SMi present their 12th annual conference on...

Advances and Progress in Drug Design

Monday 18th and Tuesday 19th February 2013, Copthorne Tara Hotel, London, UK

KEY SPEAKERS INCLUDE:

- Andrew Leach
  Director of Computational Chemistry
  GSK

- Jose Duca
  Head of CADD
  Novartis

- John Mathias
  Head of Medicinal Chemistry
  Pfizer

- Albert Pan,
  Research Scientist
  D E Shaw Research

- Harald Mauser
  Senior Scientist
  Roche

- Friedemann Schmidt
  Research Scientist
  Sanofi

- Herman van Vlijmen
  Senior Director, Molecular Sciences
  Johnson & Johnson

- Fabrizio Giordanetto
  Principal Scientist
  AstraZeneca

- Steven Charlton
  Director, Receptor Biology
  Novartis

- Mathias Frech
  Director, Molecular Interactions & Biophysics
  Merck

WHY ATTEND THIS EVENT:

- Understand the latest developments in predictive in-silico off-target profiling
- Debate the use of design-focused libraries for screening
- Analyse CADD methods in protein therapeutic applications
- Learn about water network perturbation in structure-based drug design
- Evaluate subtype selectivity in G-protein-coupled receptors
- Consider novel isoform inhibitors through structure-based fragment evolution
- Discover the value of reverse pharmacology and learning from binding events
- Network with and learn from senior industry representatives to discuss the latest in computational chemogenics

PLUS TWO INTERACTIVE HALF-DAY POST-CONFERENCE WORKSHOPS

Wednesday 20th February 2013, Copthorne Tara, London, UK

A: Fragment-Based Lead Discovery: Issues and Applications

Workshop Leader:
Ben Davis, Research Fellow, Vernalis
9.00am – 12.30pm

B: Binding kinetics for Drug Design: the Molecular and Structural Perspective

Workshop Leaders:
Xavier Barril, ICREA Research Professor, University of Barcelona
1.30pm-5.00pm

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9.10 Predictive in-silico off-target profiling in drug discovery
- Data-driven computational approaches to polypharmacology
- Practical relevance to address compound selectivity and off-target related effects in lead discovery and optimization
- Chances and limits: Domain of applicability
- Multi-criteria compound optimization

9.50 Computational Approaches to Polypharmacology and Mode-of-Action Analysis
- Current bioactivity databases are increasing in size, with the question being how to exploit them
- Applications to Mode-of-Action analysis using in silico target prediction will be presented
- A prospective application is ligand design taking bioactivity information against multiple receptors into account, for which experimental validation will be presented

Andreas Bender, Lecturer for Molecular Informatics, Cambridge University

10.30 Morning Refreshments

11.00 Can a better appreciation of statistics help and improve the field of Molecular Modeling?
- What should a toolbox of simple statistical techniques look like for a molecular modeller?
- Address the issue of method validation given the data typically available
- Describe some of the advances other fields have made using modern statistical methods

Anthony Nichols, CEO, OpenEye Software

11.40 CADD applied to protein therapeutics
- Application to Ab humanization
- Application to Ab stabilization
- Application to affinity maturation
- Application to novel formats

Nicolas Baurin, Lead Generation Group Head, Sanofi

12.20 Protein-Ligand Recognition And How Out-of-the-Box Thinking Impacts Drug Design
- Diverse targets offer different structural insights. The PDB is a rich source of information
- Unusual interactions can hint the next design steps (some of them are not so obvious)
- Intrinsic flexibility footprints and their relevance towards allosteric inhibition

Jose Duca, Head of Computer-Aided Drug Discovery, Novartis

13.00 Networking Lunch

14.20 Keynote Address: Drug Design for Antivirals: Structure - and ligand-based approaches to deal with resistance
- Structure-based design of HIV protease inhibitors has led to broadly active compounds. The resistance profile is often difficult to understand and better predictive structural modeling is needed.
- Proteochemometric modeling is a computational technology that simultaneously uses activity data of multiple compounds on multiple targets. This technology was applied to two large datasets of non-nucleoside HIV reverse transcriptase inhibitors and resulted in improved predictions.
- Water molecules are important in the binding of small molecules to protein targets. WaterMap calculations were used to analyze the SAR of Hepatitis C NS5a inhibitors, and provided new insights into the activity of these compounds

Herman Van Vlijmen, Senior Director, Molecular Science, Johnson & Johnson

15.00 Water Placement and Water Site Free Energy: Extending the 3D-RISM Solvent Analysis
- Placement of water molecules provides rationalisation of ambiguous SAR and focuses synthetic efforts
- Solution of modified 3D-RISM set of equations provides oxygen and hydrogen distributions which can be visualised three-dimensionally
- The chemical potential of water is computed using 3D-RISM and is linked to the local affinity of protein sites towards water
- Here, we identify water sites centres on which we can map the thermodynamic properties of water, and examine the idea of using water site free energy to infer water stability

