Poster Presentations

Drug Discovery & Biochemistry Conference 2017

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4th International Congress on
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BIOCHEMISTRY, MOLECULAR BIOLOGY: R&D

November 02-03, 2017 Chicago, USA

Present and future collaborative drug discovery informatics innovations

Luke S Fisher
Collaborative Drug Discovery, USA

CDD's unique IT architecture (true multi-tenant) allows for distinctive use cases compared to traditional (single tenant, virtualized) drug discovery informatics platforms. CDD's architectural principles and the application of modern engineering methodologies enable CDD to democratize traditionally expert informatics tools so that all scientists can benefit. CDD Vault was created from scratch to work with the cloud. As a natural consequence, CDD Vault's architecture and features accommodate those modern requirements. We will explain how the benefits of modern cloud IT principles can propel science forward.

Speaker Biography

Luke's background brings twenty years of experience in scientific informatics solutions. Managing Pre-Sales, Post-Sales and working in Account Management has expanded his domain knowledge of scientific informatics and provided him the ability to maintain a successful track record. Luke serves leading pharmaceutical, biotech, agricultural, chemicals, academic and government labs. Luke has experience in scientific software solutions from the smaller scale deployment of point solutions like molecular modeling packages to the larger enterprise scale of ELNs, scientific workflow technologies, data content, analysis and visualization. His background also includes managing the support complexity of software integration strategies based on numerous mergers and acquisitions.

e: luke@collaborativedrug.com

Notes:

In silico, in vitro and *in vivo* studies for analyzing the propranolol action on cholinergic and carbonic anhydrase systems

Emily L Castillo-García, Marvin A Soriano-Ursúa, Fabiola J Ciprés-Flores, Erik Andrade-Jorge and **Eunice D Farfán-García**
Instituto Politécnico Nacional, Mexico

Propranolol is a well-known antagonist of adrenergic receptors. In fact, it is classified as a non-selective blocker of beta-adrenergic receptors. However, several other biological activities have been suggested or demonstrated to that molecule. On the other hand, it is known this drug can be active on Central Nervous System (CNS) after oral administration due to its ability to entering trough the blood brain barrier after this pathway. In this work, we tested the activity of propranolol on the cholinergic and carbonic anhydrase systems, which together with the adrenoceptor systems are considered related to potential therapeutic target to CNS-disorders, particularly, those related to cognitive deficit. We approach this topic by *in silico* assays on acetylcholinesterase and carbonic anhydrase showing the ability of this compound to interact on the active sites and potentially exert an effect on these sites. But also, we used these enzymes *in vitro* for observing the capability of this compound to inhibit their action. Finally, we corroborate the improvement of performance in passive avoidance task after its administration in male rats with cognitive deficit induced by orchiectomy. By taking all together, our results suggest the attractiveness to study propranolol as a multi-target drug modulating the cognitive processes for treating CNS disorders.

Speaker Biography

Emily L Castillo-García has completed her training as Biochemistry Engineer in Instituto Tecnológico de Acapulco, Guerrero, Mexico. She is working in Medicinal Chemistry Research and neuroscience projects the last three years. She is particularly interested in the action of some molecules on neurodegenerative disease: steroid hormones, adrenergic agents and enzyme inhibitors. Currently, she is enrolled in Master in Health Sciences program in Escuela Superior de Medicina del Instituto Politécnico Nacional. Her research-advances have been presented in several national and international congresses.

e: emily.castillo.ibq@gmail.com

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Synthesis and cytotoxic activity screening of novel piperazinyl pyrimidine derivatives

Meric Koksal[1], Tugce Ozyazici[1], Ece Gürdal[1], Mine Yarım[1], Eren Demirpolat[2] and **M Betul Yerer Aycan[2]**
[1]Yeditepe University, Turkey
[2]Erciyes University, Turkey

The discovery of potent, selective and less toxic anticancer compounds is an important goal for researchers in the field of Medicinal Chemistry. In recent years, several pyrimidine derivatives have been involved in the structure of many compounds which have been used as chemotherapeutic agents and they have used in wide clinical applications. In this study, a group of novels 6-phenyl-3-[2-(substituted piperazinyl) ethyl] hexahydropyrimidine-2,4-dione derivatives to observe the desired anticancer activity due to pyrimidine and piperazine based scaffolds. Synthesized compounds purity was determined with thin layer chromatography and their molecular structures were lightened with FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques.

e: merickoksal@yeditepe.edu.tr

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Computer aided design of small molecule inhibitors of Receptor Tyrosine Kinases (RTKs)

D S Dalafave
The College of New Jersey, USA

Introduction: The development of drug resistance is a leading cause of treatment failures in many cancers. MAPK is an important cell signaling pathway. Many cancer drugs are designed to induce MAPK inhibition (MAPKi). Although MAPKi reduces cancer growth and migration, it is usually accompanied by the establishment of bypass signaling mediated by certain Receptor Tyrosine Kinases (RTKs). As a result, most patients acquire a resistance to MAPKi within a year. The simultaneous inhibition of implicated RTKs and MAPK is needed to overcome drug resistance. Most kinase inhibitors bind to the kinase ATP-binding site. The high homology of these sites among different kinases makes them challenging to target specifically. The specificity is important, since drugs that indiscriminately inhibit several kinases may harm healthy cells. Unlike ATP-competitive inhibitors, an allosteric inhibitor can retain its inhibitory effectiveness at various ATP concentrations. Allosteric sites vary between various kinases and thus allow a highly specific binding with fewer side effects. Patients that develop MAPKi resistance show a significant accumulation of certain RTKs, such as AXL and MET. AXL and MET are involved in many cellular processes. Several inhibitors of these kinases have been found. However, they all bind to the kinases' catalytic sites and, thus, lack selectivity. This work focuses on computational design of small druglike molecules that could potentially allosterically bind AXL and MET and, thus, prevent the creation of signaling that would bypass MAPK inhibition.

