The objective was to investigate the effect of 5-flurouracil (5-FU) BSA polymer nanoparticles (NPs) and ultrasonic waves (US) on hepatocellular carcinoma (HCC) induced in mice by 4-dimethylaminoazobenzene (DAB). The 5-FU loaded BSA NPs was prepared by intermittent desolvation method and then characterized. The study was carried out on 100 male mice divided into two groups: 20 mice as control and 80 mice fed on 0.06% DAB and water was replaced with 0.05% aqueous solution of Phenobarbital. After HCC development, animals were divided into three subgroups: untreated group, group injected with free 5-FU and group injected with 5-FU loaded BSA NPs. From each subgroup, half of the mice were exposed to US. Liver tissue and serum samples were collected to investigate malonyldialdehyde (MDA) level, alanine amino transferase (ALT) activity, alkaline phosphatase (ALP) activity and alpha-fetoprotein (AFP) expression. Characterization of 5-FU loaded BSA NPs revealed average particle size of 70 nm, drug loading efficacy was 19.23% and encapsulation efficacy was 62.5%. The group treated with 5-FU loaded BSA NPs and exposed to US had the lowest ALT activity, MDA levels, and a significant decrease in ALP activity and AFP expression.

Keywords: 5-flurouracil, bovine serum albumin, 4-dimethylaminoazobenzene, hepatocellular carcinoma, phenobarbital and ultrasonic waves.

PO-67

Track: *Innovative Drug Discovery and Nanotechnology*

NANOPRECIPITATION AS A SIMPLE TECHNIQUE FOR THE FORMULATION OF AN ORAL ITRACONAZOLE NANOSUSPENSION

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The aim of this study is to formulate an itraconazole (ITZ) nanosuspension with improved dissolution behavior, particularly for patients with significant dysphagia, where a lack of ITZ oral liquid dosage forms occurs. Twelve ITZ nanosuspension formulations were prepared by a precipitation technique (acid-base neutralization), using different types and concentrations of stabilizers. These include poloxamer 188 and 407, sodium lauryl sulphate, polyvinyl pyrrolidone, hydroxypropyl methylcellulose and methylcellulose. The optimized nanosuspension was then lyophilized using mannitol or sucrose as a cryoprotectant. Nanosuspensions were then characterized using photon correlation spectroscopy, transmission and scanning electron microscopy, differential scanning calorimetry, X-ray diffraction, in vitro dissolution and short term stability studies. Results revealed that nanosuspension stabilized by methylcellulose (40% of ITZ weight) showed optimum properties in terms of mean particle diameter (394 nm), polydispersity index (0.33) and dissolution efficiency (53.4% DE30). Compared to other nanosuspensions, this optimized formulation proved to be stable for 24 hours allowing possibility for lyophilization. Lyophilized powder using mannitol exhibited smaller particle size (308.9 nm) compared to sucrose (591.3nm). TEM images revealed that dried powders could be easily redispersed with methylcellulose accumulated on nanoparticle surface. *In vitro* dissolution showed that freeze dried nanosuspension preserved the high dissolution rate (68.2% DE30) compared to Sporanox® capsules (39.4% DE30). Lyophilized formulations showed an amorphous state of ITZ as indicated by differential scanning calorimetry and X-ray diffraction technique. In conclusion, ITZ nanosuspension prepared by acid-base neutralization combined with lyophilization may be promising in enhancing the *in vitro* drug release which may be reflected on improved drug bioavailability.

Keywords: Itraconazole, Methylcellulose, Nanosuspension, Precipitation.

PO-60

Track: *Women's Health Drug Discovery and Therapy*

SCREENING THE LEAF AND ROOT OF *SOLANUM DASYPHYLLUM* SCHUM & THONINGI FOR FERTILITY EFFECT IN FEMALE WISTER ALBINO RATS

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Infertility is a growing public health problem in Nigeria and very often the blame is laid on the woman. The rising interest in phyto- medicine and natural products has stimulated the need for research into plants with female fertility boosting effects. The family Solanceae is known to contain steroidal alkaloids and saponins which are being used as precursors in the synthesis of sex hormones hence the screening of *Solanum dasyphyllum* Schum & Thoningi for fertility effect in female.

The leaves and root of *S. dasyphyllum* were gradiently extracted with chloroform and methanol using the soxhelet apparatus. The extracts were administered at two doses of 250 and 500mg/kg to groups of matured virgin female albino rats for 10 days after their estrous cycle had been monitored and established. After the administration of the extracts, proven males rats were allowed to mate with the females at the ovulation stage of the estrous cycle.

The number of litter resulting from each animal's pregnancy was recorded at the end of gestation and the average weight of litter at day 1, 4, 7, 14 and 21. The results obtained were compared to that obtained from a control group which was administered with the vehicle of administration alone and a positive control group that was administered with clomiphene citrate at a dose of 1.4mg/kg.

From the results obtained the root methanol extract at 500mg/kg dose proved the most potent followed by the 500mg/kg of the chloroform extract; both having p-values of 0.725 and 0.432 respectively at 95% (0.05) confidence when compared with the clomiphene result. This shows that there is no significant difference in the value obtained from these extract's result and clomiphenes. Clomiphene however has a p-value of 0.204 when compared with the control.

This work has shown that *S. dasyphyllum* root is a potent booster of female fertility.

PO-9

STEREOSELECTIVE SYNTHESIS OF FUNCTIONALIZED CYCLOHEXANONE DERIVATIVES CONTAINING QUATERNARY CARBON CENTER AND PIPERIDINE DERIVATIVES VIA DOMINO MICHAEL/ALDOL AND IMINO-ALDOL-AZA-MICHAEL REACTIONS

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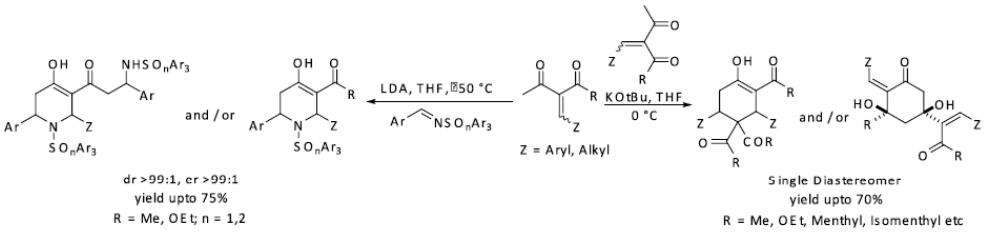

A simple and efficient protocol for the synthesis of diastereo- and enantioselective 2,6-disubstituted piperidine (de >99%, ee >99%) and 2,6-disubstituted-3-aminopropylpiperidine ring systems have been developed *via* a one pot 3 steps domino imino-aldol-aza-Michael and 5 steps domino imino-aldol-aza-Michael-imino-aldol reaction sequences. Enantiopure piperidines are strategically prepared from chiral sulfinyl imines. 2,6-disubstituted piperidines have been found to display an extensive range of biological activities such as antifungal, antibacterial, antihypertensive, anti-HIV properties *etc*. Now, cyclohexanes containing all carbon quaternary center are very frequently found in many natural products having substantial biological activities. Keeping this in mind, in place of imines, when the substrate α-arylmethylidine-β-diketone or α-arylmethylidine-β-diketoester, itself was employed as the active electrophile, highly functionalized cyclohexanone derivatives containing quaternary carbon center **(**in some cases all carbon quaternary

center**)** was obtained with excellent diastereoselectivity **(**de >99%) *via* a domino Michael-Michael/aldol-aldol reaction sequence**.**

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PO-97

Track: *Hot topics in Natural Products*

ISOLATION, IDENTIFICATION, MOLECULAR CHARACTERIZATION AND ANTI FUNGAL ACTIVITIES OF BIOACTIVE COMPOUND HEXADECANOIC ACID, METHYL ESTER FROM *ANNONA MURICATA* LINN. *(ANNONACEAE)* PLANT

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Medicinal plants are considered to be the main source of biologically actve compounds that can be used for the treatment of various ailments. *Annona muricata* Linn. *(Annonaceae)* plant commonly known as sour soup, a potential medicinal plant with antioxidant, anti-spasmodoic properties. The present work deals with the Isolation, Identification, Molecular Characterization and Antifungal activity of Bioactive compound Hexadecanoic acid, methyl ester from *Annona muricata* leaf material. The peaks obtained from GC-MS studies confirmed the presence of bioactive compound Hexadecanoic acid, methyl ester. The bioactive compound was tested for antifungal activity and found to be positive for *Alternaria solani* (NCBT 118), *A. albicans* (NCBT 120), *Aspergillus niger* (NCBT 128), *A. erithrocephalus* (NCBT 124) *A. fumicatus* (NCBT 126) *A. terrius* (NCBT 132), *Penicillium crysogenum* (NCBT 162). The isolates *A. niger* and *A. terrius* were analysed for 16S rDNA sequence *A. niger* with 575 bp, (control 595bp) and *A. terrius* with 580bp, (control 585bp) sequence obtained was analyzed between the control organism and Hexadecanoic acid, methyl ester tested organism and found that there is a difference in the sequence pattern which confirm that a direct interference of the bioactive compound Hexadecanoic acid, methyl ester in protein synthesis metabolism of the fungi and thus act as antifungal agent.

PO-26

Track: *Diabetes and Obesity Drug Discovery & Therapy*

OBESITY LEVEL RELATED TO RISK FACTORS FOR CVD IN CHILDREN

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Aim: To identify relationships between total bodies fat and abdominal fat *versus* known risk factors for CVD in young subjects.

Methods: Cross-sectional study of 170 (92 boys and 78 girls) children aged 8-11 years. Total fat mass (TBF) and abdominal fat (AFM) were measured by DXA. Total body fat was expressed as TBFs percentage of total body mass (BF %). Maximal oxygen uptake (VO_{2PEAK}) was measured with a maximal exercise test. Blood was sampled and blood pressure (BP) and resting heart rate (HR) were measured. Left atrial diameter (LA) was measured with echocardiography. Left ventricular mass (LVM) and relative wall thickness (RWT) were calculated. Z-scores were calculated. Sum of z-scores for triglycerides and lipoprotein concentrations, systolic and diastolic BP, HR, LA, LVM, and RWT and -VO_{2PEAK} were calculated and used as indices of clustered risk.

Results: Mean BF% was 18.8±8.9% (range 6.2-44.7) and mean AFM was 2.7 kg (range 0.4-11.4). Pearson correlations between ln BF% and ln AFM *versus* indices of clustered risk were in boys (r=0.58 and 0.58, P<0.05), and in girls (r=0.56 and 0.61, P<0.05).

Conclusions: Total body fat and abdominal fat were associated with a clustering of CVD risk factors, which highlight the need for early intervention.

Keywords: Children, body fat, CVD risk factors.

PO-27

Track: *Diabetes and Obesity Drug Discovery & Therapy*

FITNESS LEVEL RELATED TO RISK FACTORS FOR CVD IN CHILDREN

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Aim: To study the relationship between aerobic fitness (VO_{2PEAK}) versus known risk factors for CVD in young subjects.

Methods: Cross-sectional study of 170 (92 boys and 78 girls) children aged 8-11 years. Total fat mass (TBF) and abdominal fat (AFM) were measured by DXA. Total body fat was expressed as TBFs percentage of total body mass (BF %). VO_{2PEAK} was assessed by indirect calorimetry during a maximal exercise. Blood was sampled and blood pressure (BP) and resting heart rate (HR) were measured. Echocardiography was performed and left atrial diameter (LA) was measured and left ventricular mass (LVM) was calculated. Z-scores were calculated. Sum of z-scores for triglycerides and lipoprotein concentrations, systolic and diastolic BP, HR, LA, LVM, BF%, AFM, and AFM/TBF were calculated and used as indices of clustered risk.

Results: Pearson correlation revealed significant associations between VO_{2PEAK} and indices of clustered risk in both boys ($r=-0.49$, $P<0.05$), and in girls ($r=-0.48$, $P<0.05$). Boys and girls were divided according to tertiles of VO_{2PEAK}.

Conclusions: Findings from this population-based cohort of young children shows that low VO_{2PEAK} was associated with a clustering of CVD risk factors in both boys and girls, which highlight the need for early intervention.

Keywords: Children, VO_{2PEAK}, CVD risk factors.

PO-87

Track: *CNS Drug Discovery & Therapy*

OPTIMIZATION OF THE DRUG-LIKE PROFILE OF TREK-1 ACTIVATORS AS NOVEL ANALGESICS

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Most analgesics used today date from the 19th century. Morphine remains the analgesic of reference for the treatment of pain (nociception), even though it is responsible for serious adverse effects (constipation, respiratory depression, addiction). Research studies have recently showed that animals deprived of potassium channels (TREK-1 -/-) were over-sensitive to pain. These results suggest that TREK-1 channles control the excitability of the nociceptors and that they constitute targets of interest for the design of novel analgesics [1].

Previous studies within the CESMA team led to the identification of TREK-1 activators exhibiting analgesic activity *in vivo* [2, 3]. We present here the synthesis and pharmacological evaluation of some novel analogues that confirm their therapeutic interest.

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Keywords: Novel Analgesics, TREK-1 Activators, Medicinal Chemistry.

PO-24

Track: *Diabetes and Obesity Drug Discovery & Therapy*

EVALUATION OF THE METHANOLIC EXTRACT OF MISTLETOE (TAPINANTHUS BANGWENSIS) LEAVES GROWN ON ORANGE TREES FOR THE PHYTOCHEMICAL PROPERTIES AND ITS PHYSIOLOGICAL EFFECTS ON STREPTOZOTOCIN INDUCED DIABETES MELLITUS IN LABORATORY ANIMALS

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Mistletoe (*Tapinanthus bangwensis*) a semi-parasitic evergreen plant, that has been used traditionally in Nigeria and other parts of Africa as antihypertensive and antidiabetic agents. The aim of this research was to investigate the phytochemical properties of methanolic extract of *Tapinanthus bangwensis* (mistletoe) and its physiological effects on sugar levels in laboratory animals. The phytochemical analysis revealed the presence of saponins, flavonoids, tannins and steroidal glycosides. Treatment with aqueous *Tapinanthus bangwensis* (mistletoe) extract at the dose of 500mg/kg body weight showed that the cocnentration of blood glucose levels in the diabetic test (treated rats) were significnatly reduced as compared to the diabetic control (untreated rats). In streptozotocin induced diabetic experimental animals (rats), maximum reduction in blood glucose levels was observed after fourteen (14) days of treatment with methanolic crude extraxt of *Tapinanthus bangwensis* (mistletoe). The result showed the concentrations of blood glucose in the diabetic test (treated) group was significantly reduced to 163.75 ± 46.327 ($P < 0.05$) (mg/dl) after fourteen (14) days of administration of aqueous *Tapinanthus bangwnesis* (mistletoe) extract at 500 mg/kg body weight as compared to 377.50 ± 0.50(mg/dl) of the diabetic control (untreated) group. The result indicated that the methanolic crude extract of *Tapinanthus bangwensis* leaves possess significant anti - diabetic activity.

Keywords: Methanolic extract of mistletoe, experimental animals, streptozotocin, diabetes mellitus.

PO-119

INFLUENCE OF CYCLODEXTRINS ON THE PHOTOSTABILITY OF SELECTED DRUG MOLECULES IN SOLUTION AND THE SOLID-STATE

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The interaction between a selected drugs, namely: *antazoline, xylometazoline, naphazoline, sulfamethoxazole and trimethoprim*, and cyclodextrins have been studied in aqueous solutions by using spectroscopic and chromatographic methods. In this study, the effect of inclusion stability on the action of the proposed drug have been evaluated by determining the binding constant, the ratio of complexation between drug and cyclodextrin, and the thermodynamic parameters. The influence of inclusion complexation with cyclodextrins (CyDs) on the photostability of the proposed drugs in aqueous media has been investigated. The photodegradation reaction of these drugs molecules has been explored using UV–Vis spectrophotometery-based kinetic analysis and high performance liquid chromatography (HPLC). Quantitative evaluation of the influence of CyDs has been evluated based on the observed rate constant, half-life time of the photodegradation reaction and the peak area of the corresponding analyte after photodegradation using HPLC separation.

PO-44

Track: *Chemistry*

NOVEL THYMOQUINONE DERIVATIVES AS TELOMERIC G-QUADRUPLEX STABILIZERS AND ANTICANCER AGENTS

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Eight novel amino substituted thymoquinone derivatives TQ $_{(1-8)}$ were synthesized. Structures of the obtained products were confirmed using IR, ^{1}H-NMR, ^{13}C-NMR, MS and elemental analysis. The interactions between the obtained TQs and telomeric G-quadruplex DNA were tested. TQs showed different affinities towards G-quadruplex where TQ8 showed the highest one. Furthermore, they showed good selectivity towards G-quadruplex over ct-DNA. New synthesized thymoquinone derivatives were tested against human lung cancer cells A549, human breast cancer cells MDA-MB-231 and colorectal cancer cells HT29. Derivatives TQ2, TQ5 and TQ8 showed potency against human lung cancer cells A549 while the thymoquinone derivative TQ8 gave the highest inhibition on the growth of A549, MDA-MB-231 and HT29 carcinoma cells.

PO-120

Track: *Women*

ISOLATION, STRUCTURE ELUCIDATION AND SYNTHESIS OF BIOACTIVE PEPTIDES FROM BEE PRODUCTS

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Honey has been used in traditional medicine for thousands of years, and there is an increasing interest in the honey products applications in modern medicine. Bee products can have diverse biological activities as anticancer (Han *et al*., 2010), antimicrobial, anti-oxidant (Nakajima *et al*., 2009), anti-inflammatory, antiviral and hepatoprotective. Nowadays, there is an urgent call to find anticancer and antimicrobial agents from natural products with less ecological damage and minimum health and environmental hazards. The nature, geography and weather of Egypt provide possibly a rich source of bee products and with the help of the facilities and infrastructures in Sweden, diverse pharmaceutical leads can be discovered.

Our main aim is to identify and characterize bioactive peptides from the bee products. These peptides have been poorly characterized, partly because they are generally present in trace quantities. In turn, polar fractionation prior to screening of anticancer and antimicrobial activities will be done. Active peptides will then be isolated from the fractions and identified using techniques including High Performance Liquid Chromatography (HPLC), Mass Spectrometry (MS), LC/MS, MS/MS, Amino Acid Analysis (AAA) and 2D-Nuclear Magnetic Resonance Spectroscopy (2D-NMR). Finally, the isolated peptides (El-Seedi *et al*., 2013), and sets of analogues, will be synthesized and tested for structural-activity relationships.

