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CCC: 0377-8282/2010

PLENARY LECTURES, AWARD LECTURES, PRIZE LECTURES, LECTURES

PLENARY LECTURES – **PL.03**

DRUGGING "UNDRUGGABLE" TARGETS

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

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LECTURES – **L.14**

PHENOTYPIC SCREENING USING HUMAN NEURAL PRECURSOR CELLS AS A TRANSLATIONAL *IN VITRO* MODEL TO EXPLORE THE PROCESS OF NEUROGENESIS

R. Jagasia[1], R. Iacone[1], L. Burleigh[1], B. Bohrmann[1], S. Lazic[1], F. Knoflach[1], S. Ceccarelli[1], K. Christensen[1], P Petitjean[1], S. Zoffmann[1], L. Chicha[1], F. Metzger[1], A. Perrier[2], Y. Laâbi[2], M. Lechuga[2], A. Benchoua[2], M. Peschanski[2], M. Graf[1]

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One of the most remarkable forms of structural plasticity in the adult brain is the generation of new functional neurons from adult neural precursor cells (NPCs). There is accumulating evidence that neurogenesis in the adult hippocampus contributes to brain physiology and disease, but its precise physiological role remains elusive. Conceptually, this process can be divided into four steps: (i) proliferation; (ii) neuronal fate determination; (iii) survival and maturation of new neurons; and (iv) functional integration of new neurons into the pre-existing neuronal network. Here we describe the development of phenotypic *in vitro* screening assays using human embryonic stem cell derived NPCs as a cellular model to investigate neurogenesis. Using expression profiling of differentiating cells and exposure of NPCs to compounds, we can demonstrate that neurogenesis relevant signaling pathways are active in this *in vitro* cell model. Thus, unbiased High-Throughput Screenings (HTS) in combination with image based High Content Analysis (HCA) may represents a powerful tool to identify new active CNS compounds/targets, which may ultimately elucidate novel mechanisms impeding on adult neurogenesis.

LECTURES – **L.32**

SYSTEMS CHEMICAL BIOLOGY AND TOXICOGENOMICS

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Exposure to drugs and environmental chemicals may have a negative effect on human health. An essential step towards understanding the effect of small molecules on human health is to identify all possible molecular targets of a given chemical. Recently, various network-oriented chemical pharmacology approaches have been published. However, these methods limit the protein prediction to already known molecular drug targets. New findings can for example be made by using high-confidence protein-protein association databases.

We present a generic, computational systems chemical biology model with the aim of understanding the underlying molecular mechanisms of chemicals and the biological pathways they perturb. We generated a novel and complementary approach to existing models by integrating toxicogenomics and systems biology data. The core of our procedure is derived from the "target hopping" concept defined previously [1]. But instead of considering only binding activity, we extended the concept to gene expression. If two proteins are affected by two chemicals, then both proteins are deemed associating in chemical space. Our approach is not only a statistical model but mimics the true biological system by constructing a network of associations between human proteins defined as Protein-Protein Association Network (P-PAN). We have validated our network by comparison with two high confidence protein-protein interaction (PPI) networks [2-3], and by assessing the functional enrichment of clusters in the network generated.

Through diverse examples we will illustrate the usefulness of P-PAN in order to reveals unexpected association between chemicals and their potential toxicity.

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ERRATUM:
The abstract published as L35 will be presented as poster P525.

LECTURES – **L.40**

OPEN PHARMACOLOGICAL SPACE, AN INNOVATIVE MEDICINES INITIATIVE KNOWLEDGE MANAGEMENT PROJECT

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Drug discovery is data-hungry and all major pharmaceutical companies maintain extensive in-house instances of public data alongside internal. Analysis and hypothesis generation for drug-discovery projects requires assembly, overlay and comparison of data from many sources, requiring shared identifiers and common semantics. Expression profiles need to be overlaid with gene or pathway identifiers and reports on compound pharmacology. Alignment and integration of internal and public data and information sources is a significant effort and the process is repeated across companies, institutes and academic laboratories. This represents a significant waste and an opportunity cost.

To address these challenges, the Open Pharmacological Space IMI project aims to create an **open** knowledge infrastructure enabling facile **integration** of chemical and biological data to support **drug discovery.** This session will outline the plan and partners involved in the forthcoming initiative.