Materials and Methods: The following software and servers were used to analyze AXL and MET and their putative inhibitors: Protein Data Bank (PDB), Deep View, ArgusLab, Molinspiration, and Osiris Data Warrior. Three-dimensional structures of AXL and MET were obtained from the PDB (5TC0 and 5MJA, respectively). The DeepView program was used to simultaneously analyze the active sites, atomic distances, H-bonds, and charge densities of the molecules. The Argus Lab program was employed to analyze the docking sites and perform docking calculations. Druglike properties of designed small molecules were evaluated using the Molinspiration and Osiris Data Warrior programs. ATP-competitive inhibitors of AXL and MET were uploaded in ArgusLab and docked to the kinases. Fig. 1 a) and b) show the ATP pockets of AXL and MET, respectively, bound to their known ATP-competitive inhibitors. The figures show the AXL and MET residues within 6.0 Å from their respective inhibitors.The known inhibitors of AXL and MET were used as starting templates to computationally design new molecules that could potentially bind both AXL and MET. Atomic substitutions were done in the original inhibitors to achieve improved druglikeness of the newly designed molecules. Molecules that showed optimal druglike properties were chosen for further docking studies. The designed molecules were reconstructed and optimized in ArgusLab by using the Semiempirical Geometry Optimization. The Argus Dock function was used to dock the molecules in AXL and MET. The AScore function and a 0.4 Å grid resolution were used for the docking calculations. ArgusLab evaluated binding affinities of the designed molecules to the AXL and MET kinases.

Results and Discussion: One of the designed molecules was found to have optimal druglike properties and no indicated toxicities. The molecule formed stable complexes with AXL and MET, binding each allosterically. Fig. 2 shows the molecule docked to an allosteric site of AXL. The binding changed the configuration of the catalytic site and so prevented the binding of the ATP molecule in the site. The ATP molecule bonded in a new location. Fig. 3 shows the molecule docked allosterically in MET. The ATP molecule again bonded outside the catalytic site.

Conclusions: This work addresses computational design of putative allosteric inhibitors of the AXL and MET kinases. A designed molecule with promising druglike properties bonded to allosteric sites of the kinases. The binding caused conformational changes in the catalytic sites, which prevented the ATP molecule from binding there. The development of small molecule inhibitors that could simultaneously allosterically bind AXL and MET shows a promise for preventing the bypass signaling mediated by AXL or MET.

e: dalafave@tcnj.edu

Natural isoquinoline alkaloids as potential multi-target agents against Alzheimer's disease

Erika Plazas G, Avila M C, Sandoval A and **Cuca L E**
Universidad Nacional de Colombia, Colombia

Statement of the Problem: Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and main form of dementia in elder people. AD is a multifactorial disorder with a complex pathogenesis, characterized by a progressive loss of memory and other cognitive abilities, associated with cholinergic detriment. Currently, cholinesterase inhibitors are the only approved drugs for treatment of AD; however, these only improve cognitive ability and have significant side effects. Consequently, the development for new therapeutically agents more effective and safety is necessary. Multi-target therapy is an innovative strategy focused on the treatment of complex diseases which arises to overcome lack of traditional paradigm "one molecule-one target". New generation of multi-target agents required not only to improve symptoms, but also to modify the disease.

Methodology: We achieved the AChEI-targeted isolation of isoquinoline alkaloids from *Ocotea discolor* (*Lauraceae*) and *Zanthoxylum schreberi* (*Rutcaeea*). Based on the amyloid hypothesis, was evaluated the multimodal potential. Thus, were assessed the anticholinergic activity against acetylcholinesterase (AchE) and butyrylchlolinesterase (BChE); antioxidant capacity (DPPH and β- carotene) and LXR agonists activity.

Findings: The studied species were selected from a previous screening of antioxidant and anticholinergic activity carried out in our laboratory. From the wood of *O. discolor* were isolated 3 aporphine alkaloids ocoxilonine, ocoteine and dicentrine. On the other hand, from the stem bark of *Z. schreberi* were isolated 2 protoberberines (berberine and columbamine) and a benzophenanthridine (chelerythrine). Four of the isolated alkaloids showed strong inhibition of AChE with IC50 lower than 50 µg/mL. Most of these were more active against AChE than BChE, nevertheless, columbamine and ocoxilonine were selective against BChE. The aporphine alkaloids presented highest antioxidant capacity. Additionally, the isolated alkaloids showed potential inhibition of LXR.

Conclusion & Significance: Isoquinoline alkaloids have multimodal prospective due to their activity against different AD targets, abundant distribution and few pharmacological studies.

Speaker Biography

Erika Plazas G is a PhD student, Chemist with Master's in Science degree. Her experience in Natural Products Chemistry has been encouraging a growing interest in Medicinal Chemistry and Bioprospecting. Also, she has experience in research, evaluation, teaching and experimental work, specifically in Phytochemistry, Organic and Analytical Chemistry. Additionally, she has skills in natural products, biological activity assays, extraction, purification and identification techniques and management of instrumental (HPLC and GC) and spectroscopic (UV, IR, MS and NMR) methods, as well as, programs for multivariate statistical analysis (PCA, OPLS-DA) focused on metabolomic studies.

e: eaplazasg@unal.edu.co

Notes:

The dependence of the kNN-QSAR models on the initial descriptors set generation

Fatima T Adilova, Rifkat R Davronov and **Uygun U Jamilov**
Institute of Mathematics, Academy of Sciences, Uzbekistan

Statement of the Problem: QSAR model development and validation has led to establish a complex strategy that can be used to prioritize the selection of chemicals for the experimental validation. The high accuracy of the training set model characterized with leave-one-out cross validated R2 (q2).However, the dependence of this method on the descriptors initial set has not been previously studied.