Melittin

Gly-Ile-Gly-Ala-Val-Leu-Lys-Val-Leu-Thr-Thr-Gly-Leu-Pro-Ala-Leu-Ile-Ser-Trp-Ile-Lys Arg-Lys-Arg-Gln-Gln-NH21

Royalisin

Val-Thr-Cys-Asp-Leu-Leu-Ser-Phe-Lys-Gly-Gln-Val-Asn-Asp-Ser-Ala-Cys-Ala-Ala-Asn-Cys-Leu-Ser-Leu-Gly-Lys-Ala-Gly-Gly-His-Cys-Glu-Lys-Gly-Val-Cys-Ile-Cys-Agr-Lys-Thr-Ser-Phe-Lys-Asp-Leu-Trp-Asp-Lys-Tyr-Phe

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PO-134

Track: *Biologics*

CONTAMINATION OF THE CLINICAL MICROBIOLOGY LABORATORY IN BENGHAZI - LIBYA

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We surveyed environmental surfaces in our clinical microbiology laboratory one at Reference laboratory, Benghazi and other at Pediatric Hospital Laboratory to determine bacterial contamination during a routine working day. This study aimed to identify the extent of contamination of surfaces. Microbes may transmitte from surfaces to working staff in the Laboratories or the visiting people who visited to the laboratories for the purpose of delivering sample or receiving report. Sample of swabs were taken from some surfaces most frequently used by the workers from the reference laboratory, and some swabs taken from the Laboratory in Pediatric Hospital. The samples were cultured on the blood agar media. The contamination identified in the reference laboratory were 54(85.70%) out of 63 samples however, in Pediatric Hospital Laboratory were 15(71.40%) out of 21 samples. Conformity test was done for bacteria using Phoenix 100. The Recommendations includes personal protection and good hygienic condition of the Laboratory Environment.

PO-103

Track: *Pharmaceutical Research & Development*

IN VIVO EVALUATION OF OCULAR ANTI-INFLAMMATORY EFFECT OF SPANLASTICS ENTRAPPING TWO PREDNISOLONE SALTS IN COMPARISON TO COMMERCIAL PRODUCTS

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Spanlastics (SVs) are elastic nanovesicular carriers formulated for entrapping Prednisolone salts; Acetate (Pred A) and Sodium phosphate (Pred P) to improve their ocular anti-inflammatory efficacy compared to commercial Pred A suspension and Pred P solution. The formulated SVs were composed of span60: cholesterol (7:3 molar ratio) and 20%v/v ethanol. Irritation test was examined for the SVs followed by histological examination; the results revealed no irritation effect with no observed damaged corneal tissue of rabbit eyes. Anti-inflammatory efficacy of the SVs (50µl 1%drug) compared to commercial products was examined after induction of inflammation by topical instillation of 40 µl clove oil followed by 4 times daily 6 successive days of treatment. Inflammation was scored based on modified Draize's test. SVs showed higher anti-inflammatory efficacy compared to commercial products. Pred A and Pred P SVs were comparable in efficacy where severe inflammation became milder after 2 days, achieving complete cure after 3 days. The commercial Pred A suspension was superior to Pred P solution where severe inflammation became milder after 3 and 4 days, achieving complete cure after 5 and 6 days respectively. The side effect was assessed based on the cumulative increase in IOP after 6 days with the same dosing schedule without preinduction of inflammation. The results revealed an increase in IOP; 0.24, 0.45, 1.93 and 1.6 mmHg for Pred P SVs, Pred A SVs, commercial Pred A and Pred P respectively. In conclusion, spanlastics improved the anti-inflammatory efficacy of both salts by controlling their release and showing lesser side effects.

Keywords: Spanlastics, Prednisolone, Anti-inflammatory, Ocular, Draize's test.

PO-66

Track: *Innovative Drug Discovery and Nanotechnology*

SPANLASTICS ENTRAPPING TWO PREDNISOLONE SALTS: DEVELOPMENT, *IN VITRO* CHARACTERIZATION AND *IN VIVO* PERFORMANCE

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Spanlastics (SVs) are span based elastic nanovesicular carriers formulated for entrapping two Prednisolone salts; Acetate (Pred A) and Sodium phosphate (Pred P) for ocular drug delivery. The optimized SVs formulation composed of span 60:cholesterol (7:3 molar ratio), 20%v/v ethanol and 1% drug prepared by thin film hydration method. *In vitro* characterization included vesicle size, zeta potential, %Entrapment efficiency (%EE) and *in vitro* drug release. The SVs showed mean particle diameter of 270 and 277nm, zeta potential of -41.6 and -55mV and %EE of 90% and 34.2% for Pred A and Pred P respectively. The drug release through cellophane membrane from SVs compared to commercial products; showed sustained drug release percent after 6h (T6h 76.1% and 98.6% for Pred A and Pred P SVs respectively) whereas both commercial Pred A suspension and Pred P solution showed 100% release within 2 hours. In vivo study was conducted on rabbits by measuring the increase in IOP using SchiÖtz tonometer to predict drug concentration in ocular fluid after single dose of 50µl SVs formulation compared to commercial products. The %IOPmax were 26.82, 19.1, 15.38 and 14.75 mmHg while Tmax were 2, 1.75, 3 and 2.25 hours whereas AUC were 63.7, 37.2, 79.75 and 60 for Pred A suspension, Pred P solution, Pred A SVs and Pred P SVs respectively. Pred P and Pred A SVs lasted for 7 and 8 hours respectively compared to 4 and 5 hours for commercial Pred P and Pred A respectively. In conclusion, SVs controlled drug release and improved drug efficacy.

Keywords: Spanlastics - Prednisolone – IOP.

PO-70

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

NEW POTENTIAL AChe INHIBITOR CANDIDATES

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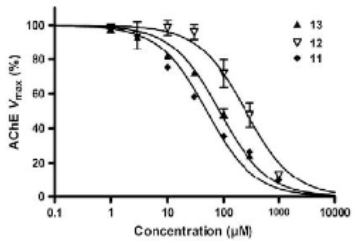
We have theoretically studied new potential candidates of acetylcholinesterase (AChE) inhibitors designed from cardanol, a non-isoprenoid phenolic lipid of cashew Anacardium occidentale nut-shell liquid. The electronic structure calculations of fifteen molecule derivatives from cardanol were performed using B3LYP level with 6-31G, 6-31G(d), and 6-311 þ G(2d,p) basis functions. For this study we used the following groups: methyl, acetyl, N, N-dimethylcarbamoyl, N, N-dimethylamine, N, N-diethylamine, piperidine, pyrrolidine, and N, N-methylbenzylamine. Among the proposed compounds we identified that the structures with substitution by N,N-dimethycarbamoyl (12), N,N-dimethylamine (11), and pyrrolidine (13) groups were better correlated to rivastigmine, and represent possible AChE inhibitors against Alzheimer disease. This fact was confirmed by synthesis and phamacological testing (Figure). Efforts to further clarify the mechanism of enzyme inhibition of these compounds are currently under way.



Pharmacological study to test the AChE activity (*Electricus Electrophorus)* in presence of cardanol derivatives.

PO-65

Track: *Enabling Technologies*

NOVEL MULTIMODAL EVALUATION TECHNOLOGY FOR SYMPTOM CHARACTERIZATION IN GI FUNCTIONAL DISEASES AND PHARMACOLOGICAL TESTING OF DRUGS

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Abnormal visceral sensory function has been demonstrated in patients with functional gastrointestinal diseases and diabetes mellitus with neuronal changes located in the enteric, peripheral and/or central nervous system. Symptom development is due to complex neuro-muscular mechanisms. To study such mechanisms advanced testing is needed. The multimodal pain test is a novel method where mechanical, electrical, thermal and chemical stimuli can be applied in the lumen of the gastrointestinal tract (figure **1**). The major advantage is involvement of distinctive receptors, various sensory nerves and different pain pathways mimicking clinical pain that favors investigation of central pain mechanisms involved in allodynia and hyperalgesia. Such detailed characterization is needed for understanding the pathophysiological mechanisms as well as drug effects.

The multimodal pain test has been used in several studies of functional diseases where it has been used to demonstrate differences between diseases such as non-cardiac chest pain, gastro-esophageal reflux disease, non-erosive gastro-esophageal reflux disease, functional dyspepsia and irritable bowel syndrome. Furthermore, it has been used to study differential effects of drugs such as morphine and derivates of morphine.

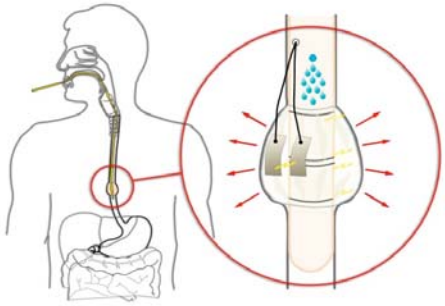

Figure 1. The multimodal probe for evaluation of symptoms and drug effects.

PO-93

Track: *Hot Topics in Medicinal Chemistry*

THE SYNTHESIS AND EVALUATION OF THE ANTICANCER POTENTIAL OF NEW HYDRAZINO-THIAZOLE DERIVATIVES

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Cancer is the second cause of death in the population and therefore the development of new medicine with improved anti-cancer activity and reduced side effects continues to be of great importance. Given recent data provided by the specialty literature showing the antiproliferative potential of thiazole derivatives [1-3], as well as our experience in this field, our aim is the synthesis of a new series of hydrazino-thiazole derivatives and their *in vitro* testing for the cytotoxic potential. 16 compounds have been synthesised using the Hantzsch condensation with good yields, and their structures were confirmed using modern spectral methods: MRN (1H and 13C), MS.

The cytotoxic activity has been tested on tumor cell lines, a triple negative breast cancer cell line (MDA-MB-231) and the cervical cancer cell line HeLa. The IC 50 values were compared to the standard substance (cisplatin). The results show a variation of the cytotoxic effect directly proportional to the concentration, and some compounds have a cytotoxic profile similar to that of the cisplatin.

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PO-106

Track: *Pharmaceutical Research & Development*

SELF MEDICATION WITH OTC PRODUCTS: CAN BE LIFE THREATENING-A SURVEY

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Over-the-counter (OTC) drugs are medicines that are sold directly to the consumer without a prescription; as compared to prescription drugs, which are sold to consumers possessing a valid prescription. India currently ranks 11th in the global OTC market and is estimated that it will reach the 9th position within five years. Currently, the Indian OTC market is estimated to represent approximately USD 1,813 million. A survey was conducted to study the self medicating patterns and interactions between Allopathic OTC products/ Ayurvedic/ Homeopathic/ Unani medicines and prescription drugs. The subjects for this survey were doctors from Mumbai, Maharashtra in India. It was observed that most of the doctors believed that 10-40% of the patients were consuming the above mentioned medicines along with prescription drugs for quick relief. Patients were also found to self medicate for clinically fatal disorders like neuropsychological disorders. The most common clinical condition for which patients self medicate was found to be fever, cold cough. Patients strive for symptomatic relief without realizing the fatality of the underlying cause. Thus there is an urgent need to create awareness among the people about the possible dangerous effects of self medication and interaction of those drugs with prescription drugs.

PO-56

THE USE OF COMPARATIVE INTRAMOLECULAR CONTACT ANALYSIS TO BUILD VALID PHARMACOPHORE MODEL(S) AGAINST SOLUBLE EPOXIDE HYDROLASE TOWARDS DEVELPOMENT OF POTENTIAL ANTI-INFLAMMATORY AGENTS

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The frequent recent use of anti-inflammatory medications combined with their less-than-optimum performance prompted continuous efforts to develop new anti-inflammatory agents that act via novel routes. Soluble epoxide hydrolase (sEH) has been considered as one of the most attractive new targets for drug discovery of anti-inflammatory drugs.

In the current project, we implemented a wide range of docking configurations to dock 248 inhibitors into the binding pocket of sEH (PDB code: 3I28). One docking engine and 7 scoring functions were utilized in the study. Furthermore, the ligands were docked in their ionized and unionized forms into the hydrous and anhydrous versions of the binding pocket. We employed a novel methodology to validate and identify the optimal docking configurations, namely docking-based Comparative Intermolecular Contacts Analysis (dbCICA). Two docking configurations were found to achieve self-consistent dbCICA models.

The resulting dbCICA models were used to derive valid structure-based pharmacophores models that were used to screen the National Cancer Institue (NCI) list of compounds. Experimental validation by absorbance-based assay proved selective she inhibitors, with the most active having % inhibition of 92%.

PO-46

Track: *Chemistry*

POLY (HYDROXYETHYL ACRYLATE -CO- ACRYLIC ACID) SOFT LENSES HYDROGELS FOR HYDROCORTIZONE AND ACETAZOLAMODE DRUG LOADING AND RELEASE SYSTEMS

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Poly (hydroxyethyl acrylate-co-acrylic acid) hydrogels containing different concentrations of acrylic acid were successfully synthesized and characterized. Hydroxyethyl acrylate (HEA) and acrylic acid (AA) was copolymerized at different ratios, (1/0, 3/2, 1/1, 2/3 and 0/1), using potassium persulphate as initiation system in presence of a cross linking agent at 70 °C to yield transparent hydrogels. The chemical structure and thermal properties of the hydrogels was determined by ATR-FTIR spectroscopy and DSC respectively. Loading studies were carried out with hydrocortisone and acetazolamide as drug molecules. Swelling capacity and kinetics of swelling of the obtained hydrogels were studied and their corresponding swelling behavior was followed in a simulated lachrymal solution at 37°C. Results showed that swelling performance and loading capacities of these new materials make them suitable for specific biomedical applications.

Keywords: pHEA-co-AA hydrogel, soft lenses, hydrocortisone, acetazolamide, swelling behavior, loading/release properties.

PO-14

METHADONE POISONING IN CHILDREN <6 YEARS WHY?!

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Introduction: Methadone is derived from heroin, this product is in drug stores in syrup form1mg/ml.Poisoning occurred because child likes to open the door of bottle and eat accidental. Methadone is a long acting drug with half life about 24 hours.

Method: We studied all of children referred to pediatric emergency room Imam Reza Hospital for cause and agent of poisoning during 2011.01.01 to 2012.01.01.

Results: In our emergency center the most common poisoning is opium compounds especially methadone. We think it reason that methadone syrup is available in the out of hospital and pharmacy. Parents use it to give up addiction.

Of 409 children with symptoms of poisoning 256 cases had different opium poisoning (27%) and 69 cases (16.8%) had methadone poisoning.

Distribution of methadone poisoning patients on age:

Age(Months)	No	Percent%
0-2	11	15.9
2-24	36	52.1
24-72	22	31.8

Conclusion: This research shows that component of methadone as syrup form should be collected and other form of methadone needs to make (Capsule, Tablets).

PO-37

Track: *Anti-infectives*

EFFECT OF POLYPHENOLS EXTRACTED HONEY ON METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

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Infections resistant Staphylococcus aureus Methicillin have different problems of nosocomial infectious disease in addition to multidrug resistance. Our work is a contribution to the evaluation of the antimicrobial effect of four (04) polyphenolic extracts of honey collected from different sites of the Algerian territory on the one hand and the study of the physicochemical quality, microbiological and pollen on the other hand. The results clearly show the sensitivity of MRSA *vis-à-vis* our polyphenolic extracts. This inhibitory effect was found for the four samples tested with varying degrees of success with the polyphenolic extract Jijel is the inhibitor. This activity is linked not only to the type of polyphenols extracted but also the type of honey as honeydew honeys are more effective than nectar, and the botanical origin.

Keywords: Antibacterial effect, honey, MRSA, nosocomial infections, polyphenols.

PO-111

Track: *Hot Topics in Natural Products*

POMEGRANATE EXTRACT BLOCKS IL-1B INDUCED ACTIVATION OF NF-KB IN HUMAN CHONDROCYTES BY DOWN REGULATING THE EXPRESSION OF IKKB AND THE ACTIVATION OF NIK

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Objective: Interleukin-1b (IL-1b) is present in osteoarthritic joints at high levels and causes an increase in many catabolic enzymes and inflammatory mediators through activation of NF-kB pathway. In the present study we investigated the mechanism of NF-kB inhibition by a polyphenol rich Pomegranate extract (PE) by determining its effect on the activation of the kinases upstream of IkB in primary human chondrocytes.

Research Methods & Procedures: OA chondrocytes were pretreated with PE followed by stimulation with IL-1b for different time points. Activation of NF-kB p65 was determined by specific ELISA-based DNA binding assay. Total protein levels and phosphorylated forms of different kinases were determined by Western immunoblotting. mRNA levels were determined by real time PCR. Total intracellular ROS was determined by DCF assay.

Results: PE inhibited IL-1b induced DNA binding activity of NF-kB p65, degradation of IkB and phosphorylation of NIK. PE also inhibited the phosphorylation of IKKb as well as down-regulated the expression of IKKb mRNA and protein. Moreover, PE strongly inhibited IL-1b-induced increase in intracellular ROS concentration in human chondrocytes.

Conclusions: Taken together the data presented here suggest a novel mechanism of NF-kB inhibition by PE acting at multiple levels. These results may help to develop pharmacological inhibitors of NF-kB derived from PE for the effective management of osteoarthritis.

PO-107

MAGNETIC NANOPARTICLES FOR CONTROLLED DRUG DELIVERY IN HYPERTHERMIA THERAPY

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This study is about multifunctional magnetic nanoparticles surface-modified with bilayer oleic acid, and coated with a thermo-responsive copolymer poly (N-isopropylacrylamide-coacrylamide) by emulsion polymerization, for controlled drug delivery and magnetic Hyperthermia applications. Nanoparticles were loaded with anticancer drug doxorubicin into the copolymer chains at 25°C. Composite nanoparticles (hydrated) of average diameter 45 nm were of core shell structure having magnetic core of about 18 nm and shell was composed of organic compounds and water. Magnetic core was superparamagnetic lacking coercive force and remanance due to the pseudo-single domain nanostructure. Lower critical solution temperature (LCST) of the thermo-responsive copolymer was observed to be around 39°C. below this temperature, copolymer was hydrophilic, hydrated and swelled. But above LCST, copolymer became hydrophobic, dehydrated and shrank in volume. UV visible spectrophotometer was used to investigate the drug loading and releasing profile at different temperatures as well as under magnetic heating. There was almost absence of drug release at around 37°C (normal body temperature). Drug was released at temperatures above LCST, which is significant for controlled drug delivery. Magnetic heat-generation was studied by exposing the magnetic fluid to alternating magnetic field of 7.2 kA m_1 having frequency 70 kHz. A simple magnetic capturing system (simulating a blood vessel) was used to analyze the capturing of magnetic nanoparticles under various applied fields for drug targeting purpose.