LECTURES – **L.72**

ATTRITION INDUCED GRINDING FOR THE SYNTHESIS OF SOME COMMERCIAL DRUGS

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A Dutch research consortium located at the Radboud University Nijmegen, DSM in Geleen and Syncom in Groningen together with Prof. Donna Blackmond, now at Scripps Institute, demonstrated that a racemizable conglomerate could be converted into a single enantiomer in essentially quantitative yield by vigorous grinding of the solid in contact with solution in which racemization takes place. Primary nucleation leads to a single enantiomer for a conglomerate; the grinding allows secondary nucleation to propagate that chirality. Three methods have been developed to carry out this process in a matter of hours. One involves cooling a homogeneous solution together with attrition induced grinding. Another involves the use of ultrasound to increase the intensity of attrition. Finally milling has also been used to achieve very rapid deracemization. Applications of these technologies to precursors of Naproxen and Clopidogrel will be discussed.

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CCC: 0377-8282/2010

POSTER COMMUNICATIONS

POSTER COMMUNICATIONS – **PC.520**

NON-DENATURING CHEMICAL PROTEOMICS FOR PROTEIN COMPLEX IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION

Ghyslain Budin,[1] Martin Moune-Dimala,[2] Geoffray Leriche,[1] Jean-Michel Saliou,[3] Julie Papillon,[4] Valérie Lamour,[4] Sarah Sanglier-Cianférani,[3] Alain Van Dorsselaer,[3] Laurent Brino[2] and Alain Wagner[1]

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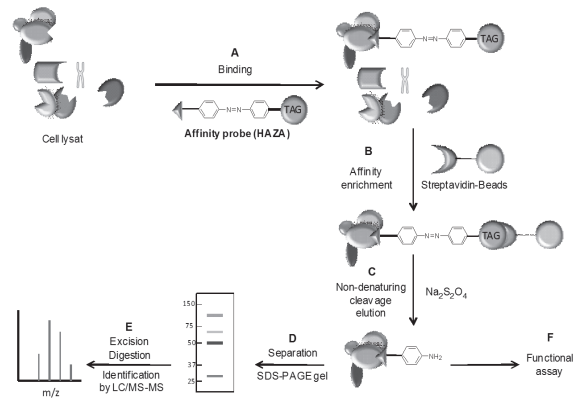
Isolation and identification of protein targets by chemical proteomic consist on the use of a chemical probe that target a specific protein class in a complex mixture and allow to extract a single protein target. Efficient recovery of the enriched protein is often carried out under harsh and denaturing conditions which involve the loss of protein partners, structural information, protein function and possible contamination by non specific materials. To reduce protein contamination, cleavable linkers have been introduced between the affinity tag and the bound protein which can be cleaved in biological media.

To avoid loss of protein partners and denaturation, we have developed an efficient azo-cleavable linker (HAZA) possessing on one side a biotin affinity tag for enrichment and on the other side a molecular probe which target specifically the DNA gyrase a topoisomerase. This linker has been cleaved in less than ten seconds with 1 mM of dithionite under physiological conditions.[1,2] Thanks to this affinity probe we have developed a native capture and release of proteins complexes as shown in the general scheme 1. We were able to pull down and released a A2B2 DNA gyrase complexe which has kept its enzymatic activity.[3] Several protein partners of DNA gyrase are currently under investigation.



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POSTER COMMUNICATIONS – **PC.521**

FRAGMENT-BASED DESIGN OF NOROVIRUS INHIBITORS USING DOCKING FOLLOWED BY MOLECULAR DYNAMICS SIMULATIONS AND BINDING FREE ENERGY CALCULATIONS

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Noroviruses are a major causative agent of gastroenteritis. There are no vaccines or drugs against noroviruses available. By preventing the virus from binding human histo-blood group antigens (HBGAs) the infection may be stopped.

500 small molecules from the Maybridge Ro3 library (Thermofischer Inc.), along with HBGAs A and B, was docked to the P protein dimer of norovirus strain VA387 (PDB ID 2OBT) using AutoDock Vina[1]. To circumvent reported weaknesses of docking program scoring functions[2] the three best conformations of the 25 top-ranked molecules were further investigated by molecular dynamics simulations, using the Q[3] program with a modified OPLS-AA[4] force field. In order to calculate binding free energies the linear interaction energy method[5] was employed. The results were carefully evaluated with the purpose of finding molecules with high affinity to different regions of the binding site. Based on this data, four potential inhibitors were assembled *in silico*. In the same way as when studying the small molecules, these leads were docked to the protein dimer and their binding free energies were calculated after MD simulations. The next step is to synthesise these molecules to verify the results in *in vitro* inhibition studies.

Binding free energy calculations based on MD simulations are very time consuming and are not suitable for high throughput virtual screening. On the other hand, when using fragment-based virtual screening a very large molecular space can be covered in a short time, facilitating detailed analyses of the docked structures and their binding free energies.