Methodology & Theoretical Orientation: In this study, following the kNN-QSAR principle, we to study the dependence of the kNN-QSAR on the initial set of descriptors, using of two other packages -rcdk , Dragon, and all calculations were carried out in the system R.

Findings: The first data set was a well-known group of ligands of corticosteroid binding globulin. From all 320 models from two training sets the best predictive model was characterized by q2 = 0.74, R2 =0.86, R0 2= 0.82, RMSE = 0.04, F = 49.3, k = 0.98 and P = 1.1 × 10−4. The second data set was the alkaloids of harmala ordinary quinazoline structure and derivatives. The original sample was randomly broken up three times divided into a training, test samples, while laying down an external sample. Three series of simulation running were conducted, in each of which 242, 99 and 10 QSAR models were built; the best predictive model produced from the first training set: q2 = 0.72, R2 =0.92, R02= 0.87, RMSE = 0.005, F = 318.88, k = 1.02 and P = 6.9 × 10−7.

Conclusion & Significance: The required dependence exists, so it is necessary to determine the criteria for the robustness of the models. In addition, it would be promising to study other methods for determining the proximity and similarity of compounds.

Speaker Biography

Adilova Fatima has completed her PhD at the age of 30 years Institute of Cybernetics, Academy of Sciences, Uzbekistan and postdoctoral studies from the Institute of Control Science, Russian Academy of Sciences. She is the Head of Biomedical Lab., Institute of Mathematics , Academy of Sciences, Uzbekistan. She has published more than 60 papers in reputed journals and has been serving as an expert of State Committee of Science &Technology.

e: fatima _adilova@rambler.ru

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Stability indicating UHPLC method for the assay of maraviroc in bulk and in formulations

Geetha Reddy M
Dr. Reddy's Laboratories, India

An Ultra High Pressure Liquid Chromatographic method was developed for the estimation of Maraviroc in bulk and in formulations. The separation was achieved on X bridge (C18 20 x 4.6 mm, 2.5 µ column) using 0.01M potassium dihydrogen phosphate (KH2PO4) (pH 7.0 adjusted with ortho phosphoric acid) and acetonitrile (60:40) as mobile phase. The flow rate kept at 0.5 mL/min, column temperature 30°C, and the column eluents were monitored at 210 nm. The forced degradation studies were done to show stability indicating power of the method. The method has been validated accordance with ICH guidelines for specificity, precision, accuracy, linearity, limit of detection, limit of quantification, robustness and ruggedness. The results were found to be well within the limits. The method can be used for the routine analysis of Maraviroc bulk and in formulations.

e: geetharm@drreddys.com

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Influence of multiprobiotic on concentration of Collagen and Non-Collagen protein monomers in rat's parodont during continuous hypoacidosis

A.O. Mykytenko, K.S. Neporada, T.V. Berehova and **D.S. Yankovsky**
Ukrainian medical stomatological academy, Ukraine

The aim of the research was to study the influence of the multiprobiotic "Symbiter forte omega" on pathological changes in soft tissues of rats' periodontal tissues under the conditions of prolonged use of omeprazole. Experiments were performed on 46 white male rats weighing 180-250 g. The animals were divided into 3 groups: I - control, 0.2 ml of water for injection intraperitoneally was administered to rats daily for 28 days; II - rats that received omeprazole daily (during 28 days) (14 mg / kg body weight intraperitoneally); III - omeprazole (14 mg / kg body weight intraperitoneally) in combination with "Symbiter forte omega" (0.14 ml / kg body weight orally) was administered. Animals were sacrificed under urethane anesthesia (50 mg / kg body weight intraperitoneally) by bloodletting. The object of the study was soft periodontal tissues, in which the content of free oxyproline (Tetyanets S.S., 1985), fucose (Sharaev PN, 1997) and glycosaminoglycans (GAG) (Sharaev PN, 1987) was determined. The content of oxyproline in soft periodontal tissues after 28-day omeprazole administration increased in 1.87 times (P <0.05) when compared with control. Content of oxyproline in soft periodontal tissues of rats which recieved multiprobiotic "Symbiter forte omega" showed a decrease in comparison with animals without correction in 1.49 times (P <0.05). We estimated that the content of GAG in soft periodontal tissues of rats under conditions of long hypoacidity on 28 day of the administration of omeprazole increased in 1.37 times (P <0.05) when compared to control group. The use of the multiprobiotic "Symbiter forte omega" during 28 days on the background of omeprazole-induced hypoacidity contributed to reduction in GAG content in 1.89 times (P <0.05) in soft periodontal tissues of rats when compared with non-corrected animal group. Investigating the content of free fucose in soft periodontal tissues under conditions of omeprazole-induced hypoacidity, the following results were obtained: the multiprobiotic "Symbiter forte omega" reduced the content of fucose in periodontal tissues in 1.61 times (P<0.05) in comparison with the control group and in 1.12 times (P <0.05) when compared to the rats without correction. Thus, in conditions of prolonged omeprazole-induced hypoacidity, there is an increased catabolism of collagen and non-collagen proteins in rats' periodontal tissues. Multiprobiotic "Symbiter forte omega" protects against depolymerization of collagen and non-collagen structures of periodontal connective tissue under conditions of long hypoacidity.