PO-41

Track: *Biologics*

ASSOCIATION BETWEEN GHRELIN GENE (LEU72MET) POLYMORPHISM AND GHRELIN SERUM LEVEL WITH CORONARY ARTERY DISEASES

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Objective: Research shows that Ghrelin gene polymorphism has some association with coronary artery diseases (CAD). Due to genetic differences among nations and the high prevalence of CAD , we conducted this study to examine the possible association between the polymorphism of Ghrelin gene Leu72Met and CAD.

Design and methods: This case-control study was undertaken with patients who were referred to referral heart center, in 2011 with chest pain or a positive exercise test. Patients with risk factors for heart disease or who were surgery candidates that underwent angiography and echocardiography were also included. DNA extractions were performed using a modified salting out method and the Ghrelin region was amplified using PCR. The presence of the Leu72Met polymorphism and the serum levels of Ghrelin were determined using the restriction fragment length polymorphism (RFLP) method and an Enzyme-Linked Immunosorbent Assay (ELISA), respectively.

Results: The results indicated that in CAD patients, the incidence of heart failure was significantly different between groups with genotypes CC or AA+CA (P=0.041). Mean serum level of Ghrelin in the CAD group was significantly higher than in the control group ($p<0.0001$). Additionally, there was a significant relationship between the distribution of Ghrelin genotypes and serum levels of Ghrelin in both the CAD and control groups ($p<0.0001$).

Conclusion: This study indicates that there was a significant association between heart failure in CAD patients and presence of the polymorphism, as well as an increase in serum levels of Ghrelin associated with genotype distribution such that Ghrelin levels have an inverse relationship with the frequency of the CC genotype.

Keywords: Ghrelin, polymorphism, coronary artery diseases, heart failure, gene susceptibility.

PO-99

Track: *Inflammation and Immunology*

NATURAL PRODUCTS ISOLATED FROM *FATSIA POLYCARPA* HAYATA TO TREAT *HELICOBACTER PYLORI* INFECTION IN MICE

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Helicobacter pylori infection is associated with chronic gastritis, peptic ulcers, and gastric cancer. About 50% of the population in the world is infected by *H. pylori*. Furthermore, 70% to 95% of *H. pylori*-infected patients are suffering from peptic ulcer. *Fatsia polycarpa* Hayata has been used as an herbal medicine to treat ankylosing spondyloarthritis, oseteoarthritis, rheumatism, rheumatoid arthritis with accompanying reactive gout, osteochondrosis, synovitis, and tendinitis in Chinese medicine for many years. We analyzed the natural products isolated from *Fatsia polycarpa* Hayata by evaluating the anti-*H. pylori* activity *in vitro* and *in vivo*. Compound DM-24-6-3-1 exhibited the strongest antibacterial activity against *H. pylori* with minimum bactericidal concentration of 4 μg/ml, but weak cytotoxicity against AGS cells ((human gastric cancer epithelial cell lines)) at IC_{50} of 158 μg/ml. It could suppress 52 % of *H. pylori* adhesion and invasion to AGS cells after 6 hr-treatment at concentration of 16 μg/ml and also decrease *H. pylori*-induced IL-8 expression Infected mice were treated with 4 or 8 μg of DM-24-6-3-1 for three days. Both treatments could suppress 80 % of *H. pylori* colonized and VacA expression and IFN-β(vacuolating cytotoxin A) in stomach and decrease infection induced IL-1γ expression. This study offers an alternative way to diminish risk of *H. pylori* infection and development of multidrug-resistant strains by using natural products for infection treatment.

Keywords: Fatsia polycarpa Hayata, *Helicobacter pylori*.

PO-88

Track: *Regenerative Medicine*

EFFECTS OF PYRITUM IN CANINE FRACTURE MODEL

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Objectives: This study was performed to investigate the bone healing effects of natural pyrite in fracture model of dogs.

Methods: A total of 140 female Sprague-Dawley rats, 4-month-old, weighed 200-230 g were randomly assigned to 4 groups (35 animals/group). The animals of group I were sham operated and group II, III and IV were ovariectomized. After eight weeks, the animals of group I and II received solvent vehicle daily, whereas those of group III and IV were administered SSP (1 mg/kg) and SSO (1 ml/kg) respectively orally daily for 30 days. The changes in the serum levels of insulin-like growth factor-I (IGF-I), IGF-II, insulin-like growth factor binding protein-3 (IGBP-3), estrogen, total alkaline phosphatase (TALP), bone-specific alkaline phosphatase (BALP), calcium and phosphorous in serum, and also histomorphology of the proximal tibia metaphysis and femur/body weight (F/B) ratio were examined in all the groups on post-treatment day 10, 20 and 30.

Results: Thirty days post-treatment, IGF-I, IGF-II, IGBP-3 and BALP levels were significantly increased ($p<0.05$) in group III and IV as compared with group I and II. There were no significant differences in serum levels of estrogen, TALP and F/B ratio between group II, III and IV, but estrogen levels were higher in group I. The trabecular bone volume in the proximal tibia metaphysis was gradually decreased in the rats of group II, whereas it was gradually increased in the animals of group III (SSP treated) and IV (SSO treated).

Conclusion: The SSP and SSO have similar effects in the protection of bones in osteoporosis induced- Ovx rats. Intake of SSP or SSO can be useful in preventing bone loss due to estrogen deficiency. However, further studies are needed for a clear understanding of their mechanism of action.

Keywords: Safflower seed, ovariectomy, IGF-I, IGF-II, IGBP-3, bone alkaline phosphatase.

PO-16

EFFECTS OF AMLODIPINE AND PERINDOPRILATE ON THE STRUCTURE AND FUNCTION OF MITOCHONDRIA IN VENTRICULAR CARDIOMYOCYTES DURING ISCHEMIA-REPERFUSION IN THE PIG

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Introduction: The aim of the present study was to determine whether amlodipine and/or perindoprilate injected intravenously (iv) prior to ischemia exerted protective effects on mitochondria structural and functional alterations induced by ischemia and aggravated by reperfusion.

Materials and Methods: Heart rate, the duration of monophasic action potentials (dMAP), the peak of the time derivative of left ventricular pressure (LV dP/dt max), mitochondria structural and functional parameters in the left ventricle ischemic area were measured after 45-min ischemia and 1-min reperfusion in domestic pigs either untreated or pretreated with amlodipine, perindoprilate or amlodipine + perindoprilate iv.

Results: Ischemia-reperfusion induced tachycardia, reduced dMAP and LV dP/dt max, and alterations of mitochondria structural and functional parameters with decreased oxygen consumption, increased reactive oxygen species production and reduced calcium retention capacity with opening of mitochondrial permeability transition pores. No drug treatment changed hemodynamic and electrophysiological parameters, but amlodipine and perindoprilate, either alone or combined, prevented mitochondrial alterations.

Conclusion: Amlodipine or perindoprilate pretreatment decreased all mitochondrial I/R lesions in this pig model. The calcium antagonistic properties of amlodipine and the prevention of NO synthesis reduction by both amlodipine and perindoprilate are suggested to account for these cardioprotective effects.

PO-128

ENANTIOSELECTIVE SYNTHESIS OF NEW SPIROOXINDOLOPYRROLIDINES USING CHIRAL CATALYST

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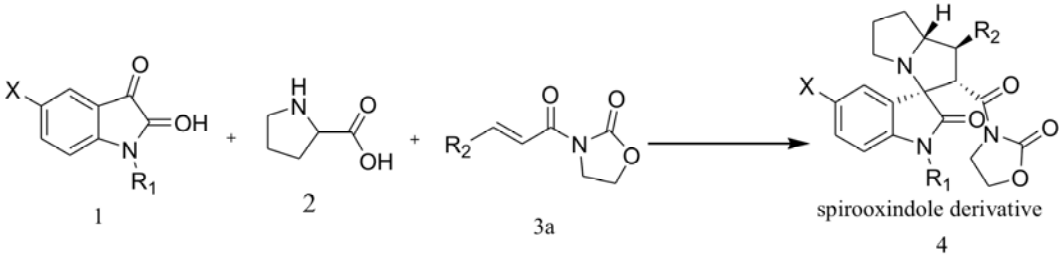
Spiro compounds are very important targets in medicinal chemistry because of their significant biological activities. In particular, spirooxindolopyrrolidine and their derivatives have served as potential synthetic intermediates and also act as antiviral, antitumor, antibiotic agents, local anesthetics, and inhibitors of human NK-1 receptor etc. Also some alkaloids and Gelsemine, formosanine, isoformosanine containing spiropyrrolidinloxindole-ring system [1-3].

The first report on catalytic highly regio-, diastereo-, and enantioselective synthesis of a small library of spiropyrrolizidineoxindoles via a four-component 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from in-situ from isatin 1 and S-proline 2 with electron-deficient dipolarophile was described. The process occurs at room temperature in aqueous ethanol as a green solvent and using 10 mol% [Cu $(OTf)_2$] complex as chiral catalyst. The reaction mechanism is discussed on the basis of the assignment of the absolute configuration of the cycloadducts.

Keywords: Chiral spiro-oxindolopyrrolizidines, Asymmetric 1, 3-dipolar, Chiral catalyst, bis (imine)–Cu (II) triflate, Azomethine ylide, Three-component reaction.



1 2 3a spirooxindole derivative 4

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PO-135

Track: *Oral Health*

REASONS FOR TOOTH EXTRACTION AND ORAL HEALTH RELATED FACTORS IN REFERRED PATIENTS IN MASHHAD SCHOOL OF DENTISTRY

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Introduction: Increasing of life expectancy giving more importance to keeping teeth, as extraction of permanent teeth in Iran is relatively high. This survey studied factors that effect on extraction of permanent teeth among patients referred to Mashhad Dental School in 2012.

Methods: 254 patients were selected in convenient Sampling manner and assessed for reasons of permanent tooth extractions, demographic characteristics, diseases, brushing, sugar intake and oral hygiene. Data were analyzed by SPSS11.5 software and Chi-Square, T-test, ANOVA and Non-Parametric tests.

Results: The mean age of the participants was 39±13.8 years. The most common cause of extraction was caries (55.1%). Women in compared with men had lower mean age, more frequencies of brushing, better oral hygiene, but there was no different in daily sugar intake. Caries and periodontal causes were associated with higher age and less frequency of brushing. Higher education was associated with high frequency of brushing and good oral hygiene, but no associating with daily sugar intake.

Conclusion: Although economic factors and lack of insurance coverage were expressed as important factors for teeth extraction, this study showed that people with the lower education, had the lower oral hygiene and brushed less frequently, that both of them showed the need for informing and health educating. In women despite the brushing more frequently and having better oral health, the age of referring extraction was lower, this suggests other reasons.

Keywords: Teeth Extraction, Caries, Oral Health, Demographic Characteristics.

PO-89

BEE VENOM OF THE HONEY BEE (*APIS MELLIFERA*) THERAPY IN EXPERIMENTAL CANINE STIFLE OSTEOARTHRITIS

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This study evaluated the therapeutic effects of the phytomedicine, bee venom (BV) of the honey bee (*Apis mellifera*) for the treatment of experimental stifle osteoarthritis (OA) in 24 skeletally mature mixed small breed dogs (age 2 to 6 years, weight 2.8 to 9 kg). One year after induction of OA, the animals were randomly allocated in 2 groups; the EACP-group received 10% solution of EACP 0.5 ml plus 0.2 ml lidocaine; and the BV-group received 10% solution of BV 0.5 ml plus 0.2 ml lidocaine intraarticularly twice in a week in the OA-induced stifles for one month. The joint tissue specimens, synovial fluid (SF) and blood samples were collected prior to and 12 months after induction of OA, and one month posttreatment. TRAP levels in SF and serum were measured using a spectrophotometer, and TRAP-positive cells in joint tissues were identified by enzyme histochemistry. TIMP-2 in SF and serum was detected by ELISA. Histochemistry revealed an increased number of TRAP positive cells in tissues from OA-affected joints which was decreased after one month treatment with BV and EACP. After one-month administration of EACP and BV, the levels of TRAP in SF of the index stifles as well as that in the serum were significantly decreased ($p<0.05$), whereas, the levels of TIMP-2 in SF of the index stifles as well as that in the serum were increased indicating the therapeutic effects of the EACP and BV on improvement of the conditions of OA. The intraarticular administration of EACP and BV were found effective for the treatment of OA in the dog.

Keywords: Osteoarthritis, Bee venom, TRAP, TIMP-2, Dog.

PO-64

Track: *Drug Discovery in Preclinical Research*

IN-VITRO BIOASSAY OF 1, 5 - DIMETHYL CITRATE MONOHYDRATE; A COMPOUND ISOLATED FROM THE FRUIT OF MANGIFERA INDICA (ANACARDIACEAE)

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In this study, an *in vitro* bioassay of 1, 5-dimethyl citrate monohydrate was carried out; 1,5-dimethyl citrate monohydrate is a hydrated citric acid derivative with molecular formula C8H12O7.H2O isolated from Mangifera indica fruit. To support the hypothesis that the compound may have effect on smooth muscles; the activity of this pure compound on the longitudinal smooth muscles of isolated guinea pig ileum, rabbit jejunum and guinea pig trachea was determined. Graded doses of the compound (0.5mg/ml and 1mg/ml) showed a dose dependent increase in contraction of the longitudinal smooth muscle of the isolated guinea pig ileum similar to histamine and this contraction was antagonized by mepyramine. The compound was thus speculated to be a histaminergic agonist who acts on the H1 histamine receptors found on smooth muscles. Activation of these H1 receptors in smooth muscle cells causes an increase in phosphoinositol hydrolysis and increase in intracellular calcium which brings about contraction of intestinal smooth muscle. The compound however at a concentration of 1mg/ml produced no remarkable effect on the rabbit jejunum. Since the compound didn't produce any remarkable effect on the rabbit jejunum, it is possible to speculate that the compound 1,5- dimethyl citrate monohydrate at 1mg/ml does not activate the cell specific receptors on the smooth muscles neither does it interact with voltage operated Ca2+ channel. The compound also at a concentration of 5mg/ml produced no appreciable response on guinea pig trachea. This suggests that the compound may not interact with the receptors present to cause any remarkable response.

PO-12

Track: *Drug Delivery & Targeting*

ENHANCING THE SOLUBILITY AND BIOAVAILABILITY OF ANTI CANCER FLAVONOID NARINGENIN UTILIZING SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS)

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The flavonoid aglycone Naringenin, present in grapefruits, possesses anti-inflammatory, anti-carcinogenic, hepato-protective and anti-lipid peroxidation effects. The therapeutic applications of Naringenin are limited because of poor solubility in water leading to slow dissolution after oral ingestion. Its bioavailability is only 5.8% in humans following oral administration. The study is an attempt to improve the solubility and permeability of Naringenin by employing self nano emulsifying drug delivery technique. SNEDDS comprising Triacetin, Tween 80 and Transcutol HP, in the ratio of 30:50:20 were developed by water titration method employing constructing pseudo-ternary phase diagrams. These are evaluated in term of size, polydispersity index, and surface morphology of nanoemulsions so obtained. Everted rat gut sac method was used to study the effect of nanodrug carriers on drug release and permeability. The TEM analysis proves that nanoemulsion shows droplet size between 20-100 nm. The SNEDDS showed a significant increase in drug release and permeability as compared to drug suspension which may be attributed to the nanosized droplets and enhanced solubility of Naringenin in the SNEDDS.

PO-115

Track: *Regenerative Medicine*

ACCELERATION OF LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN RATS SUPPLEMENTED WITH BETAINE

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The liver has a remarkable capacity to regenerate itself after injury. Our previous work suggests that hepatic S-adenosylmethionine (SAM) level critically influences the liver regenerative process via regulation of polyamine metabolism. In this study we examined the progression of liver regeneration in the rats treated with betaine, a methyl donor that is known to enhance the generation of SAM in liver. Male rats were provided with betaine (1 %) in drinking water following two-thirds partial hepatectomy (PHx). An additional group of rats received betaine from 2 week prior to the surgical treatment. Liver weight growth was significantly greater in the rats treated with betaine than the control rats from Day 2 after the surgery. The betaine-treated rats retrieved the liver weight fully on Day 7, while the liver weight in the control rats reached 80% of the normal liver. Expression of proliferating cell nuclear antigen was significantly greater in the betaine-treated rats at 24 and 48 h following PHx. Induction of cyclin D1 expression was also accelerated by betaine administration. Major metabolites/products in the transsulfuration reactions including methionine, SAM, cysteine, glutathione, and taurine were all increased by PHx. Among the changes in the sulfur-containing substances, the increases in methionine and SAM levels were intensified significantly in the rats provided with betaine. The surgical treatment elevated putrescine and spermidine, but decreased spermine levels in the remnant livers. Betaine administration markedly enhanced the elevation of hepatic putrescine and spermidine levels. The results indicate that betaine is capable of accelerating the liver regenerative process, most probably *via* elevation of hepatic SAM, a metabolic substrate for polyamine synthesis. It is suggested that betaine may be useful as a therapeutic liver-regenerating agent, which promotes improvement or normalization of hepatic functions both in the remnant liver and in the transplanted liver.

Keywords: Betaine, liver regeneration, S-adenosylmethionine, polyamines.

PO-7

CARDIAC MYOSIN SWITCHING AND MIKRORNAS IN HUMAN END-STAGE FAILING HEART

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Heart failure is a clinical syndrome (not a single disease) that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. Even with the very best of modern therapy, however, heart failure is still associated with an annual mortality rate of 10%. The search for better treatments of heart failure is one of the major challenges in cardiology. New treatments that target disease mechanisms at the molecular/cellular and whole-organ level are needed to halt and reverse the devastating consequences of this disease.