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POSTER COMMUNICATIONS – **PC.522**

SYNTHESIS OF NOVEL THIOPHENE COMPOUNDS AS PDE4 INHIBITORS

Jacob Nankervis[1], P. Ho[2], C. Morton[2], H.L. Ng[2], N. Hancock[2], M. Parker[2], T.J. Martin[2], D. Manallack[1], Philip Thompson[1]

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PDE4 inhibitors are currently under development as potential therapeutics for the treatment of chronic respiratory and immunoinflammatory diseases, including asthma, chronic obstructive pulmonary disease, cystic fibrosis and multiple sclerosis. At present, roflumilast (Daxas®, Nycomed) is under advanced clinical investigation for the maintenance of lung function in COPD. Numerous others are proceeding through or into clinical trials for the other indications, but in general toxicity has been found to be a problem, in part attributed to off-target PDE inhibition. We discovered PDE4 inhibitors that have a novel structural template and have potential to achieve specific therapeutic goals of PDE4 inhibition, with the prospect of a reduced side effect profile in comparison to the current drug candidates. Using X-ray crystallography-driven structure based design, and the development of versatile synthetic routes, we have developed analogues of increased potency and potential for PDE isoform selectivity, that is currently under investigation.

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POSTER COMMUNICATIONS – **PC.523**

STUDY OF NON COVALENT ORGANIC INHIBITORS OF PROTEASOMES DISCOVERED BY VIRTUAL SCREENING

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Due to its crucial role in cellular protein turnover in eukaryotes, proteasome is a promising target for treating cancers [1]. A highly selective inhibitor of proteasome, the peptide boronate bortezomib (Velcade®), has been approved by the FDA to treat mantle lymphoma and multiple myeloma. It also sensitizes cancer cells to chemotherapy, radiotherapy, and immunotherapy. Nevertheless, its use induces severe adverse effects including neurological disorders, and resistances. We therefore need new proteasome inhibitors. Most proteasome inhibitors, such as bortezomib, epoxomicin or synthetic peptide aldehydes bear a reactive group that forms a covalent bond with the catalytic Thr1 of the active sites (β1, β2, β5 subunits). Non covalent inhibitors have the advantage to be devoid of a reactive group that is often associated with a lack of specificity, excessive reactivity and instability. We therefore developed non covalent proteasome inhibitors by rational design leading to TMC-95 linear mimics [2] and fluorinated pseudopeptides [3]. We presented here non peptidic inhibitors developed in parallel by using a multi-step structure-based virtual-ligand screening strategy (ADME/Tox filtering, docking/scoring and visual inspection) with a compound collection that contained 300,000 organic molecules and selected about 1,000 molecules [4]. They should have better bioavailability than peptide inhibitors. Kinetic and mechanistic studies have been performed on the 3 activities of rabbit and human 20S proteasomes (submicromolar K_i or IC_{50} values). In this work, we obtained panels of inhibitors with a wide diversity of chemical structures that could inhibit 1, 2 or 3 type(s) of catalytic activity. This is of interest since inhibition of multiple active sites is required to markedly decreased protein degradation. XTT test was used to assess the cytotoxic effects of these new compounds on some human tumor cell lines.

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POSTER COMMUNICATIONS – **PC.524**

USING FREE SOFTWARE TO STUDY SAR TRENDS

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The study of Structure Activity Relationships (SAR) remains central to the process of small molecule drug discovery. Indeed, understanding the requirements for biological activity or the effect on physicochemical properties as changes are made to the lead compound is key to medicinal chemistry. Most software and algorithms that are available for studying SAR rely on 2D representations of molecules, leaving the medicinal chemist to mentally interpret how these structural changes might relate to interactions with the target protein. Additionally the majority of algorithms are only available to chemists within industry for a licence fee making it expensive to deploy solutions across multiple chemistry teams.

FieldView,[1] a recently released [2]molecular visualizer and editor, is available free to both academia and industry. Uniquely FieldView represents molecules using 3D molecular interaction Fields, enabling the comparison of the biological activities and properties of molecules from diverse chemical series. Field points describe the key binding information of a specific molecule giving a much closer representation of how a molecule interacts with a protein than using 2D structure. As well as presenting the Fields surrounding a molecule, FieldView presents a molecular spreadsheet of key physico-chemical properties and any custom data associated with the compounds that are loaded enabling multi-parameter optimisation of lead molecules.

Herein we will describe the use of FieldView to study SAR trends within a chemical series. We will show how using FieldView gives unique insight into the influence of electronic and steric effects on biological activity, enabling medicinal chemists to make more informed decisions over the cause of activity and the best next synthesis to undertake.

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CCC: 0377-8282/2010

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