e: andrey_stomat@ukr.net

Agricultural biomass production is an energy option for the future

Abdeen Omer
Energy Research Institute, UK

The demand for energy continued to outstrip supply and necessitated the development of biomass option. Residues were the most popular forms of renewable energy and currently biofuel production became much promising. Agricultural wastes contained high moisture content and could be decomposed easily by microbes. Agricultural wastes were abundantly available globally and could be converted to energy and useful chemicals by a number of microorganisms. Compost or bio-fertiliser could be produced with the inoculation of appropriated thermophilic microbes which increased the decomposition rate, shortened the maturity period and improved the compost (or bio-fertiliser) quality. The objective of the present research was to promote the biomass technology and involved adaptive research, demonstration and dissemination of results. With a view to fulfill the objective, a massive field survey was conducted to assess the availability of raw materials as well as the present situation of biomass technologies. In the present communication, an attempt had also been made to present an overview of present and future use of biomass as an industrial feedstock for production of fuels, chemicals and other materials. We may conclude from the review paper that biomass technology must be encouraged, promoted, invested, implemented, and demonstrated, not only in urban areas but also in remote rural areas. The move towards a low-carbon world, driven partly by climate science and partly by the business opportunities it offers, will need the promotion of environmentally friendly alternatives, if an acceptable stabilisation level of atmospheric carbon dioxide is to be achieved. The biomass energy, one of the important options, which might gradually replace the oil in facing the increased demand for oil and may be an advanced period in this century. Any county can depend on the biomass energy to satisfy part of local consumption. Development of biogas technology is a vital component of alternative rural energy programme, whose potential is yet to be exploited. A concerted effect is required by all if this is to be realised. The technology will find ready use in domestic, farming, and small-scale industrial applications. Support biomass research and exchange experiences with countries that are advanced in this field. In the meantime, the biomass energy can help to save exhausting the oil wealth.

e: abdeenomer2@yahoo.co.uk

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Phytochemical composition, cytotoxicity and *in-vitro* antiplasmodial activity of fractions from *Alafia barteri* olive (Hook F. Icon)-*Apocynaceae*

Lasisi A A[1], Olayiwola M A[2], Balogun S A[1], Akinloye O A[1] and **Ojo D O[1]**
[1]Federal University of Agriculture, Nigeria
[2]Federal College of Education, Nigeria

The ethanolic extract of *Alafia barteri* (Hook F. Icon) was dissolved in distilled water and successively partitioned in n-hexane, chloroform, ethyl acetate and n-butanol. The fractions were evaluated for phytochemical composition, lethality against brine shrimp larvae and *in-vitro* antiplasmodial activity against *Plasmodium falciparum* strain. The obtained results revealed that the roots and leaf extracts of *A. barteri* exhibited broad spectrum of antiplasmodial activity (IC50 1.5±0.7 - 6.2±0.80 µg/mL). The aqueous leaf fractions displayed the most potent antiplasmodial activity with an IC50 value of 1.5±0.7 µg/mL, which is comparable to reference antimalarial drug (IC_{50} value of 1.3±0.2 µg/mL). The leaf fractions displayed higher activity than the root extracts. The highest minimum lethal concentration (105.2±0.8 ppm) was exhibited by the aqueous leaf extract followed closely by the root extract (120.2±1.1 ppm). The leaf extracts contained higher polyphenols (45.3±0.85 mgGAE/g) and flavonoids (18.10±0.2 mgCTE/g) than the root extracts. The n-hexane and EtOAc extracts/fractions displayed lower activity on brine shrimp larvae.

e: lasialiyu@yahoo.com

Separation of synthetic peptides and proteins by polystyrene bound silica monolith particles as HPLC stationary phase

Ashraf Ali and **Won Jo Cheong**
Inha University, South Korea

Partially or fully sub-1 µm and sub-2 µm porous silica particles have achieved more interests as column packing materials in separation due to enhanced separation efficiency, fast separation and high separation resolution. Sub-1 µm porous silica monolith particles have been prepared successfully prepared by sol-gel process followed by grinding and calcinations at 550. A high-efficient HPLC stationary phase based on porous silica monolith particles has been prepared by reacting 4-chloromehtylphenylisocynate (4-CPI) to porous partially sub-1 µm monolithic silica particles via isocyanate-hydroxyl reaction using dibutyltin dichloride (DBTDC) as a catalyst followed by initiator attachment and RAFT polymerization of styrene. The resultant phase was packed in glass lined stainless steel micro-column (1.0 mm x 300 mm), and the separation efficiencies as high as 60,000 plates (200,000/meter) were achieved for the separation of peptides and proteins using 60/40 acetonitrile/50 mM ammonium format (v/v %) with at a flow rate of 25 µL/min. The separation efficiency of this new phase is comparable or even better than some of commercial available stationary phases. This phase has shown some encouraging possibility for fast analysis when packed in a short column. This study offers a promising vision towards commercialization of chromatographic phases based on silica monolith particles.

e: ashrafaliswati@gmail.com

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Cellular zinc homeostatic mechanisms function as an off switch for zinc metallochaperone mediated reactivation of mutant p53

Xin Yu[1, 2], Samuel Kogan[1, 2, 3], Ying Chen[2], Ashley T Tsang[1, 2, 5], Tracy Withers[2], Hongxia Lin[2], Chunxia Chen[2], Dirk F Moore[2], Joseph Bertino[2], Chang Chan[2, 4] and **Darren R Carpizo[1, 2, 3]**