The aim of our work was to focus on molecular potential biomarkers of heart failure and description of their relationship to selected clinical parameters and to cardiac injury in explanted human hearts. We have focused to analyse of "cardiac myosin switching" *via* gene expression of myosin heavy chain isoforms and role of microRNAs in failing hearts. In the heart, three distinct isoforms MYH6, MYH7, MYH7B coexist in delicate balance. As has been recently shown, the shift from one myosin isoform to other may be one of key factors causing heart failure.

Patients with terminal-stage heart failure (n=41), indicated for heart transplantation in The National Institute of Cardiovascular Diseases, Bratislava. The follow clinical data from hospital records we collected: age, sex, BMI, blood pressure, type of heart failure (DCM, CAD, RCMP, AS, ECG, ECHO catheterization data, serum biochemistry, coexisting and pharmacotherapy. We examined samples from left ventricles of 41 patients with end-stage heart failure indicated for heart transplantation and five controls. We used quantitative RT-PCR to measure mRNA levels of cardiac myosin heavy chain isoforms (MYH6, MYH7, MYH7B), related transcription factors (GATA4, SRF, NKX-2.5, YY1,

SOX6) and microRNAs (miR-1, -133a, -29b) and miR-208a is expressed from an intron of MYH6, miR-208b from an intron of MYH7, and miR-499 from an intron of MYH7B), based on bioinformatic predictions and databases.

In adult human failing hearts, we found the slow-twitch myosin heavy chain MYH7 (~98%) to be the predominantly expressed isoform whereas fast-twitch MYH6 isoform constitutes just about 1% of all myosin isoforms. This excessive expression of MYH7 is regulated by several transcription factors and microRNA, The increase expression of miRNA-208a and miRNA 208b has no correlation with expression contractile apparatus of the heart – cardiac myosin switching. miR-1 and miRNA-133a seems to be in close relation with other cardiac microRNA included in this study. The consequent change from fast-twitch alpha-isoform to the slow-twitch beta-isoform (known as myosin switching) could be one of the main causes of heart failure. Expression of myosin heavy chain isoforms is regulated through a complex net of relationships between MHCs – transcription factors – epigenetic modulators – microRNAs.

Conclusively, dysregulated gene expression of myosin heavy chains resulting in MYH7 upregulation and MYH6 downregulation might be an adaptation in heart failure and interesting target for future pharmacotherapy.

PO-25

Track: *Diabetes and Obesity Drug Discovery & Therapy*

EFFECT OF ASTAXANTHIN ON THE EXPRESSION OF PPARγ: A *IN VITRO* STUDY

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Peroxisome proliferator-activated receptor gamma (PPARγ) is important for the regulation of insulin sensitization. Astaxanthin has been reported to lower insulin resistance in animal model of diet-induced obesity. The aim of this study was to evaluate the effect of astaxanthin on the expression of PPARγ *in vitro*. 3T3-L1 cell was used to be the tested cell model. In part I study, different concentrations of astaxanthin (0.01-10 mg/mL) were prepared for the MTT assay and to evaluate the cell viability. In part II study, different concentrations of astaxanthin (20 μg/mL-20 mg/mL) were prepared for the PPAR ELISA and to measure the ability of astaxanthin to activate the PPARγ. Results showed that the cell viability was enhanced in astaxanthin concentrations between 0.01-10 mg/mL. Astaxanthin activated the expression of PPARγ significantly in 3T3-L1 cell under the concentration of 10 and 20 mg/mL. The PPARγ stimulation index at 10 and 20 mg/mL is 3 and 5 times compared to positive control group. We concluded that astaxanthin may have the potential to activate the PPARγ in the 3T3-L1 cell model. Further animal or human studies are needed to make sure the biological effect of astaxanthin on the PPARγ.

Keywords: Astaxanthin, PPARγ, 3T3-L1 cell.

PO-100

Track: *Inflammation and Immunology*

IMMUNOSUPPRESSIVE EFFECT OF CARYOPHYLLATA FLOS AND ITS ACTIVE COMPOUND ON DENDRITIC CELL ACTIVATION AND FUNCTION

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Caryophyllata Flos, dried flower buds of Eugenia caryophyllata Thunb. Which belong to the family Myrtaceae is widely applied to Chinese medicine? It has been reported to have an activity of asthma and allergic relief. However, the molecular and cellular mechanisms of the immune response remain unclear. Especially, the critical compounds contribute the effect on dendritic cell (DC), a critical role in regulation of innate and adaptive immunity is still unknown. In this study, the effects of methanolic extract and the major compound eugenol of Caryophyllata Flos on DC activation. Our results clearly showed that methanolic extract and eugenol decreased the production of cytokines (IL-12 and IL-6) in a dose-dependent manner in LPS-induced DCs and inhibited LPS-induced DC maturation as the expression levels of MHC class I, MHC class II and costimulatory molecules on LPS-induced DCs were decreased. In addition, contact

hypersensitivity responses were inhibited in mice cosensitized with the methanolic extract or eugenol. Therefore, we demonstrate for the first time that the Caryophyllata Flos and its active ingredient eugenol exhibit an immunosuppressive effect on DC function.

Keywords: Dendritic cell, immunosuppressive, contact hypersensitivity, Caryophyllata Flos, eugenol.

PO-39

Track: *Anti-Infective*

EFFICACY AND SAFETY OF POLYMYXINS FOR THE TREATMENT OF *ACINECTOBACTER BAUMANNII* INFECTION: A META-ANALYSIS

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Multi-drug resistance among *Acinetobacter baumannii* increases the need for polymyxins. We conducted a meta-analysis aimed to assess the efficacy and safety of polymyxins for the treatment of *Acinetobacter baumannii* infection.12 controlled studies, comparing 677 patients, were included. Although clinical (odds ratio 1.421, 95%CI 0.722-2.797) and microbiological (OR 1.416, 95%CI 0.369-5.425) response rates favored the polymyxins group, these differences were not significant. Treatment with polymyxins *vs.* controls did not affect hospital mortality (OR 0.506, 95%CI 0.101-2.536), lengths of hospital stay SMD-0.221, 5%CI -0.899-0.458) or nephrotoxicity (OR1.192, 95%CI 0.436-3.261). The combination of polymyxins with other antibiotics achieved similar clinical response rates to its monotherapy regimen (OR0.601, 95%CI 0.320-1.130). Our results suggest that polymyxins may be as safe and as efficacious as standard antibiotics for the treatment of *Acinetobacter baumannii* infection. There is no strong evidence that combination regimen of polymyxins is superior to monotherapy.

Keywords: Polymyxins, *Acinectobacter baumannii*, infection, meta-analysis.

PO-118

Track: *Traditional Chinese Medicine*

CHEMICAL CONSTITUENTS FROM PLEIONE BULBOCODIOIDES

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The tubers of Pleione bulbocodioides（Franch.）Rolfe have been used in Chinese medicine as anti-cancer and anti-bacteria agents. A number of stilbenoids have been isolated from *P. bulbocodioides*, and various biological activities, such as antimicrobial and antiallergic activities have been reported. During our search for anticancer compounds from Chinese herbal medicine, we investigated the constituents of *P. bulbocodioides*, which led to the isolation of seven phenolic compounds by repeated column chromatography with silica gel、Sephadex LH-20 and ODS-HPLC. Their structures were elucidated by analysis of spectroscopic data (1H-NMR, 13C-NMR, 2D-NMR, HR-MS) as bulbocol (1), Kayaflavone (2), coelonin (3), 4-Oxopentanoic acid (4) β-daucosterol (5), 3-hydroxybenzcic acid (6), 5-hydroxymethyl furfural (7). Compounds 2, 4, 5, 6, 7 were isolated from the plants of *Pleione bulbocodioides* for the first time, and two of them showed moderate cytotoxic activity against the LA795 tumor cell line.

Keywords: *Pleione bulbocodioides*, Chemical constituents, Stilbenoids.

PO-42

Track: *Cardiovascular Drug Discovery & Therapy*

INFLUENCE OF BOTH NMDA AND NON-NMDA GLUTAMATE RECEPTORS ON THE CARDIOVASCULAR RESPONSE OF THE L-PROLINE INTO THE PARAVENTRIULAR NUCLEUS OF RATS

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L-Proline (L-Pro) shares a number of properties with recognized neurotransmitters and has been postulated to be involved in the cardiovascular control. In the present study we characterized central mechanisms involved in the cardiovascular responses evoked by the injection of L-Pro into the paraventricular nucleus (PVN). Guide cannulas were implanted into the PVN. Polyethylene catheter was introduced into the femoral artery for mean arterial pressure (MAP) and heart rate (HR) recordings. Pretreatment with aCFS did not affect the pressor (ΔMAP= 28.0±1.8mmHg *vs* 27.1±2.6mmHg) and bradycardic responses (ΔHR=-57.0±6.5bpm *vs* -50.5±3.2bpm) to the microinjection of 33nmol/100nL L-Pro into the PVN. The local pretreatment with increasing doses of the selective non-NMDA receptor antagonist NBQX inhibited the pressor (r^2=0.87) and bradycardiac (r^2=0.89) responses to the microinjection of L-Pro into PVN of unanesthetized rats, in a dose-related manner. Similarly, the local pretreatment with crescent doses of the selective NMDA receptor antagonist LY235959 also blocked the pressor (r^2=0.94) and bradycardiac (r^2=0.87) responses to the microinjection of L-Pro into PVN of unanesthetized rats, in a dose-related manner. The ID50 for NBQX was approximately 1nmol/100nL, while for LY235959 was approximately 0.05nmol/100nL, thus indicating that LY235959 was at least 20 times more potent than NBQX to inhibit the pressor and bradycardiac responses to the microinjection of L-Pro into the PVN. These results suggest L-Pro acts on specific prolinergic receptors which are sensitive to the NMDA and non-NMDA antagonists. FAPESP2010/11303-6.

PO-110

ASSESSMENT OF KNOWLEDGE, ATTITUDE AND PRACTICE OF COMMUNITY PHARMACIST TOWARDS PHARMACEUTICAL CARE IN KADUNA STATE, NORTH WESTERN NIGERIA

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This study evaluates pharmaceutical care services in community pharmacies in Zaria and Sabon gari local government areas of Kaduna State. The main objective is to assess the knowledge, attitude and practice of community pharmacist towards pharmaceutical care. The research employed the use of a self-administered questionnaire which was constructed based on pharmaceutical activities, dispensing, interprofessional relationship, practice standards and barriers to its implementation. A total of forty (40) registered community pharmacists were employed for the study. Data collected were subjected to statistical analysis using simple percentages, cross tabulations and frequency distribution. 32(80%) of the respondents believed that dispensing of medication only is pharmaceutical care while 26(65%) believed that pc is a mandate of pharmacists only.14 (35%) normally collect data from their patients and only one out of seventeen that had reported cases of ADR's completed med watch report. Lack of pharmacists access to full medical records received 80% response, poor relationship with other healthcare providers received 82.5% response, and lack of confidence of community pharmacists 55%. Lack of trained personnel and support staffs 75%. These were the identified barriers to implementation of pharmaceutical care. Pharmacists in the study area have positive attitude with limited knowledge on pharmaceutical care. They are somewhat distant from the practice of pharmaceutical care.

Keywords: Attitude, knowledge, community pharmacists, pharmaceutical care.

PO-40

Track: *Anti-Infectives*

METHYL PANTOTHENAMIDES ARE POTENT ANTIPLASMODIAL AGENTS RESISTANT TO PANTETHEINASE-MEDIATED DEGRADATION

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Background: Novel antimalarial chemotherapies are desperately needed since the most virulent parasite that causes malaria in humans, *Plasmodium falciparum*, has become resistant to all drugs in use. The pipeline for erythrocytic-stage antimalarials is robust. However, most such compounds target the same parasite pathways and/or molecules and are based on limited chemical scaffolds. This study investigated the antiplasmodial activity of pantothenamides (pantothenate amide analogues) aiming to identify more potent compounds than previously reported counterparts under standard parasite growth conditions with pantetheinase activity - the activity of enzymes that hydrolyze pantetheine (a pantothenate metabolite) and also degrade pantothenamides.

Methods: Pantothenamides were prepared following previously described methods and modified with introduction of methyl groups on the *alpha* or *beta* position of the core structure (β-alanine moiety). The compounds were then tested *in vitro* against *P. falciparum* 3D7 using the SYBR-green fluorescence assay.

Results: The small modifications of pantothenamides were sufficient to confer resistance to pantetheinase-mediated degradation and improve antiplasmodial potency by more than 880-fold, reaching sub-micromolar IC_{50} values. The modified compounds continued to inhibit parasite proliferation by targeting pantothenate-dependent processes.

Conclusions: Pantothenamides modification markedly improves antiplasmodial potency and provides further support for exploiting pantothenate utilization as an attractive target in antimalarial drug discovery.

PO-35

Track: *Anti-infectives*

THE ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF THE ESSENTIAL OIL OF LAWSONIA INERMIS HENNA - *IN VITRO*

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Lawsonia inermis Linn, known as “Henna” is traditionally used as a cosmetic and for its medicinal virtues especially in the treatment of infectious diseases. Our work was studying antibacterial and antifungal activities of the essential oil from the leaves of this plant; it was obtained by steam distillation ten bacterial strains, three yeast were selected for the evaluation of antimicrobial activity, determination of MIC and MFC by the method of diffusion in a solid medium.

A very compelling activity appeared on all species tested, including strains resistant to antibiotics, and frequent infections in hospital as *Acinetobater baumannii* and *Pseudomonas aeruginosa* MRSA.

The use of this oil rich on volatile substances is recommended for sanitation system air treatment in hospital by micronization in air conditioning systems in operating rooms, clinical and cleanroom.

PO-102

Track: *Pharmaceutical Research & Development*

IDENTIFICATION OF TWENTY PHOSPHODIESTERASE-TYPE 5 ENZYME (PDE-5) INHIBITORS USING GAS CHROMATOGRAPH-MASS SPECTROMETRY

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Phosphodiesterase type-5 enzyme (PDE-5) inhibitors are drugs used in the treatment of erectile dysfunction. PDE-5 inhibitors such as sildenafil, tadalafil, vardenafil and their banned analogues have been found adulterated in health products such as herbal preparations, dietary supplements and food products that claim to have natural aphrodisiacs. New analogues have been synthesized and growing rapidly. Due to their natural origins, these health products are often perceived to be safe and therefore their uses have becoming popular globally. PDE-5 inhibitors can cause adverse health effects such as back pains, headaches, nasal congestion, dyspepsia, myalgia, flushing and limb pains. These drugs are commonly identified using liquid chromatography-mass spectrometry (MS) or -tandem mass (MS/MS). In this study, a gas chromatography-mass spectrometry (GC-MS) assay was developed for the identification of twenty PDE-5 inhibitors. A very small amount of sample (50 mg), good chromatographic separation and no sample clean-up was required prior to GC-MS analysis thus making the assay a fast and cost effective assay. The assay is also sensitive and selective as the identification the PDE-5 inhibitor was based on characteristic mass fragmentation ions. We also found the precursors for the screening of sildenafil and vardenafil analogues in health product matrices. The developed assay was validated using thirteen PDE-5 inhibitors for linearity, within- and between assays accuracies and precisions, limit of quantitation, limit of detection, and recovery. The application of the developed assay had shown that most of the herbs and food products in Malaysian market that claimed to promote men health were adulterated with PDE-5. Similar trends are observed in other countries. Regular monitoring and surveillance works are required to check the health products as well as public educations. Collaboration and exchange of information among health regulators, academicians, researchers and industries are crucial to stem the fast growing adulteration by PDE-5 inhibitors.

Keywords: PDE-5 inhibitors, Sildenafil, vardenafil, tadalafil and analogues, GC-MS, herbal preparations, food products.

PO-32

Track: *Anti-infectives*

IN VITRO SIGNIFICANT REDUCTION IN BIOFILM SYNTHESIS IN *PSEUDOMONAS AERUGINOSA* POST MICAFUNGIN TREATMENT AT A TERTIARY CARE CENTER

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Background: *Pseudomonas aeruginosa* is an opportunistic pathogen, considered to be the leading cause of nosocomial infections in immunocompromised patients. It has the ability to produce biofilms which confer antimicrobial resistance. In this study we are assessing the effect of Micafungin on biofilm formation in *P. aeruginosa* since it has in its cell wall 1,3-β-D-glucan, an essential glucose polymer, similar to that of *C. albicans*, which synthesis is blocked by Micafungin.

Methods: Eighteen *P. aeruginosa* isolates from patients with nosocomial infections were used. Biofilm production was confirmed using adherence testing to polystyrene microtiter plates. The effect of Micafungin (10 mg/ml) on *P. aeruginosa* biofilm producing cells was assessed *in vitro*. RNA extraction followed by c-DNA synthesis was done. qRT-PCR for selected biofilm encoding genes to determine the relative gene expression levels was performed. These consisted of alginate encoding gene, *algC*, pellicle encoding gene, *pelC* , and 1,3-β-D-glucan encoding gene, *ndvB*. Relative gene expression of *algC*, *pelC* and of *ndvB* was done on isolates showing phenotypic reduction in biofilm synthesis.

Results: Reduction in biofilm synthesis was significant in 13 (72.2 %) out of 18 isolates grown on microtiter plates upon the addition of Micafungin. The OD within the remaining 5 isolates did not show a significant change between untreated and treated wells of the same isolate. The relative expression of *algC, pelC* and *ndvB* genes was significantly decreased in all tested isolates as compared to untreated isolates.

Conclusion: Reduction in biofilm formation in *P. aeruginosa* isolates tested highlights the importance of Micafungin in treating biofilm producing *Pseudomonas* infections. Studies assessing the effect of Micafungin *in vivo* using mice model are underway. Future work will focus on the translational and post-translational modifications to establish a cause-and-effect relation between the observed decreased expression levels of the genes and their corresponding proteins.

PO-49

Track: *Chemistry*

NON-NUCLEOSIDE INHIBITORS OF NS5B POLYMERASE DERIVED FROM THE NATURALLY OCCURRING AURONES: POTENTIAL AGENTS AGAINST HEPATITIS C VIRUS INFECTION

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Hepatitis C virus (HCV) infection is a global public health problem. The World Health Organisation (WHO) estimates that 170 million people are infected worldwide. The current therapeutical treatments consist of a combination of pegylated interferon alpha (peg-IFN) and Ribavirin (RBV). Unfortunately, the response rate is low, especially among patients infected by HCV genotype 1, the most frequent genotype. The HCV RNA-dependent RNA polymerase NS5B constitutes an interesting target because of its key role in viral replication and being not functional in mammalian cells.We recently identified through a screening process that the naturally occurring 2-benzylidenebenzofuran-3-ones, namely (aurones) as new inhibitors of NS5B. The aurone active site, identified by site-directed mutagenesis, is located in Thumb Pocket I of HCV RdRp. Molecular docking studies were used to determine how aurones bind to NS5B and to predict their range of inhibitory activity. Several aurones were found to have potent inhibitory effects on HCV RdRp, with excellent selectivity index (inhibition activity versus cellular cytotoxicity). More very recent promising results obtained on aurones dimers will be presented. The potent NS5B inhibitory activity combined with their low toxicity make aurones attractive drug candidates against HCV infection.