Paul Labute, Chief Executive Officer, Chemical Computing Group

15.40 Afternoon Tea

16.10 Improvements in docking performance with a new type of scoring functions derived from molecular dynamics simulations of mixed solvents
- Theoretical approaches for the representation of the solvent effect on structure and reactivity
- Discussion into the different methods available for analysis
- Challenges in computational approaches and how to overcome them

Xavier Barri, ICREA Research Professor, University of Barcelona

16.50 Water network perturbation in Structure-Based Drug Design: How far can we go?
- Recent efforts in the computational evaluation of the thermodynamic properties of water molecules resulted in the development of new promising in-silico methods to evaluate the water role in ligand binding.
- GRID (Molecular Discovery), SZMAP (OpenEye), WaterMap (Schrödinger) & 3D-RISM (Chemical Computing Group) used to evaluate the role of the solvent in protein function and druggability, structure-activity relationship elucidation, ligand free energy of binding prediction and ligand residence time evaluation.
- Test case applying the methods to the Adenosine A2A receptor, and an extension exploiting a recursive partitioning method (Random Forest)

Andrea Bortolato, Senior Computational Chemist, Heptares

17.30 Chairman’s Closing Remarks

17.40 Close of Day One

17.45 The first day of the conference will be followed by a Networking Drinks Reception hosted by Chemical Computing Group

19.15 End of Drinks Reception
Day Two | Tuesday 19th February 2013

14.00 Prolonged target binding and rebinding as mechanisms to enhance duration of drug action
• The influence of dissociation rate on drug efficacy and duration of action
• Modelling restricted diffusion in micro-anatomic structures and introducing the concept of drug rebinding and its influence on duration of action
• Enhancing the likelihood of rebinding by optimising affinity for the local target environment
• How these phenomena may complicate interpretation of the pharmacology of new drugs
Steven Charlton, Director, Receptor Biology, Novartis

14.35 Design of Libraries Targeting Protein-Protein Interfaces
• Rational design of PPI disruptors
• Results of biological profiling
• PPI disruptors with favourable physicochemical properties
• New approaches of identifying druggable PPIs
Harald Hauser, Senior Scientist, Roche

15.10 Drug binding and subtype selectivity in G-protein-coupled receptors
• The development of small molecule ligands that selectively act on one of the five mAChR subtypes (M1–M5) has proven extremely challenging, primarily owing to the high degree of sequence similarity in the transmembrane core of these receptors
• We characterized the pathway by which drugs bind to and dissociate from the M2 and M3 receptors using long timescale molecular dynamics simulations
• These simulations suggest a metastable drug-binding site in the extracellular vestibule of both receptors, and also provide a potential rationale for the slower dissociation rates of certain M3 antagonists
• Our findings may facilitate the design of improved subtype-selective therapeutics targeting these critical receptors
Albert Pan, Research Scientist, D E Shaw Research

15.45 Afternoon Tea

16.10 Reverse Pharmacology - Predicting cellular and in vivo pharmacology from binding evidence
• The availability of isolated receptor conformations in active and inactive states opens the door to the concept of ‘reverse pharmacology’, whereby the functional pharmacology of ligands can be characterised in a system-independent manner by their affinity for a pair [or set] of GPCR conformations
• Rationalisation of the pharmacology observed by ligand docking into the known crystal structures of the A2A receptor: e.g., inverse agonists vs neutral antagonists
• The promise of predicting cellular and in vivo pharmacology of GPCR ligands using this ‘reverse pharmacology’ approach on the basis of affinity, or even free energy of binding calculations
Benjamin Tehan, Senior Computational Chemist, Heptares

16.50 Interfering with protein-protein interactions
• What libraries can be used for screening?
• Is there a need to design focused libraries for the target
• How do fragment approaches effect interactions
Gyorgy Keseru, Manager, Discovery Chemistry, Gedeon Richter

17.30 Chairman’s Closing Remarks

17.40 Close of Day One

Who should attend this conference:
This event is unmissable VPs, Directors, Heads, Senior Managers and Principal Scientists from the following departments:
• Structure and Informatics
• Computer-Added Drug Design
• Computational Chemistry
• Cancer Research
• Molecular Interaction
• Medicinal Chemistry
• Pharmacology
• Molecular Imaging
• Neuroscience Chemistry
• Drug Discovery & Design
• Target Discovery
• Translational Sciences
• Biophysics
• Screening
• Clinical Development
• Structural Biology
• Crystallography
• Medicinal Chemistry

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Contact Margaret Mugama, SMi Marketing on +44 (0) 20 7827 6072 or email mmugama@smi-online.co.uk
Overview of workshop

With the expertise of the team from Vernalis, this unique workshop will provide the perfect platform to discuss and develop fragment-based discovery strategies. This case-study led session will present attendees with success stories to learn from and adapt into their own drug discovery systems. With structure-based drug development playing a larger and more important role in drug design this workshop is not to be missed.