[1]Rutgers Robert Wood Johnson Medical School, USA
[2]Rutgers Cancer Institute of New Jersey, USA
[3]Rutgers University, USA
[4]Rutgers Robert Wood Johnson Medical School, USA
[5]Mount Sinai St. Luke's and Mount Sinai West, USA

The p53 transcription factor functions as one of cancer's most potent tumor suppressors and is the most frequently mutated gene in human cancer. The majority of p53 mutations (>70%) are missense that generate a defective protein found at high levels in cells that is targetable. Restoration of wild type structure and function of mutant p53 with a small molecule (so-called reactivation) is a highly sought-after goal in anti-cancer drug development. The p53 protein requires the binding of a single zinc ion to fold properly and mutations that impair the protein's ability to bind zinc (and cause it to misfold) are highly prevalent in cancer. We recently discovered a new class of small molecule zinc chelators named zinc metallochaperones (ZMCs) that reactivate zinc deficient mutant p53 through a novel mechanism involving both zinc ionophore activity to raise intracellular zinc concentrations and donation to restore zinc binding to mutant p53. This induces a wild type conformation change and a p53 mediated apoptotic program. The lead compound (ZMC1) displays a transient pharmacodynamics (p21 levels) *in vitro*. We hypothesized that the regulation of these pharmacodynamics is governed by cellular zinc homeostatic mechanisms that function to restore zinc to its physiologic picomolar levels. We examined the entire suite of zinc homeostatic genes in response to ZMC1 and manipulated several metallothionein genes by knockout and knockdown. The net effect of this was to increase the peak and duration of intracellular zinc levels that lead to a more potent and sustained duration of p21 expression. This translated to increased sensitivity to ZMC1. We further postulated that this pharmacodynamics would allow the drug to function with very minimal exposure and colony formation studies *in vitro* indicated that a two-hour exposure was as effective as a 72-hour exposure. We then sought to translate this mechanism *in vivo* using a genetically engineered murine model of KPC pancreatic cancer (Pdx-1Cre; KrasG12D) that expresses either the p53R172H (zinc deficient) allele or p53R270H (non-zinc deficient). Pharmacokinetic (PK) studies of the drug revealed a short half-life (15 minutes) indicating a minimal exposure. Despite this, daily, intermittent dosing at the maximum tolerated dose resulted in a statistically significant increase in the overall survival of the KPC-p53R172H mice while having no such effect in the KPC-p53R270H. We sought to improve the efficacy of ZMC1 by preloading it with zinc in a 2:1 molar ratio based on the crystal structure. The drug-zinc complex (Zn-1) increased the median survival of KPCp53-R172H mice from 26 days to 35 days (ZMC1 monomer versus Zn-1). These studies indicate that cellular zinc homeostatic mechanisms function as an "off" switch for ZMC's which has important implications for the translation of ZMCs in humans. Principally, this allows the drug to function with minimal exposure which minimizes potential zinc toxicity. ZMC1 as monotherapy improves survival in an allele-specific mutant p53 manner. Furthermore, ZMC1 can be optimized by synthesizing it complexed with zinc. Overall, this "off" switch is novel for a targeted molecular therapeutic and represents a significant departure from the traditional paradigm where the goal is to develop a compound that binds the target with a PK profile that provides maximal exposure.

e: carpizdr@cinj.rutgers.edu

Reprogramming lipid synthesis in Chinese Hamster Ovary (CHO) cells for enhanced recombinant protein production

Folasade Ajayi
University of Kent, UK

The endoplasmic reticulum (ER) plays a critical role in protein folding, protein secretion, calcium homeostasis, and lipid biosynthesis. Mammalian cells are often used for the production of recombinant biotherapeutic proteins where the secretory pathway machinery, including the ER, is essential to the correct folding, assembly and post-translation modifications required of the target protein. However, expression of recombinant proteins in high amounts in mammalian cells can result in ER stress, which can result in cellular responses and multiple stimuli from the ER that activate the unfolded protein response (UPR), slow protein synthesis and can negatively impact upon protein yields and quality. The maintenance of the ER and secretory pathway system requires a carefully coordination of lipid biosynthesis. Here we investigate approaches and strategies to design new hosts and cellular circuits to reprogramme the CHO cell ER with a view to either expanding its capacity and/or subsequent secretory vesicle system to improve cell growth, yields and quality of recombinant secreted proteins. Our hypothesis is that controlled manipulation of lipid biosynthesis will result in an enhancement of the efficiency of the CHO platform as a recombinant protein expression system. Here we report on the manipulation of the CHO lipid biosynthesis machinery by altering key components. We have transiently and stably over-expressed two proteins in particular reported to led to expansion of the ER in CHO cells. Stable cell pools have subsequently been cloned via limited dilution cloning to obtain clonal cell lines. Over-expression of the lipid biosynthesis proteins did not impact upon cell growth behaviour, however transient expression of two model recombinant proteins (EPO and Etanercept – a TNFR-Fc fusion protein) that are difficult to express in CHO cells was enhanced in CHO cells engineered to over-express the lipid biosynthesis proteins. Here we present implications for this and potential applications.

e: faa8@kent.ac.uk

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Preliminary investigation of the phytochemical properties of aqueous and ethanolic crude extracts of *Hunteria umbellata K.* (Schum) seeds and its antihypertensive effects on salt induced hypertension in Wistar Rats