Keywords: Aurones dimers, inhibition, NS5B, HCV, organic synthesis.

PO-130

Track: *Hot Topic in Natural Products*

ENDOPHYTES- A TREASURE OF BIOACTIVE COMPOUNDS

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Throughout the ages humans have relied on Nature to cater for their basic needs, not the least of which are medicines for the treatment of a wide spectrum of diseases. However; increasing number of pathogenic microorganisms and emerging new diseases has necessitated the search for novel chemical entities with improved antimicrobial properties. Among natural sources, plants are valuable sources, but microorganisms are exemplary in production of pharmaceutically useful compounds. The most recent of such exciting discoveries have originated from microorganisms living in unusual ecological niches such as endophytic microorganisms. These are microorganisms that reside asymptomatically in the tissues of higher plants and are relatively unstudied and a promising source of pharmaceutically important metabolites. Northern areas of Pakistan have rich biodiversity of *Taxus* species. Endophytic fungi isolated from indigenous species of *Taxus baccata* have been grown on different culture media both solid and liquid, crude extracts obtained have been screened in various biological assays. These extracts have shown promising activities in antibacterial, antifungal,

antioxidant and especially in antileishmanial assay. Cytotoxcity of the crude extracts has been evaluated by brine shrimp assay. These preliminarily studies will serve as a foundation for formulating drugs effective against disease like leishmaniasis. It will also be helpful in preserving flora of the region and stabilizing the economy of the country through local as well as global commercialization of the compounds of pharmaceutical importance.

PO-74

Track: *Radiotargeted Therapy*

PRECLINICAL EVALUATION OF HOLMIUM-166 LABELLED ANTI-VEGF-A (BEVACIZUMAB)

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Radiolabeled antiangiogenic monoclonal antibodies are potential agents for targeted therapy in specific types of malignancies. In this study, 166Ho-DOTA-Bevacizumab was used in biodistribution studies using SPECT to acquire dosimetric aspects of the radiolabeled antibody in mice. The liver toxicity of the radiolabeled antibody was also determined using SGPT, SGOT and Alkaline phosphatase assay 2-7 days post injection.

The SPECT biodistribution demonstrated a similar pattern as the other radiolabeled anti-VEGF-A immuno-conjugates.166Ho-DOTA-Bevacizumab was revealed as a potential compound for therapy/imaging of VEGF-A expression in oncology.

Keywords: Holmium-166, bevacizumab, radiolabeling, conjugation, biodistribution.

PO-73

Track: *Pharmaceutical Biotechnology*

PREPARATIVE MICROBIOLOGICAL SYNTHESIS OF HIHGLY DEUTERATED [2H] INOSINE BY GRAM-POSITIVE CHEMOHETEROTROPHIC BACTERIUM BACILLUS SUBTILIS B-3157 ON HEAVY WATER ($2H_2O$) MEDIUM

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Natural nucleosides labeled with deuterium (^2H) are of considerable interest for various biochemical and diagnostic purposes, structure-function studies, and research of cell metabolism. In particular, deuterated ribonucleosides and their analogs are used in template-directed syntheses of deuterated RNA molecules for studying their spatial structure and conformational changes.

We have applied an aerobic Gram-positive chemoheterotrophic bacterium Bacillus subtilis B-3157, polyauxotrophic for histidine, tyrosine, adenine, and uracil (demand, 10 mg/l), for preparative microbiological synthesis of purine ribonucleoside [^2H]inosine (output, 3.9 g/l of liquid microbial culture (LC). The initial bacterium was adapted to deuterium by plating individual colonies onto 2% (w/v) agarose growth media with stepwise increasing gradient of ^2H_2O concentration (from 0 up to 98 (%,w/w) $2H_2O$) and subsequent selection of individual cell colonies stable to $2H_2O$. After that procedure the bacterium was grown on heavy water (HW) medium with high degree of deuterium content (99.8 atom% ^2H) containing 2% (v/v) hydrolysate of deuterated biomass of the methylotrophic bacterium Brevibacterium methylicum B-5662 as a source of ^2H-labeled growth substrates, obtained on minimal M9 growth medium with 98% (v/v) $2H_2O$ and 2% (v/v) [^2H] methanol. The composition of HW growth medium (%, w/v): glucose - 12, hydrolysate of deuterated biomass of *B. methylicum* - 2; NH_4NO_3 - 2; $MgSO_4$ $7H_2O$ - 1; $CaCO_3$ - 2; adenine - 0,01, uracil - 0,01. Bacteria were grown in 500 ml Erlenmeyer flasks (containing 100 ml of the growth medium) for 3-4 days at 32°C under intensive aeration on an orbital shaker. The maximal output of inosine in LC (17 g/l) was observed on protonated growth medium at a glucose assimilation rate 10 g/l. The output of inosine on the HW medium decreased in 4.4-fold, reaching 3.9 g/l, and the level of glucose assimilation - 4-fold, as testified by the remaining 40 g/l of non-assimilated glucose in

LC. This demonstrates that glucose is less efficiently assimilated on HW medium as compared to the control conditions in H_2O.

[^{2}H] inosine was isolated from LC by consecutive adsorption/desorption on activated carbon as adsorbent at 4°C with following desorption of total ribonucleosides with EtOH-NH_3-solution at 60°C, extraction of [^{2}H]inosine with 0.3 M ammonium-formate buffer (pH = 8.9), subsequent crystallization in 80% (v/v) ethanol, and ion exchange chromatography on a column with AG50WX-4 cation exchange resin equilibrated with 0.3 M ammonium-formate buffer and 0.045 M NH4Cl under isocratic conditions (chromatographic purity, 92%). The presence of major absorbance band, corresponding to natural inosine (λmax = 249 nm, ε249 = 7100 M-1 cm-1), and the absence of secondary metabolites in the analyzed sample, demonstrates the homogeneity of isolated product and the efficiency of the isolation method. ^{2}H-inosine: output, 3.1 g/l (80%); Tm = 68-70°C; [a]D20 = 1.61 (ethanol); Rf = 0.5; pKa = 1.2 (phosphate buffer with pH = 6.87). UV-spectrum (0.1 N HCl): λmax = 249 nm; ε249 = 7100 M-1 cm-1. FAB mass spectrum (glycerol matrix, Cs+; accelerating voltage, 5 kV; ion current, 0.6-0.8 mA): [M + H]+ m/z (I, %) 273, 20% (4 atoms ^{2}H); 274, 38 % (5 atoms ^{2}H); 275, 28% (6 atoms ^{2}H); 276, 14% (7 atoms ^{2}H); [A + H]+ 136, 46%; [B + H]+ 138, 55%; [B - HCN]+ 111, 49%; [B - HCN]+ 84, 43%.

The evaluation of the level of deuterium enrichment, performed by FAB mass spectrometry, demonstrated incorporation of 5 deuterium atoms into the inosine molecule (the total level of deuterium enrichment - 65.5 atom% ^{2}H); 3 deuterium atoms were included into the ribose and 2 deuterium atoms - into the hypoxanthine residue of the molecule.

Keywords: ^{2}H-labeled inosine, microbiological synthesis, FAB-mass spectrometry; heavy water, *Bacillus subtilis.*

PO-47

Track: *Chemistry*

FUNCTIONALIZED MESOPOROUS SILICA NANOPARTICLES TARGETED FOR APPLICATION IN NANO-BIOTECHNOLOGY

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Because of the good control of the particle size, morphology, uniformity thus large specific surface area of mesoporous silica nanoparticles (MSN) provides for large adsorption capacities interesting for biotechnology, also biomedicine.

This work demonstrates the application of a delivery strategy prodrug using mesoporous silica nanoparticles. Our effort primarily is addressed to modify the surface of mesoporous silica nanoparticles by the grafting of organic products: caffeic acid and madecassic acid to show their biocompatibility.

The use of the cell line $CaCO_2$ in the cell viability test, and the test of measurement of oxidative stress shows the protective effect of the mesoporous silica nanoparticles.

Keywords: Nanoparticles, mesoporous silica, oxidative stress, cell viability test.

PO-101

Track: *Nutraceuticals*

DEVELOPMENT OF STABILIZED MUCO ADHESIVE TABLETS FOR BUCCAL DELIVERY OF CURCUMIN

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Curcumin (cur), a natural compound elicit a spectrum of potent responses both locally and systemically. However its local effect in buccal conditions is largely hindered by its extremely limited water solubility, and its hydrolytic degradation in salivary pH. The aim of the present study was to develop buccal muco adhesive tablets of cur with accepted release and stability at salivary pH as well as to design a simple in vitro dissolution test ensuring its stability. Chemical stability in phosphate buffer saline(PBS) pH 6.8 was tested using a group

of stabilizers of which sodiumlauryl sulfate (SLS) proved to be the most suitable. Different Mucco adhesive tablets formulations were prepared by direct compression technique using a mixture of ydroxypropylmethylcellulose (HPMC)K15M and Carboxymethyl celluose sodium (NaCMC) in different ratios with or without SLS as stabilizer, curas pure untreated drug or in the form of rapidly dissolving solid dispersion(SD) with PVP (Kollidon®25). Formulations were evaluated for muco adhesive strength, *in vivo* and *in vitro* residence time, release studies and clinical evaluation of the selected formulation. The best muco adhesive performance and *in vitro* sustained release profile (70% released over 12 hours) were exhibited by tablets containing HPMC.K15M: CMC sodium (5:1), SD (1:3) with 15 mg SLS .Salivary concentration (conc) was significantly increased compared to undetectable conc for pure cur due to poor solubility and SD without SLS due to hydrolytic degradation. Preliminary clinical study revealed an excellent anti-inflammatory and healing effect. Cur in this delivery system is an excellent candidate for local buccal delivery.

PO-4

Track: *Anti-Cancer Drug Discovery & Therapy*

INVESTIGATION OF COMPOUNDS WITH CYTOTOXIC ACTIVITY IN *CARICA PAPAYA* LEAVES

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In traditional medicine, various parts of *Carica papaya* such as leaves, bark, roots, latex, fruits, flowers and seeds have been used for a wide range of therapeutic applications. *Carica papaya* leaves have been reported to possess healing capabilities against cancer in an increasing number of anecdotal reports. Therefore, we investigated the cytotoxic activities as well as the chromatographic profiles of different extracts from *Carica papaya* leaves in order to detect bioactive compounds with anticancer activities. Assessment of cell death using a validated MTT assay indicated that all studied extracts affected the viability of human oral squamous cell carcinoma (SCC25) cells. Ultra High Performance Liquid Chromatography-Quadrupole Time of Flight Mass Spectrometry was used to acquire chromatographic profiles and mass spectra with high mass accuracy and sensitivity. A list of the features found to be similar in all the extracts was explored to generate putative molecular formulae of potential therapeutic compounds. Further work, including confirmation viaauthentic standard comparison and tandem mass spectrometry, as well as cytotoxicity studies of pure compounds will confirm the identity and the therapeutic activities of the bioactive compounds in *Carica papaya* leaves.

PO-68

Track: *Innovative Drug Discovery and Nanotechnology*

NEW ANTIOXIDANTS IN THERAPY OF NEURODEGENERATIVE DISEASES TESTED IN ANIMAL MODELS

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Neurodegenerative diseases, accompanied by cognitive disturbances, i.e. gradual memory loss (dementia), are characterized by late onset, relentless progression, and finally death. Molecular-genetic studies of the human genome have emphasized the evolutionary conservation of homologous genes from different organisms. Drosophila mutants with phenotypes similar to neurodegenerative diseases accompanied by dementia might help to unravel the etiology of these polygenic disorders. Neurodegenerative diseases are characterized by altered content of the intermediates of the kynurenine pathway of trypthophan metabolism (KPTM). We developed Drosophila mutant model which reproduces main symptoms of neurodegenerative diseases. Mutant cardinal (cd, excess of 3-hydroxykynurenine, 3-HOK, and the generator of oxidative stress) can serve as model for dementia, since it is characterized by age-dependent memory loss, synaptic pathology, and Congo red positive inclusions. Here, we tested the

effects of a synthetic hybrid antioxidant conjugated to polyethylene glycol on the main disease manifestation - impairments in learning/memory. It is shown that this antioxidant possesses strongly expressed therapeutic action, normalizing defects of memory in the mutant after HS, and has no impact on memory formation at normal conditions. Therefore, the cd mutant may be regarded as an appropriate model for study of possibilities of antioxidant therapy for dementia-like diseases.

PO-91

Track: *HIV Research*

POTENTIAL DRUG-DRUG INTERACTIONS IN HIV-INFECTED CHILDREN ON ANTIRETROVIRAL THERAPY IN LAGOS, NIGERIA

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Background: Multi-therapy is common in HIV-infected children and the risk for clinically significant drug interactions (CSDIs) is high. We investigated the prevalence of CSDIs between antiretroviral (ARV) and co-prescribed drugs for children attending a large HIV clinic in Lagos, Nigeria.

Methods: The case files of paediatric patients receiving treatment at the HIV clinic of the Lagos University Teaching Hospital (LUTH), Idi-Araba, between January 2005 and December 2010 were reviewed. The ARV and co-prescribed drug pairs were evaluated for potential interactions using the Liverpool HIV Pharmacology Group website. The potential interactions were rated as A (no known interaction), B (minor/no action needed), C (moderate/monitor therapy), D (major/therapy modification), and X (contraindicated/avoid combination).

Results: Of the 310 cases reviewed, 208 (67.1%) patients were at risk of CSDIs. Artemisinin-based combination therapy (ACT) was prescribed for over one-half of the patients, accounting for 40% of the CSDIs. Excluding this drug class, the prevalence of CSDIs reduced from 67.1% to 18.7% in 58 patients. Most of the CSDIs (579; 97.2%) were moderately significant and frequently involved nevirapine and fluconazole (58; 9.7%), zidovudine and fluconazole (55; 9.2%), zidovudine and rifampicin (35; 5.9%), and nevirapine and prednisolone (31; 5.2%). Age (P= 0.392), gender (P= 0.783), and moderate (P= 0.632) or severe (P= 0.755) malnutrition were not associated with risk for CSDIs.

Conclusions: There is a tendency for CSDIs between ARV and co-prescribed drugs among the group of children evaluated in this study. Measures are necessary to prevent important drug interactions and to manage those that were unavoidable.

Keywords: HIV, infection, children, antiretroviral drug, co-prescribed drug, interactions.

PO-127

Track: *Cardiovascular Drug Discovery & Therapy*

SOME ARGUMENTS IN FAVOR OF USING INHIBITORS OF FATTY ACID SYNTHESIS AND ANTINEOPLASTIC AGENTS AS COATINGS FOR STENTS

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Our study has revealed significantly less difference in fatty acid (FA) composition between intact and atherosclerotic vessels, then between arterial wall and blood plasma (both in healthy people and in patients with coronary heart disease). FA composition of atheroma is also similar to FA ratio of intact artery wall. Herewith the FA ratio of atheroma differs substantially from blood plasma FA composition. It is concluded that most of atherosclerotic plaques FA were formed due to synthetic processes in smooth

muscle cells, and not as a result of their intake from blood plasma. In case of advanced atherosclerotic lesions in aorta, reduction in relative levels of stearic and arachidic saturated FA is observed in aortic wall, when compared with the saturated palmitic acid, what indicates increased activity of fatty acid synthase (FAS). It is shown that increased activity of FAS is always accompanied by the active proliferation of the tumor cells while an inhibition of the FAS leads to its cessation. Thus, we believe that an active search for new stent-coatings between antineoplastic agents, and between inhibitors of FA synthesis is required.

Keywords: Fatty acids, atherosclerotic plaques, antineoplastic agents, inhibitors of fatty acid synthesis.

PO-129

Track: *Bioactive Lipids*

POSSIBILITY OF APPLYING MEDICATIONS STIMULATING PEROXISOME PROLIFERATION IN TREATMENT OF MULTIPLE ORGAN DYSFUNCTION SYNDROMES

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Low level of plasmalogens is an important marker of peroxisomal dysfunction. The primary-OH group in glycerol plasmalogens was not substituted by the acyl group (fatty acid) as in diacylphospholipids but by the aldehydogenic alkenyl group (fatty aldehyde) found in the form of vinyl ether. Diacylphospholipids and plasmalogens participate in exchange of polyunsaturated fatty acids with a large number of double bonds, acting as an intermediate station, through which these fatty acids are transported to cell membranes. Our research of blood plasma samples from patients with multiple organ dysfunction syndromes (MODS) of different etiology has shown substantial decrease of fatty aldehyde level in comparison with level of fatty acid with multiple double bonds. This fact indicates a significant reduction in the proportion of plasmalogens to total phospholipid content. Thus, peroxisomal dysfunction may play an important role in development of critical conditions associated with MODS. In addition, peroxisome dysfunction may also explain the violation of detoxification processes, neurological disorders, the decline in plasma cholesterol level, and the decreased blood antioxidant capacity, which is also related to depression of catalase activity in severe conditions. Thus, the treatment of such patients may include administration of medications stimulating peroxisome proliferation.

Keywords: Plasmalogens, peroxisomal dysfunction, multiple organ dysfunction syndromes, medications stimulating peroxisome proliferation.

PO-61

Track: *Drug Discovery from Natural Product*

ANALGESIC, ANTI-INFLAMMATORY AND HYPOTENSIVE EFFECTS OF *SCHINUS MOLLE* EXTRACT AND THE ISOLATION OF TWO TRITERPENOIDS

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Schinus molle seeds were subjected to sequential extraction. Dichloromethane extract of the seed of *Schinus molle* was tested for its analgesic, inflammatory and hypotensive potential based on folklore medicine. The analgesic effect of the mixtures was tested using the tail flick test which determined the pain threshold of female Sprague Dawley rats by measuring their tail flick response time to a painful stimulus. Anti-inflammatory properties of fractions and compounds were studied using the albumin-induced inflammatory model. Paw volumes were measured plethysmographically before and at predetermined intervals after injection of albumin. While hypotensive properties, the blood pressure of normotensive Sprague Dawley rats was measured non-invasively before and 2 hours after drug administration. Column chromatographic of the DCM fraction lead to the isolation of two compounds. FT-IR and NMR spectroscopy were used to establish the structures as isomasticadienonic acid and masticatrienonate, the latter being a previously undiscovered compound.

