

Genomics and Chemical Space: a new Locus for Drug Discovery

12 October 2007

- 9:15 – 9:45 **Registration**
- 9:45 – 10:00 **Introduction by the Chair:** Prof Sir Tom Blundell, Cambridge University, UK
This will consist of be a brief overview of Prof Sir Blundell's ideas of biological space – structural genomics and computation – and chemical space identifying fragments, and how they interact.
- 10:00 – 10:25 **Family-Based Structural Genomics for Targeting Binding Space**
Dr. Frank Von Delft, University of Oxford, UK
This talk will describe the experimental approaches to defining biological space, painting the international picture of Structural Genomics.
- 10:25 – 10:50 **Chemical space and drug likeness**
Dr. Andrew Hopkins, Pfizer Sandwich, UK
- 10:50 – 11:00 **Group and Speakers photo**
- 11:00 – 11:30 **Morning Tea/Coffee and Poster Viewing**
- 11:30 – 11:55 **High throughput fragment screening using X-ray crystallography**
Dr. Miles Congreve, Astex Therapeutics, UK
Astex uses a combination of biophysical methods including x-ray crystallography and protein-ligand NMR to discover novel low molecular weight molecules (or fragments) binding to drug targets. This approach (or Pyramid™) has identified fragment ligands for each target studied. An insight into the structure-based optimisation of hits into potent leads for a number of representative case studies will be outlined. Screening approaches will be discussed plus some success stories with chemical structures. This talk will introduce the concept of fragments – not only as practised at Astex but also its origins.
- 11:55 – 12:20 **Physicochemical Property Trends in Drugs and Current Medicinal Chemistry**
Dr Paul Leeson, Astra Zeneca Charnwood
Significant physicochemical property 'inflation' is evident amongst oral drugs marketed over the past 25 years. Application of drug-like principles such as the rule-of-5, as well as toxicological, pharmacokinetic and metabolic optimisation, suggest better control of physicochemical properties will improve the unacceptably high levels of attrition seen in drug company pipelines. Despite this, further increases in physicochemical properties are observed in compounds from current medicinal chemistry patents. The pursuit of less 'druggable' targets may explain this in part, but it is also clear that medicinal chemical decision-making in lead selection and optimisation strategies are highly influential in determining outcomes
- 12:20 – 12:40 **Tour of the BioPark**
- 12:40 – 13:40 **Lunch and Poster Viewing**

- 13:40 – 14:05 **Fragment-based lead generation at AstraZeneca: Philosophy, strategy and some case studies**
Dr Alex Breeze, Global Structural Chemistry, AstraZeneca, UK
Fragment-based lead generation (FBLG) has recently emerged as an alternative to traditional high throughput screening (HTS) to identify initial chemistry starting points for drug discovery programs. In comparison to HTS screening libraries, the screening sets for FBLG tend to contain orders of magnitude fewer compounds, and the compounds themselves are smaller and less structurally complex. This talk will describe experiences using FBLG at AstraZeneca. Topics covered will include screening library design, hit detection, evaluation of hit quality, and approaches to evolve fragments towards drug-like leads. Our use of FBLG will be exemplified with a number of case studies from varied classes of therapeutic target
- 14:05 – 14:30 **One simple step to sequencing secrets: The Roche Genome Sequencer FLX**
Dr Steve Baker, Roche Diagnostics Ltd
Genome Sequencer FLX allows unique research in to every aspect of DNA from disease causing mutations or unique traits to actual gene expression. The FLX is capable of counting nearly every expressed gene in the human cell. With this technology disease recognition, be it DNA mutations, bacterial or viral will be achieved at much greater speed and reduced cost.
- 14:30 – 14:55 **Fragments**
Professor Chris Abell, University of Cambridge, UK
Fragment based approaches are providing a powerful way to identify protein ligand interactions. The talk will describe the use of a range of biophysical techniques to screen for enzyme-ligand interactions as a starting point in the development of enzyme inhibitors
- 14:55 – 15:30 **Afternoon Tea/Coffee and Last Poster Viewing**
- 15:30 – 15:55 **The input of thermodynamic data to the drug development process**
Professor John Ladbury, UCL, UK
Isothermal titration calorimetry (ITC) provides a direct method for determining thermodynamic parameters associated with biomolecular interactions. The understanding of the correlation between the change in thermodynamic parameters for a binding event and the perturbation in structure forms one cornerstone of biophysical science. Clearly, if correlations can be defined then predictive algorithms can be produced which will permit improvements in our understanding of biomolecular interactions. This would have dramatic effects on the temporally and financially expensive processes associated with compound development in the pharmaceutical industry. The use of calorimetric data in the decision making process in drug development will be presented.
- 15:55- 16:20 **Lead Discovery by Virtual Screening**
Prof. Dr. Gerhard Klebe, Institute of Pharmaceutical Chemistry, Germany
Structure-based virtual screening starts with a detailed analysis of the target protein. Based on a protein-based pharmacophore criteria to be matched by putative ligands are defined. Docking and scoring assist the final selection of likely candidates. Crystal structure analysis of micromolar hits discovered by virtual screening deviate sometimes from the predicted binding mode and possess additional functional groups not required for binding. Furthermore, their molecular weight usually matches with the size of typical drug molecules. These shortcomings complicate further optimization and do not leave much room for improvement. In consequence, virtual screening has been moved towards candidates falling into the range of so-called fragments. As an alternative, a protein-based cavity search to retrieve molecular fragments occupying similar pockets can be used. The retrieved fragments are assembled in a combinatorial fashion to suggest novel leads for the target protein.
- 16:20 – 16:45 **Drug Discovery: A finite problem**
Dr Colin R Groom, UCB, Cambridge
Given that there are only a limited number of diseases affecting mankind, potential drug targets and potential drug molecules, surely drug discovery is simply a matter of finding suitable combinations? This presentation will challenge these assumptions, but illustrate how viewing the challenge as establishing relationships between medicinal, biological and chemical space encourages the adoption of different strategies in drug discovery
- 16:45 – 17:00 **Chairman's summing up**