O C Udinyiwe, F I Okolafor, S Uwansojie and **F O Ekhaise**
University of Benin, Nigeria

Hunteria umbellata seeds are used ethnomedicinally to treat obesity, pain, swellings, anaemia and as immune booster. However there has been no scientific proof of its uses in the managements of hypertension ethnomedicinally, hence the aim of this study, therefore, was to investigate the preliminary phytochemical properties of aqueous and ethanolic crude extracts of *Hunteria umbellata* seeds and its physiological effects on salt induced hypertension in experimental animals. The phytochemical studies were carried out according to the methods of Association of Official Analytical Chemist (A.O.A.C). Twenty-five (25) female adult Wistar rats were administered with 8% of NaCl (salt) for 2 weeks and shared into five groups of five animals in each group. Group I was normal control, Group II was treated with 8% of NaCl, while Group III was treated with 8% of NaCl and 40 mg propranolol. Group IV was treated with 8% of NaCl and aqueous extract (500 mg/kg) of *Hunteria umbellate* and Group V was treated with 8% of NaCl and ethanolic extract (500 mg/kg) of *Hunteria umbellata*. The results of the quantitative phytochemical components of aqueous and ethanolic extracts revealed the presence of oxalate, phytate, tannins, flavonoids, saponins, alkaloids, phenols, cyanogenic glycoside and anthraquinones. The blood pressures of the animals were taken before and after salt treatments at a weekly interval. The administration of the standard drug (propranolol) caused a reduction in high systolic blood pressure of the hypertensive experimental animals from 162.00 mmHg to 134.00 mmHg, while the diastolic pressure was recorded to fall from 103.00 mmHg to 73.67 mmHg. The administration of aqueous extract of *H. umbellata* seeds caused a reduction of the systolic blood pressure of the hypertensive experimental animals from 159.20 mmHg to 136.25 mmHg, while the diastolic blood pressure was recorded to fall from 103.80 mmHg to 80.25 mmHg. The administration of ethanolic extract of *H. umbellata* seeds caused a reduction in systolic blood of the hypertensive experimental animals from 160.20 mmHg to 133.00 mmHg, while the diastolic pressure was recorded to drop from 102.20 mmHg to 76.75 mmHg. The results of this study showed that the systolic and diastolic blood pressure of the animals treated with the ethanolic extract and propranolol were reduced compared to control ($p<0.05$). The histological results of both aqueous and ethanolic extracts of *H. umbellata* seeds revealed appreciable recovery of the degenerating tissues. Medicinal plants have become a great source of medicine for the treatments and managements of hypertension and researches on the medicinal values of *H. umbellata* seeds and its therapeutic effects to health sector should be encouraged.

e: frederick.ekhaise@uniben.edu

Application of computer aided drug design strategies for optimization of anticancer activity of phenazinamine derivatives

Gajanan Sonwane and **Mayura Kale**
Government College of Pharmacy, India

We have efficient group based quantitative structure–activity relationships (G-QSAR). Exploring the relationship between the structures of a new promising family of 2- phenazinamine derivatives and their anticancer activities. We have residential evocative model, to aid in further optimization and expansion of newer anticancer agents containing pharmacophore. G-QSAR was performed on VLife molecular design suite (MDS) 4.2 version software. The extrapolative authority of the G-QSAR was checked through the cross-validation method and by separation some compounds as fraction of external test set. Synthesis of 5 novel derivatives 2- phenazinamine derivative by using result of GQSAR and screening of *in vitro* anticancer activity on K562 cell line was done in Tata Memorial Cancer Research Center Mumbai, India, showing improve anticancer activity. Phenazinamine and the analogues have better binding interactions with Oxidoreductase (PDB: 1YYD.) The binding energies of the protein-ligand interactions also confirm that the ligands are fit into the active pockets of receptor tightly. Docking perform in Autodock 4.2 version software.

e: sonwane.gajanan@rediffmail.com

Small molecule inhibition of apicomplexan FtsH1 disrupts plastid biogenesis in human pathogens

Katherine Amberg-Johnson
Stanford University, USA

The malaria parasite *Plasmodium falciparum* and related apicomplexan pathogens contain an essential plastid organelle, the apicoplast, which is a key anti-parasitic target. Derived from secondary endosymbiosis, the apicoplast depends on novel, but largely cryptic, mechanisms for protein/lipid import and organelle inheritance during parasite replication. These critical biogenesis pathways present untapped opportunities to discover new parasite-specific drug targets. We used an innovative screen to identify actinonin as having a novel mechanism-of action inhibiting apicoplast biogenesis. Resistant mutation, chemical-genetic interaction, and biochemical inhibition demonstrate that the unexpected target of actinonin in *P. falciparum* and *Toxoplasma gondii* is FtsH1, a homolog of a bacterial membrane AAA+ metalloprotease. P*f*FtsH1 is the first novel factor required for apicoplast biogenesis identified in a phenotypic screen. Our findings demonstrate that FtsH1 is a novel and, importantly, druggable antimalarial target. Development of FtsH1 inhibitors will have significant advantages with improved drug kinetics and multistage efficacy against multiple human parasites.

e: katieambergjohnson@gmail.com

Design, synthesis and biological evaluation of polyfunctional flavonoids: Anti-Alzheimer's agents