Comparison of untreated rats with treated rats with various DCM extract fractions were found to have lower blood pressure, reduced peak and shorter period of inflammation as well as an increased pain threshold. Rats treated with Isomasticadienonic acid also demonstrated an increased pain threshold compared to untreated rats. Pharmacological studies carried out with extracts and isolates from *Schinus molle* confirmed that this plant have, among others, hypotensive, anti-inflammatory and analgesic effects.

PO-98

Track: *Inflammation and Immunology*

PHARMACOLOGICAL STUDIES ON THE ANTI-INFLAMMATORY AND IMMUNOMODULATORY ROLE OF PHOSPHODIESTERASE-IV INHIBITOR (ROLIPRAM) IN OVALBUMIN-INDUCED ASTHMA IN RATS

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Objective: To evaluate anti-inflammatory and immunomodulatory role of phosphodiesaterase (PDE)-IV inhibitor (rolipram) in ovalbumin-induced asthma in rats.

Method: The study was conducted on Wistar rats (200-250 gm) 6 animals per group. All animals were immunized on day '0' with 2 mg/kg ovalbumin (OVA) in Freund's complete adjuvant and they were divided into experimental and control groups. From day 15 each animal was challenged with the antigen (OVA) aerosol by nabulization and subsequently rolipram treatment was done upto 21 days. On day 21, right paw was challenged with antigen and paw volume as marker of DTH reaction was obtained after 24 hr. for each group. On day 22, serum samples and mesenteries were collected for the analysis of a) IgE levels b) inflammatory cytokine (TNF-α) levels c) anti-inflammatory (IL-4) cytokine levels and d) mast cell degranulation respectively. All the data were analysed by one-way ANOVA and $p<0.05$ was considerd as level of significance.

Results: The present studies showed the anti-inflammatory and immunomodulatory effects of rolipram on ovalbumin-induced asthma in rats. Pretreatment with rolipram (0.5 mg/kg) significantly ($p<0.05$) decreased ovalbumin-induced elevated levels of (a) paw volume (b) IgE antibody titre (c) TNF-α cytokine levels and (d) number of mesentric mast cell degranulation and significant reversal of increased anti-inflammatory (IL-4) cytokine levels as compared to non treated control group. Rolipram at higher doses (1 mg/kg and 2 mg/kg) further, significantly reversed antigen-induced these immunological markers ($p<0.001$).

Conclusion: Results of the present studies suggests anti-inflammatory and immunomodulatory role of rolipram, a specific phosphodiesterase (PDE)-IV inhibitor in ovalbumin-induced asthma. The protective mechanisms of rolipram in asthma may be mediated through regulation of transcription factors and anti-inflammatory & immunomodulatory cytokine networks. Rolipram needs further molecular pharmacological studies to explain its protective mechanisms in immunological disorders.

Keywords: Inflammation, Cytokine, Asthma, Phosphodiesterase, Rolipram.

PO-76

Track: *Women's Health Drug Discovery and Therapy*

FORMULATION AND INVESTIGATION OF NEW VAGINAL DOUBLE LAYER SUPPOSITORIES CONTAINING LACTOBACILLI AND HERBAL EXTRACTS FOR TREATMENT AND PROPHYLAXIS OF VAGINOSIS

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The objective of this study is to develop vaginal double layer suppositories, containing probiotics in core and antibacterial drugs in outer layer for simultaneously treatment of bacterial vaginosis and recolonization vagina by lactobacilli. The suppositories are specially designated in a way, that the

herbal extract releases from outer layer and beginning act on pathogen microorganisms, then lyophilized lactobacilli released from the core, and while they revitalized the concentration of drug reduced above MIC, not able to kill lactobacilli. Four kinds of double layer vaginal suppositories containing lyophilized *L. delbrueckii* MH -10 in core and dried extract of *Achillea millefolium* (Yarrow) in outer layer have been prepared by use two diferent sized specially designed metallic molds. The release kinetic of lactobacilli and herbal extract from different bases were determined by rotating basket dissolution method and agar diffusion method respectively. The highest release of herbal extract observed from Witepsol H -15, although Oleum Cacao is melted rapidly, but drug release is not completely. Novata ABPH base gave the highest release of *L. delbrueckii* MH -10 and was microbiological stable after storage at 2-8°C over the period of 12 months.

Keywords: Vaginosis, probiotic lactobacilli, herbal extract, double layer suppository.

PO-121

EFFECT OF AQUEOUS EXTRACT OF *THYMUS VULGARIS* ON SERUM LIPID PROFILE AND LIVER FUNCTION TESTS IN RATS UNDER NATURAL CONDITION OF HYPERLIPIDEMIA

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Thymus vulgaris is a species of flowering plant native to Iran. It is also the main source of thyme as an ingredient in cooking and as an herbal medicine. The aim of this study was to evaluate the effect of aqueous solution of thyme on lipid profile, under natural condition of hyperlipidemia in rats. Fifteen rats were allocated into five equal groups. The treatments were as follows: Group 1; normal diet, group 2; high fat diet, group 3; aqueous solution of thyme via an oral gavage along with high fat diet, group 4; normal diet in combination with aqueous solution of thyme and the last group; high fat diet in combination with atorvastatin (4 mg/kg). At the end all the rats were bled and serum was separated. Results showed that aqueous solution of thyme had a lowering effect on serum lipid profile. This effect was comparable to that of atorvastatin group. It was also revealed that aqueous solution of thyme had beneficial effect on liver function test. As it is stated that atorvastatin has some detrimental effects on liver function, it seems that thyme could be a potential alternative substitute for chemical drugs.

PO-122

SERUM LIPID PROFILE IN RATS FED NORMAL AND FAT RICH DIET FOLLOWING ADMINISTRATION OF AQUEOUS EXTRACT OF *PORTULACA OLERACEA*

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Portulaca Oleracea, also known as Pigweed, is found on every populated continent and is one of the eight most common plants in the world. Much research has been done on this wondrous plant and yet its benefits are relatively unknown to the average individual. The purpose of the experiment was to investigate the effect of administration of aqueous extract of *Portulaca oleracea* in rats fed fat rich diet. To carry out the study, fifteen rats underwent the experiment in five equal groups. Different groups comprising: group 1; normal diet, group 2; high fat diet, group 3; aqueous solution of *portulaca oleracea* along with high fat diet, group 4; normal diet in combination with aqueous solution of *portulaca oleracea* and group 5; high fat diet along with *atorvastatin* (4 mg/kg). After the end of the experiments, all rats were anesthetized and bled. Results showed that there was no significant difference between the *atorvastatin* and aqueous solution of *portulaca oleracea* groups in regard to lipid profile. It could be stated that the medicinal benefits of the *portulaca oleracea* should become conventional knowledge, allowing *purslane* to be utilized more often.

PO-22

Track: *CNS Drug Discovery & Therapy*

SYNTHESIS AND ANALGESIC ACTIVITY OF SOME N-SUBSTITUTED-PHTHALIMIDE ANALOGS

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Signaling molecules produced in the vicinity of the damaged tissues usually cause the inflammation process. To control pain due to inflammation, analgesic drugs are administered, which can be classified as narcotic, when acting on the central nervous system, and non-narcotic or peripheral, when acting directly on the damaged tissue [1]. Peripheral analgesics are drugs that, independent of their mode of action, show a therapeutic effect by supressing the production of prostaglandins, which are lipids responsible for inflammation and pain. Non-steroidal anti-inflammatory drugs (NSAIDs) [2]. A series of N-substituted-phthalimides were synthesized for the purpose of determining the analgesic activity. The compounds were synthesized using phthalic anhydride and various appropriate amines in microwave and reflux synthesizer.

The structures of the synthesized derivatives were confirmed by means of physical and spectral analysis. The analgesic activity of the selected compounds was evaluated by ip carboxymethylcellulose and acetic acid- induced ' writhing' test in mice. It was found that these compounds 2-7 have much better activity than the carboxymethylcellulose and aspirin.

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PO-17

Track: *Drug Discovery in Preclinical Research*

A SENSITIVE AND RAPID METHODOLOGICAL DEVELOPMENT FOR STERILITY TESTING BY MICROCALORIMETRY COUPLED WITH FULL-ENCLOSED FILTRATION-CULTURE AMPOULE SYSTEM

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Sterility test is one of the routine inspection item for security guarantee of aseptic preparation, but the routine observation method for sterility test is time-consuming, low sensitivity and prone to miscarriage. In this study, microcalorimetry with a modified full-enclosed membrane filtration-culture ampoule system was applied as a alternative method for sterility; meanwhile, positive detection time (*T*d) was defined as $P_d/|P_0| \geq 3$ when $k \geq 0$ (growth rate of exponential period). *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escheichia coli*, *Bacillus subtilis*, *Clostridium sporogenes* and *Candida albicans* were serial 10-fold diluted and cultured to determinate the accurate detection limits of microcalorimetry method; meanwhile, routine observation method was adopted as comparison. The results showed that most stains could be detected within 24 hours with the detection limit even less than 1 colony-forming unit (CFU) by microcalorimetry; which was more sensitive and faster when compared with routine observation method. The thermogenic power-time curves were species-specific, the curve shape, peak time and maximum power were stable, which could be used for bacterial contamination identification. The sterility test based on microcalorimetry with modified culture system was high sensitivity, low time consumption, and quantitative with fingerprinting compared with routine observation method, could be widely applied in sterility testing of drugs, feed and surgical instrument.

Keywords: Sterility Test, Microcalorimetry, Detection Time, Sensitivity.

PO-38

Track: *Anti-Infectives*

THE EVALUATION OF THE ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF THE EXTRACTS OF *IN VITRO* LAWSONIA INERMIS

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Lawsonia inermis Linn, known under the name of "henna" is used as cosmetic product and for her medicinal virtues in particular in the treatment (processing) of the dermatophytiques and infectious diseases. Our work screw to be studied the antibacterial, antioxydant activities by DPPH of the polar extracts of the air part (party) of this plant, the latter were obtained by maceration. Nine bacterial strains namely: *E. coli*, *Enterobacter cancerogenus*, *Salmonella typhimurium*, *Staphylococcus aureus* MecA +, *Staphylococcus aureus* Mu50, *Acenitobacter baumannii*, *Pseudomonas aeruginosa*, *Bacillus polymyxae*, and SARM, were selected to be tested by the method of distribution(broadcasting) in solid environment(middle) .Certains extracts gave very convincing results(profits) to puor both activities as extract of ethyl acetate with resistant origins(stumps) in antibiotics.

Keywords: Lawsonia inermis, antibacterien activity, anti-oxydante activity.

PO-113

Track: *Anti-Infectives*

LEISHMANICIDAL ACTIVITY CONFIRMED FOR DRUGS SELECTED BY BIOINFOR-MACTIC: A SECOND USE FOR OLD DRUGS

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Few drugs are available to treat cutaneous leishmaniasis (CL) and although effective they have important concerns regarding to their toxicity, way of administration and cost. Bioinformatic represents a useful tool that allows a fast and effective way to indentify new drugs with potential anti-leishmanial activity. Drugs exhibiting different properties such anti-inflammatory or wound healing were identified by bioinformatic and then evaluated in vitro for their cytotoxicity and anti-leishmanial activities. The therapeutic response was also determined using the hasmter model for CL. The in vitro activity against intracellular amastigotes of L. panamensis was confirmed in several of the tested compounds and even some of them were able to produce cure or clinical improvement of hamsters with CL. Results suggest that modifying the therapeutic scheme or the pharmaceutical formulation the therapeutic response could be optimized. The results also confirm that bioinformatic is a promising methodology to identify effective potential drugs with anti-leishmanial activity yielding reliable results in short time.

PO-92

Track: *Hot Topics in Medicinal Chemistry*

NOVEL QUINAZOLINE DERIVATIVES AS CELL-CYCLE INHIBITORS OF BREAST CANCER CELL LINES: DESIGN, SYNTHESIS, AND MOLECULAR MODELLING STUDIES

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Quinazolinones with fused heterocyclic structures including triazolo[4,3-a]quinazolin-7-ones (3), [1, 2, 4, 5]-tetrazino [4,3-a]-quinazolin-8-ones (5) and Schiff's bases of isatin derivatives with 2-hydrazinoquinazolin-4-ones (7) have been synthesized. Biological evaluation of these compounds showed variable and significant in vitro antiproliferative activity against the MCF-7 cells. Compounds 3a-3c, 6, 7a-7f showed promising activity (IC50 = 12.45-15.79 μM). Compound 7f

possessed notable cell cycle disrupting and apoptotic activities with enhanced selectivity against cancer cells, suggesting the potential for the development of new selective cell cycle inhibitors. In silico docking study of the compound 7f with EGFR enzyme postulated that the designed compound might act on the same enzyme target where DJK_3021_A x-ray structure acted.

Keywords: Anticancer, Quinazolines, Synthesis, Molecular modelling.

PO-62

Track: *Drug Discovery in Preclinical Research*

HYPOGLYCEMIC PROPERTY OF GINGER AND GREEN TEA AND THEIR POSSIBLE MECHANISMS IN DIABETES. REVIEW ARTICLE

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Diabetes mellitus disease is increasing rapidly and the incidence in 2010 was about 285 million people worldwide, and is projected to increase to 438 million in 2030. The conventionally used drugs possess many side effects, in addition, the cost of modern antidiabetic drugs is beyond the reach of most people with low income, and hence the need for alternatives that are effective, cheap, and safe is very common.

Plants and many plant derived preparations have long been used as traditional remedies for the treatment of diabetes in many parts of the world. Recently, ginger (*Zingiber officinale*) and green tea (*Camellia sinensis*) have been widely studied to assess their beneficial effects in treatment and prevention of diabetes mellitus. *In vitro* and *In vivo* studies evidenced the potential of ginger and green tea to normalize blood glucose level in diabetes mellitus. In this article we reviewed the various mechanisms through which ginger and green tea exert their hypoglycemic effect; their pharmacokinetics and safety are also discussed. Our study showed that ginger and green tea share some mechanisms of action to reduce blood glucose level in diabetes mellitus and several studies exhibited their safety as complementary antidiabetic agent, therefore, a study on the administration of these two herbs simutanously may be needed as they may exhibit a potential hypoglycemic action due to their synergistic or additive mechanisms of action in diabetes mellitus.

Keywords: Ginger, Green tea, hypoglycemic action.

PO-21

Track: *Chemistry (Asymmetric Synthesis)*

STEREOSELECTIVE SYNTHESIS OF HETEROCYCLES AND CARBOCYCLES USING DIANION CHEMISTRY / DOMINO REACTION

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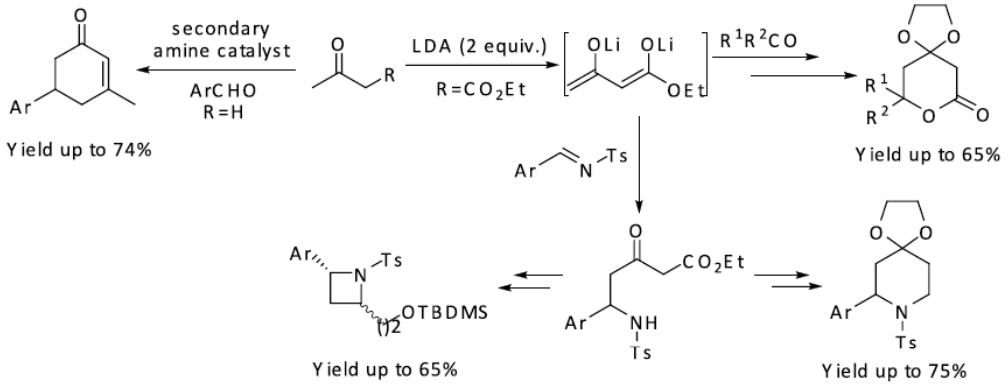
Heterocycles (especially aza- and oxa-cycles) and Carbocycles are very important subunits found in various natural products and bioactive molecules. Diverse reactivity pattern of ethyl acetoacetate and acetone produces a wide verity functionalized heterocycle and carbocycle derivatives. We have developed a new strategy for the stereoselective synthesis of substituted azetidines, piperidines and pyrones *via* the regioselective addition of 1,3-dicarbonyl dianion of ethyl acetoacetate to *N*-activated imines and aldehydes/ketones. A stereoselective synthesis of 5-substituted-3-methyl-cyclohex-2-en-1-ones has been developed via a secondary amine catalyzed five steps domino reaction for the starting from acetone and aromatic aldehydes.



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PO-63

Track: *Drug Discovery in Preclinical Research*

ADVANCES AND APPLICATIONS FOR POSITRON EMISSION TOMOGRAPHY - MAGNETIC RESONANCE HYBRID IMAGING

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Combined PET/MRI imaging systems operating either sequentially or in simultaneous measurement modes made possible the readout of several disease features in the same imaging session with good anatomic localization. The synergy of the two methods improves quality of information of some important physiologic and pathologic processes such as brain activation or tissue blood perfusion and receptor expression. PET/MRI validates pharmacokinetic and physiologic measurements by using two methods for the same readout. When combined with the application of dual contrast agents, improved increased throughput and increased signal levels are achieved such as in PET/MRI reading out the immune system. Novel probes with dual readout enable to image heterogeneity data in tumours combining advantages of both MRI and PET. Chemical Shift Imaging (CSI) with hyperpolarized compounds and metabolic PET offer pivotal understanding of *in vivo* changes in many pathologies of the cardiovascular and central nervous system. Smart remote sensing of tissue characteristics is made possible by the use of special PET/MRI reporter systems such as dual-modality nanoparticles with relaxivity changes in function of tissue properties or enzyme activity.

Keywords: PET, MRI, Dual-modality.