Programme

8.30  Registration and Coffee
9.00  Welcome and Introductions
9.10  Overview and Perspective
   • Current technologies in fragment-based lead discovery
   • Discussing lead discovery for more complex classes of therapeutic targets
9.45  Case Studies
   • Success Stories - highlighting the importance of structure-based technology in drug design
   • Problems encountered - how to overcome them?
10.30  Morning Coffee
11.00  Applications and Issues
   • Techniques to improve drug design strategies
   • Characterising receptor-ligand interactions
   • Preparing for the future of drug design
11.50  Discussion Session
12.30  Close of Workshop

About the workshop host

Ben Davis, Research Fellow, Vernalis

Dr Ben Davis studied protein folding by NMR for his PhD with Professor Alan Fersht at Cambridge University Chemical Laboratory, before moving to Dr Paul Driscoll’s NMR group at University College London where he worked in protein-ligand interactions in collaboration with Yamanouchi Pharmaceutical Company. In 1998 he joined RiboTargets, a biotech company formed out of the Laboratory of Molecular Biology in Cambridge, where he worked on applying structure-based drug discovery techniques to a variety of RNA and protein targets. In 2003 RiboTargets merge with Vernalis Plc, and focussed research towards protein targets. Since 2001, he has been heavily involved in the development and application of fragment-based lead discovery technologies to a wide range of therapeutic targets.

About Vernalis

Vernalis is a world leader in structure and fragment-based drug discovery, with an excellent track record for innovation and delivery of clinical candidates in a range of therapeutic areas. We have on product on the market, three programmes in Phase II clinical trials and a broad pipeline of candidates derived from successful collaborations with a number of global pharmaceutical businesses and form our own research activities.
HALF-DAY POST-CONFERENCE
PM WORKSHOP
13.30pm – 17.30pm
Wednesday 20th February 2013
Copthorne Tara Hotel, London, UK

B: Binding kinetics for Drug Design: the Molecular and Structural Perspective

Workshop Leaders:
Xavier Barril, ICREA Research Professor,
University of Barcelona
In association with ICREA

Overview:
This unique workshop will explore the latest developments in Structure-Kinetic Relationships and explore the importance of binding kinetics on pharmacological responses. Led by Xavier Barril, this exciting event will focus on current methods to study and analyse kinetics as well as understand structural determinants of binding kinetics. This case-study and discussion led workshop will be a perfect forum for discussing the key developments in structure kinetic relationships in the drug design process with key industry professionals.

Why you should attend:
• Learn the importance of kinetics on pharmacological responses and the drug-design process
• Consider the latest developments in studying kinetics; focussing on different rate constants and thermodynamic parameters
• Understand and predict potential obstacles in structural determinants and discuss how best to prepare and avoid them
• Network with key industry professionals
• Utilize the experience of an expert in the field

13.30  Registration & Coffee
14.00  Welcome & Introductions
14.10  Binding Kinetics: importance in Drug Design
• Introduction to binding kinetics
• Impact on pharmacological response
14.40  Studying Kinetics: Methods and Basic Concepts
• Measuring kinetic parameters
• Macroscopic vs. Microscopic rate constants
• Relationship with Thermodynamic parameters
• What does association/dissociation look like?
15.30  Afternoon Tea
15.50  Structural Determinants of Binding Kinetics
• Structural elements affecting on-rates
• Trapping mechanisms decreasing off-rates
• Binding coupled to rare events
16.50  Case Study and Discussion Session
• Understanding (and predicting) kinetics in practice
17.20  Close of Workshop

About the workshop host:
Xavier Barril is an ICREA Research Professor at Barcelona University’s School of Pharmacy. His research focuses on the discovery of bioactive molecules exploiting unusual mechanisms of action through a combined use of computational and experimental techniques. In parallel, his group develops new computational tools to tackle such tough targets and strives to improve the molecular understanding of pharmacologically important biological events, including the discovery and optimization of Hsp90 inhibitors currently undergoing Phase II clinical trials (licensed to Novartis). In 2005 he was appointed ICREA Research Professor and joined Barcelona University’s School of Pharmacy. He has co-authored 50 scientific publications, including research papers, reviews and book chapters, as well as 7 patents.

About ICREA:
ICREA, the Catalan Institution for Research and Advanced Studies, is a foundation supported by the Catalan Government whose aim is to recruit top scientists for the Catalan R&D system. The University of Barcelona is the largest public institution of higher education in Catalonia as well as the principal centre of university research in Spain.
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Workshops: Wednesday 20th February 2013, London, UK

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Early Bird Discount
- Book by 31st October 2012 to receive a £300 off the conference price
- Book by 30th November 2012 to receive a £100 off the conference price

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- 1 Workshop only £599.00 + VAT £718.80
- 2 Workshops £1198.00 + VAT £1437.60

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