Manjinder Singh and **Om Silakari**
Punjabi University, India

Alzheimer's disease (AD), a complex neurodegenerative brain disorder, a most common cause of dementia among elderly people. To date, the AD is being managed by maintaining the levels of acetylcholine by inhibiting acetylcholinesterase (AChE). Polyfunctional compounds comprise a novel class of therapeutic agents for the treatment of multi-factorial disease like AD. Following this approach integrated with polyfunctional nature of flavonoids, a novel flavonoid based compounds were designed, synthesized and biologically evaluated against AChE, advanced glycation end products (AGEs) formation with additional free radical scavenging activity. The *in vitro* studies showed that the majority of synthesized derivatives inhibited AChE with IC_{50} values in the nanomolar range along with good AGEs inhibitory and radical scavenging activity. Among them, 7m, strongly inhibited AChE and was found to be more potent than the reference compound donepezil. Its potent inhibitory activity has been justified by docking analysis that revealed its dual binding simultaneously to catalytic active site (CAS) and peripheral anionic site (PAS) of AChE. Besides, this compound also exhibited greater ability to inhibit advanced glycation end products formation with additional radical scavenging property. It (7m) also ameliorated scopolamine-induced memory deficit in mice employing Morris water maze test, at the dose of 2, 5 and 10 mg/kg. Thus, flavonoids might be the promising lead compound as potential poly-functional anti-Alzheimer's agents.

e: manjinder2007@gmail.com

Recent advances in microbicide delivery

Namita Giri
West Coast University, USA

Statement of the Problem: HIV-1 (Human immunodeficiency virus) is the virus that causes AIDS (acquired immunodeficiency syndrome) and continues to be major global public health issues. HIV/AIDS is the leading cause of death among the women of reproductive age (15-49 years) and 62% of the new infections among adolescents occurred among adolescent girls. There were an estimated 2.1 million new HIV infections in 2013 and despite significant efforts; the rate of new HIV infections worldwide remains unacceptably high.

Findings: Therapeutic interventions could be targeted towards various steps in HIV-1 replication cycle. Highly active antiretroviral therapy (HAART) resulted in reduced viral replication/load and enabled immune system recovery, which finally led to increased life expectancy. Along with this other interventions under developments involves vaccines, treatment of other sexually transmitted diseases, ARTs for HIV infected population, and development of pre-exposure prophylaxis against HIV using ARVs and microbicides for vaginal and rectal use. Prevention strategy based on antiretroviral agents targeted as following approaches microbicides, preexposure prophylaxis (PrEP), and treatment as prevention. Microbicides are topical PrEP products (such as gels, capsules, tablets, films, and intravaginal rings (IVR)) designed to be applied either around the time of coitus, used daily (gels and films), or to deliver product over a prolonged period (IVR).

Conclusion & Future Perspective: Fate and future of AIDS mainly depends on how and to what extent preventive strategies against HIV 1 infection among women are effective? Future research should focus on developing true sterilizing cure with complete eradication of the virus, and a functional cure, which is a permanent suppression of the virus without significant replication in the absence of ART. Microbicides will provide a user-friendly technology that will widen the range of protective options and, will be under the control of women.

e: nGiri@westcoastuniversity.edu

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An unexpected tolerance of silicatein activity to mutations revealed due to a novel water-soluble silica precursor

Natalia V. Povarova[1], Nikolay A. Barinov[2], Nadezda M. Markina[1], Mikhail S. Baranov[1], Valery B. Kozhemyako[3] and **Konstantin A. Lukyanov[1]**
[1]Institute of bioorganic chemistry, Russia
[2]Federal Research and Clinical Center of Physical-Chemical Medicine, Russia
[3]Pacific Institute of Bioorganic Chemistry, Russia

Silicateins play the major role in formation of silica skeletal structures in marine sponges. They are members of the cathepsin family of cysteine proteases with 65% homology with human *Cathepsin L.* The critical substitution that turns proteolytic activity to silica polymerization is supposed to be Cys to Ser substitution in the catalytic triad (Cys-His-Asn). We synthesized a novel silica precursor for silicateins – tetrakis(glycerol)orthosilicate (TGS). We have tested TGS as a substrate for silicatein A1 from the marine sponge Latrunculia oparinae. It effectively formed silica particles with and the amount of polymerized silica 1000-fold greater than previously described for silicatein alpha S.domuncula and tetraethyl orthosilicate. Then we investigated the activity of few silicatein point mutants – we substituted catalytic Ser and its flanking residues to the residues from its cathepsin homolog (S25C, Y26W, GAS23-25KSC). All the proteins retain silicatein activity. Alanine mutants of the catalytic triad (S25A, H163A, or N187A) still have silicatein activity. We hyposized that mechanism of silicatein enzymatic activity involves some other features of the protein and checked human cathepsin L for the presence of silicatein activity. And found that it is also capable to polymerise silica from TGS. So, new more available precursor allowed us to find new enzymatic activity of human cathepsin L and showed that our understanding of silicatein activity mechanism call for reevaluation.

e: povarovanv@gmail.com

MMP-9 targeted by hsa-miR-494 promotes silybin-inhibited osteosarcoma

Tianhao Sun, Frankie Leung and **William W Lu**
University of Hong Kong, China

Osteosarcoma (OS) is the most common malignant tumor that develops in bone. Its mortality is very high. Therefore, study of mechanisms of pathogenesis of the OS is urgently required. Previous studies of microarray showed that the expression levels of matrix metallopeptidase 9 (MMP-9) altered significantly in OS. In addition, overexpression of MMP-9 is recognized as an indicator in cancer. However, the exact roles of MMP-9 in OS are not fully investigated. Thus, we firstly studied the roles of MMP-9 in OS and revealed that silence of MMP-9 inhibited OS cell proliferation as determined by MTT assay and colony formation assay. Secondly, we conducted TUNEL assay and found loss of functions of MMP-9 induced OS cell apoptosis. Next, we used lentivector packaging method to overexpress MMP-9 and found that overexpression of MMP-9 promoted OS cell migration. Fourthly, the results of luciferase assay showed that MMP-9 was targeted by hsa-miR-494, which inhibited OS. Fifthly, we revealed that the levels of hsa-miR-494 were upregulated by the drug silybin which inhibited OS cell proliferation. Finally, we revealed that silybin inhibited OS cell viability by altering the protein levels of β-catenin and Runt-related transcription factor 2 (RUNX2) as determined by western blot and immunocytochemistry (ICC).