PO-1

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

HIGH-THROUGHPUT HOMOGENOUS TIME RESOLVED – FLUORESCENCE RESONANCE ENERGY TRANSFER COMPETITIVE BINDING ASSAY FOR SECRETIN RECEPTOR (CLASS B – GPCR)

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Human secretin (Class-B GPCR ligand) is involved in various physiological functions in energy and water homeostasis making secretin receptor a promising target for drug research. For GPCRs,

radioligands are used in the conventional binding assay to characterize and establish the binding affinity of the ligands. An alternative non-hazardous fluorescence labeled binding assay is lucrative over the radioligand assays. Here we have developed a FRET (Fluorescence Resonance Energy Transfer) competitive binding assay for human secretin receptor.

The receptor gene sequence is cloned in SNAP tag-plasmid and expressed in CHO-K1 cells. Its expression in the plasma membrane is confirmed with immunofluorescence localization. The receptor and the ligand are labeled with fluorescent donor (Tb) and acceptor (Alexa488). FRET signals are produced when the labeled ligand is bound to the receptor and the signals drop when it is displaced by the test compounds. The saturation concentration of the donor receptor-labeling is identified as 100 nM. The Kd value of fluorescent ligand at donor saturation point is determined as 500 nM. At these fixed labeled ligand and receptor concentration, the IC50 of unlabeled secretin is $1.69\pm1.28x10^{-8}$ M. GIP, GLU, VIP and PACAP are screened and hold good correlation with the traditional radio-ligand assay. Therefore, this FRET binding assay can be efficiently used as a primary screening tool for peptide analogs to identify potential agonist and/or antagonist in the future.

PO-55

COMPUTATIONAL STUDIES OF STRUCTURAL AND ELECTRONIC PROPERTIES THROUGH DENSITY FUNCTIONAL THEORY(DFT), NATURAL BOND ORBITAL, AND ENERGIES FOR THE 2,15-DIOXA-7,18,19,20,23-PENTAAZAHEPTACYCLO[21.6.1.117,20.01, 8.03,7.09,14.024,29]HENTRIACONTA-9,11,13,17(31),18,24,26,28-OCTAEN-30-ONE

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In this paper, the molecular structure, chemical formula, and electronic properties of 2,15-Dioxa-7,18,19,20,23-pentaazaheptacyclo[21.6.1.117,20.01,8.03,7.09,14.024,29]hentriaconta-9,11,13,17(31), 18,24,26,28-octaen-30-one were calculated by the B3LYP density functional model using 6-31G, 6-311G, 6-311G++ and 6-311++(d, p) basis sets for this molecule. B3LYP calculation results indicated some selected bond length and bond angle values for this molecule. The optimized geometries and frequencies of the stationary point and the minimum-energy paths of this structure were recognized. The obtained results were compared with the corresponding experimental data. Trustworthiness of this results is confirmed by good agreement with the experimental analyzes of this structure. The results obtained by different basis sets are compared and the necessity of correlational methods for studying these systems is discussed. Pyrrole constitute an important class of five-membered ring heterocycles with notable biological properties, [1,3] such as antitumour, [1] analgesic, [2,3] antidepressant, [4] antihistaminic [5], anti-inflammatory [6], and anti-parkinson [7,8]. Furthermore, they are useful structures in the synthesis of natural products and heterocycles and are also extensively used in material science. Consequently, the massive numbers of procedures have been developed for the construction of pyrroles in the literature. The well-known occurrence of substituted pyrrole shape amongst biologically important natural products and pharmaceuticals has stimulated great interest in its synthetic methods [9]. The program Gaussian 03/DFT10 was employed to fully optimize the geometries without any symmetry limitations at the restricted Hartree-Fock (RHF) [11] with the standard basis sets, 6-31G, 6 -311G++, LANL2DZ, 6-311++G(d, p).

Keywords: Electronic structure, Density functional theory (DFT) Calculations, Vibrational analysis, B3LYP level, Natural bond orbital (NBO).

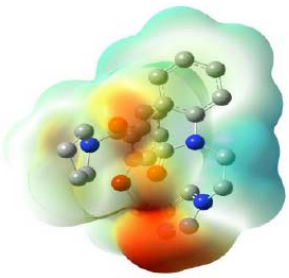

Fig. 1. Electron Density from total SCF Density (mapped with SCF). The electrostatic potential varies between -0.118 (red) and +0.118 (blue) au.

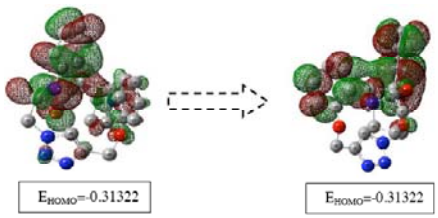

Fig. 2. Localization of the HOMO & LUMO orbitals by 6-311G.

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PO-52

STUDIES ON THE DEGREE OF ENHANCEMENT OF ACTIVITY OF AMOXYCILLIN BY CLAVULANTE AT VARIOUS RATIOS ON SOME INFECTIOUS BACTERIA

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The study was carried out with the aim of assessing the effect of increasing ratio of amoxicillin with Augment in against clinical isolates of *Staphylococcus aureus, E. coli, Klebsiella* spp. Disc diffusion susceptibility test results indicate that 4:1 preparations are more effective against the clinical isolates with mean zone diameter of 23mm, 17.6mm and 16.2mm for *S. aureus, E. coli* and *K.* spp respectively, followed by 2:1 with mean zone diameter of 19.4mm, 13.4mm and 11.4mm for *S. aureus, E. coli* and *K.* spp respectively, followed by the rest of the preparations i.e. 6:1, 8:1, 10:1. The susceptibility of 4:1 decreases from 80%, 60%, 40% for *S. aureus, E. coli* and *Klebsiella* Spp. The result of the Statistical analysis indicates that there was a highly significant difference between 4:1 and the rest of the preparations against *S. aureus,* and *E. coli* but there was no significant difference between the preparations against *Klebsiella* Species.

Keywords: Effects, Increasing ratio, Amoxicillin, Augment in, Bacterial Isolate.

PO-71

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

MODELING ACETYLCHOLINESTERASE INHIBITOR MOLECULES DERIVED FROM CARDOL

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Alzheimer's disease is the leading cause of dementia for elderly people. The main active therapeutics is supported on increasing levels of acetylcholine in the synaptic cleft based on reversible inhibition of the acetylcholinesterase (AChE) enzyme. The aim of this work is to study new cardol derivatives, using density functional theory (DFT) to obtain electronic structure descriptors. DFT has been largely used in several works in the literature for pharmaco-receptor modeling. These descriptors are used in a principal component analysis to determine a small set of most favorable structures to act as AchE inhibitors. These electronic properties are obtained through B3LYP/6-311+G (2d, p) calculation level. Principal component analysis reveals that from the set of studied molecular structures a small group is correlated with donepezil, a drug with known biological activity. The analysis predicted a possible activity of these compounds as inhibitors of acetylcholinesterase. The mode of binding between the receptor and the studied molecules was found to be a hydrogen bonding involving acyl pocket and the pi stacking with the anionic peripheric site.

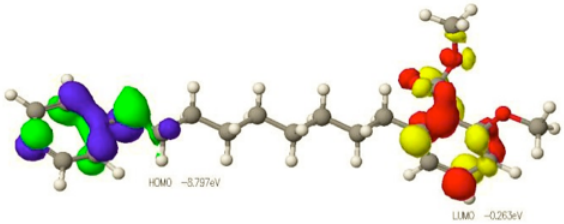

Figure. HOMO and LUMO orbitals plotted for the equilibrium geometry of the cardol derivative molecule.

PO-75

Track: *Regenerative Medicine*

UMBILICAL CORD BLOOD CELLS (HUCBC) ADMINISTRATION IS EFFECTIVE IN SEVERE SPINAL CORD INJURY IN RATS

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Restoration of spinal cord function after damage is one of the important problems that may be solved by methods of regenerative medicine, in particular, by cell therapy. The aim of this study was to evaluate the effectiveness of intravenous HUCBC administration after spinal cord injury.

Methods: Severe spinal cord contusion injury in rats was performed by "weight drop" after laminectomy at the level of Th9. 10^7 cells per animal were injected into tail vein at 1st or 5th day after contusion. Visualization of the spinal cord injury was performed by MRI and anatomical and histological techniques. Recovery of motor function of the hind limbs was monitored using functional tests including "Rota-rod", "Narrow- beam test" and "Open field". Tests were performed weekly for 8 weeks starting from 1st day after contusion.

Results: Animals were divided into five groups: 1st – trauma + self-healing; 2nd – injury + injection of HUCBC on 1st day after injury; 3rd – injury +injection of HUCBC on 5th day after injury; 4th – only laminectomy; 5th –laminectomy + HUCBC injection. Changes in locomotion of the hind limbs in 4th and 5th groups were absent. In groups 1, 2 and 3, there was a strong hind limb paraplegia. Self-recovery of motor function of hind limbs was observed 4-5 weeks after injury and the level of recovery in "Open field" test was 4-5 points on BBB scale. Restoration of motor activity in groups 2 and 3 was registered after same period following injury, but its level on a BBB scale was 6-7 points. Significant differences in effect between 1st and 5th day after infusion were not detected.

Conclusion. The results demonstrate that one intravenous injection of HUCBC on 1st and/or 5th day after severe spinal cord injury can improve recovery of spinal cord related to locomotion of hind limbs. Therapeutic effect ($p < 0,05$) after HUCBC injection to rats with severe spinal cord injury was 14-16%.

Keywords: Spinal cord injury, cord blood cells.

PO-80

EFFECT OF BISPHENOL A AND PASSIVE AVOIDANCE LEARNING ON DOPAMINE D_1 RECEPTOR DISTRIBUTION IN ANTERIOR STRIATUM OF PREFRONTAL CORTEX OF MALE RAT

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Introduction: Bisphenol A (BPA) used to make certain plastics and epoxy resins; it has been in commercial use since 1957. In November 2009, the WHO announced it would organize an expert consultation in 2010 to assess low dose BPA exposure health effects, focusing on the nervous and behavioral system and exposure to young children. The aim of present study was to investigate: 1- The effect of BPA on D1 subunit of dopamine receptor distribution in anterior

striatum of prefrontal cortex 2- The effect of BPA and Passive avoidance learning on D1 subunit of dopamine receptor distribution in anterior striatum of prefrontal cortex of male rats.

Methods: Thirty five male rats weighting 220- 300 g were used. Animals were divided into 3 groups: 1-; Sham group (sesame oil the same volume of experimental with learning and non learning); 2- experimental 1 (received BPA 5 and 50 mg/kg/day without learning); 3- experimental 2 (received BPA 5 and 50 mg/kg/day with learning). BPA was used by oral intake for 15 days. Learning and memory were performed by a passive avoidance shuttle-box. Distribution of D1 subunit of dopamine receptor was investigated by immunohistochemical procedure. For determination of color difference the software of Image Analyzer were used. Data was analyzed by student T-test and one ways ANOVA measuring and Tucky's test as post-hoc tests. The level of significant was $P< 0.05$.

Results: Datas showed in this present study that BPA in two dose decrease significantly effect in two doses and both groups distribution of D1 subunit of dopamine receptor in anterior striatum of prefrontal cortex of male rats.

Conclusion: According to these results BPA had negative effect on distribution of D1subunit of dopamine receptor in anterior striatum of prefrontal cortex of male rats.

Keywords: BPA, Passive avoidance learning, prefrontal cortex, D1 subunit of dopamine receptor, Male rats.

PO-81

EFFECT OF BISPHENOL A AND PASSIVE AVOIDANCE LEARNING ON SEROTONIN D_1 RECEPTOR DISTRIBUTION IN ANTERIOR CINGULATE CORTEX OF PREFRONTAL CORTEX OF MALE RAT

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Introduction: Bisphenol A (BPA) is a chemical produced in large quantities for use primarily in the production of polycarbonate plastics and epoxy resins. On the other hand BPA induces harmfull effects on the mammalian CNS. The aim of present study was to investigate: 1- The effect of BPA on 5HT2α subunit of serotonin receptor distribution in anterior cingulate cortex of prefrontal cortex 2- The effect of BPA and Passive avoidance learning on 5HT2 α subunit of serotonin receptor distribution in anterior cingulate cortex of prefrontal cortex of male rats.

Methods: Thirty five male rats weighting 220- 300 g were used. Animals were divided into 3 groups: 1-; Sham group (sesame oil the same volume of experimental with learning and non learning); 2- experimental 1 (received BPA 5 and 50 mg/kg/day without learning); 3- experimental 2 (received BPA 5 and 50 mg/kg/day with learning). BPA was used by oral intake for 15 days. Learning and memory were performed by a passive avoidance shuttle-box. Distribution of 5HT2α subunit of serotonin receptor was investigated by immunohistochemical procedure. For determination of color difference the software of Image Analyzer were used. Data was analyzed by student T-test and one ways ANOVA measuring and Tucky's test as post-hoc tests. The level of significant was $P< 0.05$.

Results: Data according to image analyzer program showed that BPA in two dose of present study significantly decreased but in learning groups in high dose significantly decreased distribution of 5HT2α subunit of serotonin receptor in anterior cingulate cortex of prefrontal cortex of male rats.

Conclusion: According to these results BPA had negative effect on distribution of 5HT2α subunit of serotonin receptor in prefrontal cortex of male rats.

Keywords: BPA, passive avoidance learning, shuttle-box, prefrontal cortex Immunohistochemistry, 5HT2α subunit of serotonin receptor, male rats.

PO-50

EVALUATION OF ANTIFUNGAL SUSCEPTIBILITY PROFILE OF CANDIDA SPECIES ISOLATED FROM FEMALE PATIENTS ATTENDING AMINU KANO TEACHING HOSPITAL (AKTH)

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Candida as a cause of sexually transmitted disease. No other mycotic pathogen produces as diverse a spectrum of opportunistic disease in humans as does *Candida*. The study was aimed at the evaluating the antifungal susceptibility profile of Candida species isolated from female patients attending Aminu Kano Teaching Hospital (AKTH) with suspected *Candidal* infections. Five hundred and twenty one (521) clinical samples comprising 342 urine and 179hvs between October, 2012 to August, 2013 were cultured on sabouraud dextrose agar. The *Candida species* isolated were identified to species level using Chromogenic agar and API 20 C AUX test kit. Antifungal susceptibility tests were performed using commercially prepared single antifungal disc (Bioanalysed Turkey). Out of these 521 samples analyzed only 59 yielded *Candida species* giving the overall prevalence of 11.3% with Candida *albicans* 22 (37.3%) as the common species isolated followed by *C. glabrata* 19(32.2%) *C. tropicalis* 5(8.5%) *C. krusei* 3(5.1%) *C. magnoliae* 3(5.1%) *C. lusitaniae* 2(3.4%) *C. parapsilopsis* 2(3.4%) *C. famata* 2(3.4%) and C. guilliermondii 1(1.7%) the antifungal susceptibility test shows that 81.4% of the isolates were susceptible to ketoconazole and only 3.4% to nystatin. However, 33.9% were susceptible 13.9% intermediate susceptible and 52.5 resistant to fluconazole. Similarly 28.8% were susceptible 11.9 intermediate susceptible and 62.7% resistant to flucytosine. All the *C. krusei* isolates were completely resistant to azole drugs while *C. famata* were resistant to all the drugs tested.

Keywords: Evaluation, Antifungal, Susceptibility profile, Candida species.

PO-51

RESISTANCE AMONG CANDIDA SPECIES FROM PATIENTS WITH GENITOURINARY TRACT INFECTIONS AT MUHAMMAD ABDULLAHI WASE SPECIALIST HOSPITAL, KANO- NIGERIA.

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The increasing incidence of *Candidiasis* affecting the genitourinary tracts as well as the introduction of new antifungal drugs has recently encouraged the need for performing fungal susceptibility tests. To determine the antifungal resistance among *Candida* species from the genitourinary tracts, 689 Urine and High vaginal swab (HVS) samples were collected from female patients clinically diagnosed with genitourinary tract infection between September 2012 to January 2013. The samples were inoculated onto Sabouraud dextrose agar (SDA). Isolates from SDA were placed on Corn Med agar (CMA) to ensure detection of mixed cultures. Germ tube tests were performed for identification of the isolates. Susceptibility tests were carried on the isolates using broth dilution method. The occurrence rate of Candida species were as follows: *Candida albicans* 124(48.4%), *Candida glabrata* 89(34.8%), *Candida krusei* 23(9.0%) and *Candida Tropicalis* 20(7.8%). The rate of occurrence of Candida species in high vaginal swab 76(61.3%) was significantly higher than that of urine 48(38.7%) using Chi-square test for statistical analysis. Distribution of Candida species among different age groups showed that, the highest incidence in age brackets 20 – 30 158(61.7%), while that of 41-50 and above 8(3.1%) had the least. High rate of susceptibility was observed for each isolate against Fluconazole 23(65.7%) and Ketoconazole 22(62.9%). The resistance rate was 12(34.3%) for Fluconazole and Ketoconazole 13(37.1%). These results incriminated *C. albicans* as the most common Candida species causing genitourinary tract infection in women. This surveillance study has established Fluconazole and Ketoconazole as very effective antifungal agents for the treatment of genitourinary tract infections caused by Candida species.

Keywords: Antifungal resistance, *Candida* species, Genitourinary tract, Infections.

PO-95

Track: *Hot Topics in Medicinal Chemistry*

LIPID PEROXIDATION INHIBITION BY PERIOPERATIVELY USED DRUGS AND MEMBRANE INTERACTION AS ONE OF THEIR POSSIBLE MECHANISMS

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Background: Oxidative stress, an imbalance between reactive oxygen species production and biological antioxidant defense, is induced by not only a wide range of diseases but also anesthesia and surgical trauma. In search of the drugs to reduce oxidative stress in the perioperative period, we studied the lipid peroxidation-inhibitory effects of structurally different drugs associated with surgery and one of their possible mechanisms.

Methods: The lipid peroxidation-inhibitory effect was fluorometrically determined using diphenyl-1-pyrenylphosphine (DPPP)-incorporated liposomal membranes which were treated with 10-200 μM drugs and reference antioxidants, and then peroxidized with 20 μM peroxynitrite. The membrane interaction was analyzed by measuring the fluorescence polarization of 1, 6-diphenyl-1, 3, 5-hexatriene (DPH)-labeled biomimetic membranes after treating with drugs and reference antioxidants at 10 and 200 μM.