e: sunmishu@126.com

Cytochrome c assisted escape of cardiolipin from a model mitochondrial membrane

Valeria Tsoukanova and **Aby Thong**
York University, Canada

Binding of cytochrome c (Cytc) to cardiolipin (CL) in the inner mitochondrial membrane is involved with the onset of apoptosis. In this study, we make use of CLcontaining phospholipid monolayers to mimic the inner mitochondrial membrane.Constant pressure insertion assay was employed to monitor the Cytc-induced expansion of membrane area. Simultaneous epifluorescence microscopy imaging afforded the *in-situ* visualization of phospholipid demixing and sorting in the membrane. The formation of a CL-rich Ld phase has been observed to prelude the insertion of Cytc. We will demonstrate that the insertion of Cytc disrupts the membrane in a way facilitating the escape of CL. The findings of our study may aid in understanding the early events leading to the remodeling of inner mitochondrial membrane and loss of its function during apoptosis.

e: valeriat@yorku.ca

Biomarker-directed drug development in oncology-20 years and counting

Baolin Zhang
Food and Drug Administration, USA

Most recently approved oncology drugs target discrete molecular aberrations or pathways in tumor cells and consequently are active on a subset of the patient population. The problem mainly lies in the vast heterogeneity that exists between tumor types, individuals with the same type of tumor, and within one tumor of a patient at any given time. The Predictive biomarkers, measured using *in vitro* companion diagnostics (IVD), help identify patients likely to respond to treatment and are increasingly integrated into drug development programs. This presentation will provide an update of biomarker-directed oncology drugs approved by the US Food and Drug Administration. Case studies will be presented on therapeutic monoclonal antibodies selectively targeting HER2, EGFR, or PD-1/PD-L1 signaling pathways. This information will be further discussed with respect to biomarker qualification in the development of novel cancer therapeutics.

e: baolin.zhang@fda.hhs.gov

A new three-dimensional live cell model to screen SERM, based on real time cell growth and death indicators

Swati Kaushik
RGCB, India

Researchers have devised a vast array of model systems to study the complex components of tumors and their treatments. The most simplistic cancer models are cell lines grown as flat monolayers submerged in media. 2D cell culture has contributed tremendous amounts of knowledge about cell growth and cell death. Selective estrogen receptor modulators (SERMs) most often induce growth arrest as well as cell death in the ERα+cells. Since cell growth and cell death induced by these compounds are very slow, the use of 2D models representing increased cell proliferation is not an appropriate model. Cells *in vivo* grow and divide very slowly as seen by 3D model system. The primary objective of the study was to develop better 3D screening approach utilizing fluorescence based cell death sensors. The cell death sensor consisting of FRET pair of ECFP-EYFP linked in between with caspase specific DEVD sequence was developed and utilized for visualization and quantification of caspase activation in 3D culture by FRET microscopy. Developed 3D model has shown significant difference in cell death and cell cycle proliferation determined against a panel of SERMs compared to 2D system and results confirmed closed *in vivo* similarities. The *in vitro* models utilizing FRET caspase probe and FACS analysis were also employed for screening of novel compounds in relation to clinically relevant SERMs. The primary objective is to develop a model of cell growth and cell death in 3D culture system was achieved. The results with known SERMs and novel compounds substantiated the efficacy of model system. In this seminar, I will discuss the model, we developed to monitor cell growth and cell death in 3D culture system. The results with known SERMs and novel compounds will also be discussed.

e: swatikaushik@rgcb.res.in

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Characterization of *papaya ring spot virus* (PRSV) genome encoded proteins for silencing suppression characteristics

Debosmita Lahiri[1] and **Kodetham Gopinath**[2]
[1]VIT University, India
[2]University of Hyderabad, India

One of the most harmful and destructive disease of papaya is the papaya ringspot (PRS) disease caused due to the PRSV (*Papaya ringspot virus*). It belongs to the family *Potyviridae* and genus *Potyvirus*. PRSV virions are filamentous, flexuous in nature, approximately 780 nm x 2 nm long and it contains a single molecule of linear positive sense ssRNA approximately 10.3 kb in length. The entire virus consists of the following genes: *P1, HC-Pro, P3, 6K1, CI, 6K2, VPg, NIa, NIb* and *CP*. These genes were cloned into pGEMT-easy vector and sub cloned into binary vector pCB302. After that agroinfiltration and on-spot silencing assay of the individual genes were done using UV Fluorescence Spectrophotometer to check the silencing suppression characteristics of individual genes. An emission spectrum was obtained using UV Fluorescence Spectrophotometer to further confirm the obtained results. In UV Fluorescence Spectrophotometer the excitation wavelength was set as 309 nm and the emission wavelength was set as 509 nm. From the spectrum obtained it can be presumed that CI and HC-Pro Hyd are potent silencing suppressors of PRSV-Hyd. The main objective of this project was characterization of PRSV (*Papaya ringspot virus*) encoded proteins for silencing suppression characteristics.

e: ldebosmita@gmail.com