Results: The tested drugs concentration-dependently inhibited peroxynitrite-induced peroxidation of membrane lipids as well as antioxidant α-tocopherol, quercetin and (–)-epigallocatechin-3-gallate. The inhibition at each 10 μM was greatest in propofol, followed by guaiacol, thiopental, thymol, phenol, midazolam, diazepam, lidocaine, eugenol, procaine, bupivacaine, ropivacaine, sevoflurane, ketamine, mepivacaine and prilocaine. All of these drugs and antioxidants interacted with biomimetic membranes consisting of phospholipids and cholesterol to modify the membrane fluidity, suggesting that the interactivity with membrane lipid bilayers is, at least in part, responsible for the lipid peroxidation-inhibitory effects of perioperatively used anesthetic, disinfectant and analgesic drugs.

Conclusion: In addition to their inherent effects, propofol and other drugs to inhibit lipid peroxidation may be effective against perioperative oxidative stress. The membrane interactivity could be a guide for discovering novel antioxidant drugs.

Keywords: Antioxidant, Lipid peroxidation, Membrane interaction, Oxidative stress, Perioperative.

PO-86

Track: *Chemistry*

HUMAN BIO-MONITORING STUDY - TOXIC ELEMENTS IN BLOOD

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The content of toxic heavy metals (As, Cd, Cr, Hg, and Pb) in blood depends on locality, industry and social status of habitants. We studied this determination in detail in 1994. The blood of the young healthy blood donors without any metal exposure was analysed by the atomic absorption spectrophotometry. The results were used as the reference values of the average non-exposed population. These results did not differ from those gained in other European countries. There is no regular human bio - monitoring in Slovakia but there are monitors practiced in neighbouring countries like Czech Republic or Germany. We could suppose the level of exposure in our region from these results and from literature. After 20 years the industry changed and the new technologies bring better quality of environment. We cannot compare the recent concentrations to the old results.

We aimed to prepare the new bio-monitoring procedures containing recent data obtained by an inductively coupled plasma-mass spectrometry as a new reference values for measurements evaluation.

Keywords: Bio-monitoring, toxic heavy metals, reference values.

PO-72

Track: *Medical Imaging*

GOLD NANOPROBE AS POTENTIAL IMAGING, DIAGNOSTIC AND THERAPEUTIC TOOLS FOR BIOMEDICAL APPLICATIONS

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Gold nanoprobes represent enormous promise for diagnosis and treatment of human diseases. These probes with their unique optical properties have been employed for detection of a variety of pathogenic microorganism including bacteria, viruses and fungi. *Escherichia coli*, Pseudomonas syringae, Influenza and Hepatitis virus are among the pathogens detected by nanoprobes. Gold nanoprobes have also gained significance as novel pharmaceutical compounds to be used for imaging purposes and targeted delivery of therapeutic cargoes into cancer cells. Gold nanoprobes can be functionalized by conjugation of biofunctional groups such as thiol.

Colorimetric methods for gold nanoprobe-based detection of biological targets (DNA, RNA, Protein, Aptamers and Lipids) are rapid, easy and sensitive in the clinical context. Colorimetric detection is preformed through color changes resulting from aggregation of nanoprobes. Taken together, special features of nanoprobes and their diverse range of applications highlight their importance as valuable diagnostic and therapeutic tools.

We made attempt to design next generation nanochips through using gold nanoprobes particularly gold nanoparticles and nanorods for imaging and detection of pathogens and cancer cells. To this end, we attached bio-barcodes to gold nanoprobes to achieve detection and therapeutic objectives.

Keywords: Gold Nanoprobe, imaging, diagnosis, treatment, pathogenic microorganisms, cancer.

PO-112

Track: *Anti-Infectives*

DEVELOPMENT OF ANFOLEISH (3% AMPHOTERICIN B CREAM), A TOPICAL TREATMENT FOR CUTANEOUS LEISHMANIASIS

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Cutaneous leishmaniasis (CL) is a parasitic disease affecting millions of people in the world. The few available drugs are systemic, highly toxic, costly, and their efficacy is decreasing. Therefore, new effective drugs are needed. Systemic Amphotericin B (AmB) has been used for the treatment of visceral leishmaniasis and less frequently for CL. In vitro and in vivo studies have shown that AmB is active against all species of *Leishmania* ever tested, and so far, there is no evidence of resistance development in affected populations. In order to provide an effective local treatment for CL without associated systemic toxicity, Anfoleish, a new formulation of 3% AmB, was developed. The oil in water formulation with 3% AmB is stable and safe. Cure rates for 2x/day or once/day for 15 day treatment were 87.5% and 62.5% for Anfoleish and 25% and 12.5% for placebo (respectively). The cure rate for pentavalent antimonial was 71.4% and no healing was seen in negative control group. No toxicity was observed in animals treated with Anfoleish. Systemic exposure is minimal, which corroborates for its safety. Furthermore, observational studies in 16 volunteers with CL caused by *L. panamensis* have shown that Anfoleish is safe, with very promising healing results.

PO-2

Track: *Anti-Cancer Discovery & Therapy*

THE ROLE OF MITOGEN-ACTIVATED PROTEIN KINASES (MAPKS) IN HUMAN PROSTATE CANCER CELL DEATH INDUCED BY [PtCl2(4,4′-DIALKOXY-2,2′-BIPYRIDINE)] COMPLEXES

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Cisplatin is a platinum (Pt)-containing chemotherapeutic drug frequently prescribed for the treatment of various cancers. A multitude of signaling pathways are activated by cisplatin, one of which is the mitogen-activated protein kinase (MAPK) pathway. Three major MAPK members, extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinases (JNK), and p38 kinases have been shown to be activated by cisplatin. We recently reported on the synthesis of a series of Pt(II) complexes containing a 4,4′-dialkoxy-2,2′-bipyridine structure (with the alkoxy having 1-6 carbons) and demonstrated their high anti-proliferative activity against different types of human cancer cells. Prostate cancer is one of the most commonly diagnosed and cause of death in men. Thus, to further study the effects of these new Pt-complexes in prostate cancer, all six complexes were tested in PC3 and DU145 cells. Our data indicated that the complexes reduced the viability of PC3 and DU145 cells in a concentration-dependent manner. Pt-4C induced activation of ERK, JNK, and p38 in DU145 cells. Moreover, co-treatment of Pt-4C with JNK and p38 inhibitors resulted in increased cell viability compared to Pt-4C treatment alone. This suggests that JNK and p38 may be involved in signaling for cell death in DU145 cells in response to Pt-4C treatment.

Keywords: Cisplatin, platinum complexes, MAPK, prostate cancer.

PO-19

Track: *Inflammation and Immunology*

PRE-CLP CENTRAL IL-1R ANTAGONIST ADMINISTRATION DECREASES HYPOTHALAMIC IL-1 GENE EXPRESSION IN SEPTIC RATS

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Several studies have implicated an excessive local production of interleukin (IL)-1 as an important factor responsible for the impairment of AVP secretion during late phase of sepsis, but this question has not yet been directly assessed by IL-1ra central administration. We herein investigated the effect of IL-1ra treatment on the sepsis-induced increase in IL-1 expression in the hypothalamus of rats. Rats were pre-cecal-ligation and puncture (CLP)-treated with i.c.v. injection of IL-1ra (9-nmol) or vehicle (PBS) and then sepsis was induced by CLP. IL-1ra and vehicle were also given to naive control animals. After 4-, 6- and 24-h, the animals were decapitated (n=8/group) for blood samples and hypothalamic tissues collection. IL-1 transcript levels were quantified by real-time PCR. A specific ELISA assay was used for AVP analysis. Hypothalamic IL-1 mRNA levels were significantly ($P<0.005$) increased at 4-, 6- and 24-h post-CLP, as compared to control animals. IL-1ra administration significantly decreased IL-1 gene expression at all time points when compared to vehicle treated as well as the naive controls. AVP concentration and survival rate of IL-1ra treated rat was significantly higher in comparison to vehicle treatment. Our results showed that blocking the IL-1/IL-1r signaling pathway by central administration of an IL-1r antagonist decreases IL-1 gene expression during sepsis, this leading to an increase in AVP levels and, in turn, a higher survival rate.

ACKNOWLEDGEMENTS

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PO-53

IS THERE A PROPHYLACTIC MEDICATION IN ALZHEIMER'S AND PARKINSON'S DISEASES, E.G. COMBINED GABAA AGONISTS AND NMDA ANTAGONISTS?

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Introduction: Alzheimer's and Parkinson's diseases are uncurable neurodegenerative diseases. The question arises whether combined GABAA agonists and NMDA antagonists might have a therapeutic and maybe a prophylactic effect.

Methods/Material: In both diseases neural networks are developed in the involved brain regions in order to point the efficacy of such drugs.

Results: In Parkinson's disease exists a dopaminergic cholinergic and GABAergic glutaminergic neurotransmitter imbalance in the extrapyramidal system. In the caudate nucleus D2 dopaminergic neurons weakly activate GABAergic neurons in the external globus pallidus which inhibit glutaminergic neurons in the subthalamic nucleus. GABAergic neurons in the internal globus pallidus, activated by glutaminergic neurons, weakly inhibit *via* GABAA receptors M4 muscarinic cholinergic neurons in the putamen which strongly activate glutaminergic neurons. The latter neurons enhance dopamine deficiency through a strongy presynaptic inhibition *via* NMDA receptors.

In Alzheimer's disease might exist a noradrenergic cholinergic and glutaminergic GABAergic neurotransmitter imbalance in the hippocampus and the temporal cortex. In these brain regions M1 muscarinic cholinergic neurons weakly activite GABAergic neurons which weakly inhibit noradrenergic neurons *via* GABAA receptors. The alpha1 noradrenergic neurons strongly activiate glutaminergic neurons which strongly inhibit muscarinic cholinergic neurons *via* NMDA receptors.

Conclusion: Examining neural networks enables to develop a prophylactic medication.

PO-29

Track: *Drug Delivery & Targeting*

ELECTROSPUN PCL BASED ANTI-INFECTION DRUG-LOADED GUIDED TISSUE REGENERATION MEMBRANES

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Infection is the major reason causing the GTR/GBR membrane failure in clinical. Herein, we developed a localized anti-infection drug delivery system to prevent infection by inhibiting the bacterial colonization and reducing the foreign body response. An antibiotic, metronidazole (MNA), was successfully incorporated into electrospun polycaprolactone (PCL) nanofibers at different concentrations (0, 1, 5, 10, 20, 30 and 40 wt. % polymer) in a single-step process. To obtain the most suitable drug loading content, the physical-chemical and mechanical properties of the drug delivery system with different drug content were systemic investigated in-depth. The interaction between PCL and MNA was identified by molecular dynamics simulation. In vitro drug release studies demonstrated that MNA released in a controlled sustained manner over 2 weeks and the released MNA remained antibacterial activity which was assessed by *in vitro* static experiment against Fusobacterium nucleatum bacteria. The incorporation of MNA improved the hydrophilicity and *in vitro* degradation rate of PCL nanofibers. The nano-fibrous membranes allowed cells to adhere to and proliferate on them, and all showed excellent barrier function. From *in vitro* experimental results, we concluded that the membrane with 30% MNA had the best comprehensive properties. Analysis of subcutaneous implants demonstrated that MNA encapsulated nanofibers evoked a less severe inflammatory response than the pure PCL nanofibers examined. These results demonstrate their potential as GTR/GBR membrane with antibacterial and anti-inflammatory function and may be broadly applied to more biomedical applications.

Keywords: Guided tissue regeneration, Electrospinning, PCL, Metronidazole, Anti-infection, Controlled delivery.

PO-94

Track: *Medical Imaging*

GADOLINIUM (III) INCORPORATING QUANTUM DOT-SIZED CONJUGATED POLYMER-BASED BIOCOMPATIBLE DOTS AS A DUAL-MODALITY PROBE FOR CANCER DISGNOSIS

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Understanding the localization and engraftment of tumor cells is of high importance in cancer diagnosis and treatment. Advanced fluorescent probes and facile methodologies play a key role for cell tracing in cancer diagnosis. We have designed and synthesized a dual-modality imaging dots with both optical and magnetic contrast through integration of a magnetic resonance imaging (MRI) contrast agent, gadolinium (III) chelate, into a novel long-term cell tracing probe in far-red/near-infrared region. The obtained fluorescent-magnetic dots have both high fluorescence quantum yield (25%) and T_1 relaxivity (7.91 $mM^{-1}s^{-1}$) in aqueous suspension. After further conjugation with a cell membrane penetrating peptide, the dual-modality dots can be efficiently internalized into living cells. The gadolinium (III) chelate allows accurate quantification of biodistribution of cancer cells via intraveneous injection, while the high fluorescence provides engraftment information of cells at single cellular level. The dual-modality dots shows obvious synergistic advantages over either single imaging modality and hold great promises in advanced biomedical studies.

PO-96

Track: *Hot Topics in Medicinal Chemistry*

SYNTHESIS AND ANTI-HCV ACTIVITY EVALUATION OF ANILINOCOUMARIN DERIVATIVES

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The hepatitis C virus (HCV) is a major cause of liver disease worldwide, including hepatic fibrosis, liver cirrhosis, and hepatocellular carcinoma (HCC). Novel anilinocoumarins were synthesized, and their efficacy against HCV replication was evaluated. We demonstrated that 3-(3',4',5'-trimethoxyanilin-1'-yl)-methylaminocoumarin (6) exhibited strong anti-HCV activity at protein and RNA levels at non-toxic concentrations, with an EC50 value of 12 ± 0.3 μM and a selective index (SI) value of 10. Combined treatment of compound 6 and interferon-α (IFN) or telaprevir induced a significant decrease in HCV RNA levels, respectively. We also found that the anti-HCV replication effect of compound 6 was due to the induction of IFN-mediated antiviral responses. This is the first report demonstrating that coumarins inhibit viral replication through an IFN-mediated anti-viral response. Collectively, compound 6 possessed potent activities against HCV replication and could be a new lead compound with higher selectivity and less toxicity.

Keywords: Aanti-HCV, anilinocoumarin, selective index.

PO-82

METHYLSULFONYLMETHANE SUPPRESSES BREAST CANCER GROWTH THROUGH DOWN-REGULATING STAT3 AND STAT5B PATHWAYS

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Breast cancer is the most aggressive form of all cancers, with high incidence and mortality rates. The purpose of the present study was to investigate the molecular mechanism by which methylsulfonylmethane (MSM) inhibits breast

cancer growth in mice xenografts. MSM is an organic sulfur-containing natural compound without any toxicity. In this study, we demonstrated that MSM substantially decreased the viability of human breast cancer cells in a dose-dependent manner. MSM also suppressed the phosphorylation of STAT3, STAT5b, expression of IGF-1R, HIF-1α, VEGF, BrK, and p-IGF-1R and inhibited triple-negative receptor expression in receptor-positive cell lines. Moreover, MSM decreased the DNA-binding activities of STAT5b and STAT3, to the target gene promoters in MDA-MB 231 or co-transfected COS-7 cells. We confirmed that MSM significantly decreased the relative luciferase activities indicating crosstalk between STAT5b/IGF-1R, STAT5b/HSP90a, and STAT3/VEGF. To confirm these findings *in vivo*, xenografts were established in Balb/c athymic nude mice with MDA-MB 231 cells and MSM was administered for 30 days. Concurring to our *in vitro* analysis, these xenografts showed decreased expression of STAT3, STAT5b, IGF-1R and VEGF. Through *in vitro* and *in vivo* analysis, we confirmed that MSM can effectively regulate multiple targets including STAT3/VEGF and STAT5b/IGF-1R. These are the major molecules involved in tumor development, progression, and metastasis. Thus, we strongly recommend the use of MSM as a trial drug for treating all types of breast cancers including triple-negative cancers.

PO-54

Track: *HIV Research*

EFFECT OF JIN'AN TABLET FOR THE TREATMENT OF DYSMENORRHEA IN RATS

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Jin'an tablet is a traditional Chinese Medicine preparation for the treatment of dysmenorrhea in clinic. To study the effect of Jin'an table on dysmenorrhea. The dysmenorrhea rats were given Jin'an tablet with 0.4 g/kg, 0.8 g/kg and 1.6 g/kg after treated with diethylstilbestrol, then modeled by oxytocin. The antinociceptive effect of Jin'an tablet was examined by writhing test *in vivo*. The anti-contractile effect on uterine smooth muscles of Jin'an tablet was evaluated *in vivo* and *vitro*. Results are expressed as mean ± S.E.M. The data were analyzed by t–test. The Jin'an tablet significantly reduced the writhing times and prolonged the latency period ($P<0.01$). The amplitude and frequency of contraction were significantly reduced by Jin'an tablet above 0.4 g/kg, $P < 0.05$. The spontaneous contraction was also significantly depressed by Jin'an tablet solution above 8 % ($P<0.05$) and the frequencies and amplitude of contraction increased by diethylstillbestrol can be contradicted by Jin'an tablet solution above 4 % ($P<0.05$). These results suggested that Jin'an tablet had good anti- dysmenorrhea effect.

PO-109

6-SHOGAOL INHIBITS PANCREATIC TUMORS AND SENSITIZES THEM TO GEMCITABINE TREATMENT BY MODULATING NF-κB SIGNALING

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Previous studies have shown that 6-shogaol, a phenolic alkanone isolated from ginger, possesses anti-cancer activities in many cancer cell lines. However, the anti-tumor potential of 6-shogaol has been unexplored in pancreatic cancers. NF-κB has been reported to play a major role in chemoresistance of pancreatic cancer cells. In the present study, we investigated whether 6-shogaol could enhance anti-tumor activity of gemcitabine in treatment of pancreatic cancer. We used two human pancreatic cancer cell lines PANC-1 and BxPC-3 with variable *K-ras* status. *In vitro* studies, we found that co-treatment with 6-shogaol and gemcitabine resulted in more growth inhibition compared with either agent used alone. These effects were correlated with suppression of NF-κB-regulated gene products COX-2, cyclinD_1, survivin, and cIAP-1, XIAP, Bcl-2 and MMP-9. In a xenograft nude mice model of human pancreatic cancer, intraperitoneal injection of 6-shogaol inhibited tumor growth and enhanced the anti-tumor effects of gemcitabine. Immunohistochemical analysis results showed less expression of Ki-67 and more TUNEL staining in tumor tissues from combination treatment group. This was consistent with inhibition of NF-κB activity. On the whole, our results indicate that 6-shogaol can sensitize pancreatic cancer cells to gemcitabine by suppressing of NF-κB signaling, which is an inflammatory pathway linked to tumorigenesis.

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