The Society for Medicines Research

NEWSLETTER

November 2015

Editorial

Newsletter relaunch

Welcome to the first edition of a relaunched SMR Newsletter which the committee hope you will find useful in keeping up to date with the activities of the Society. Playing to our strengths as a Society with members from many different drug discovery disciplines we have introduced a short gallery of literature references, which the committee have found useful. We hope that you will find the diversity of topics covered valuable in your own work and in your continuing professional development.

Check out our references section for a range of drug discovery topics featured by your committee

Our next meeting

Trends in Medicinal Chemistry Thursday 3rd Dec 2015 NHLI, London

Approaches to drug discovery continue to undergo rapid and significant change, presenting both opportunity and challenges. This meeting will look at some of the ways that medicinal chemistry has been responding to these changes organizationally, through the application of new technology and by applying the many lessons learned from past failures. It will also focus on the many new opportunities where the application of medicinal chemistry skills could lead to even broader impact in the drug discovery process.

This meeting brings together experts to discuss changes in organization that companies have made to respond to changes in the research environment. Application of one emerging technology and its potential to support drug discovery will also be discussed. Later sessions will examine the role of the host of metrics for assessing compound quality in drug discovery that have emerged and how they may evolve and be used most effectively to drive discovery programs. Finally looking to new areas of opportunity for medicinal chemistry, we will hear about the application of medicinal chemistry in stem cell research and the role of chemical biology in the drug discovery process.

This meeting will be of interest to all involved in the drug discovery process.

To see the full programme and to register please visit the SMR website.

Membership

Becoming a member

Those of you who have attended recent AGMs held at our December meeting will be aware that the Society has been suffering a gradual decline in membership which the committee believes reflects a number of changes that have been occurring in our industry and the different payment methods used – credit cards for paying membership are a particular problem for renewals. We are looking at ways of addressing this, in particular trying to make paying membership easier. We expect to present some changes at the December 3rd AGM at the National Heart and Lung Institute. Existing members could be a great assistance by firstly checking that they have paid this year's subscription and, if moving between jobs, ensure contact details are updated with our secretariat. Remember membership fees can be offset against tax if paying yourself.

The members are the Society so the committee would encourage all members to promote the Society and its meetings to their contacts.

We are particularly keen to encourage students and colleagues from the academic community to attend our meetings. As an incentive for students we have a number of student bursaries available, please see the side box for more details.

Future SMR meetings

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New developments in translational technologies
Royal Veterinary College, London
17th March 2016
Hosted by Transpharmation
Sponsored by Transpharmation and Pharmidex

Progress in Alzheimers Research (provisional title) to be held in Brussels 10th June 2016 sponsored by Janssen Pharmaceuticals

A planned addition to the SMR meetings calendar

An early stage researcher discovery symposium

Very much in the planning phase at the moment is a meeting focused on the young drug discovery research worker designed to engage those who are still at university or who have only recently moved into industry. The intention is to expose the audience to the range of activities relevant to drug discovery. Our current thinking is that this will be run immediately prior to the March 2017 meeting and will probably be held in London. Any suggestions for the shape and content of this meeting will be gratefully received by the organizing team. Please send suggestions to

rod.porter@rodporterconsultancy.com.

Please also let any academic contacts you may have know that this meeting will be taking place.

Previous meetings

Our autumn meeting was **Biotherapeutics - Innovative Future Medicines** was held at the NHLI, London, UK on Thursday 8th October and was sponsored by UCB

In the last decades, bio-therapeutic medicines have been developed for the treatment of severe diseases such as metabolic disorders, cancer and many autoimmune diseases and multiple rare diseases. Biotherapeutics are especially attractive due to their highly targeted and specific nature and their relatively low safety risk. This meeting with speakers from both industry and academia covered a wide range of topics in biotherapeutics including accounts of drug discovery of sclerostin antibodies to increase bone formation and density, antibody cocktails to treat pertussis and collaborative strategies in immune-oncology. Other talks featured discussion on peptide immunotherapy, data mining to help invent new vaccines and finally a discussion of the role of oligonucleotides as therapeutics.

Keep an eye out for the full meeting report appearing in Drugs of the Future which we will announce on Linked-In and Twitter

The summer meeting **Opportunities and Challenges in Cancer R&D** sponsored by Cancer Research UK was held at the CR-UK Beatson Institute, Glasgow on Friday 5th June. The meeting was very well attended with lively discussion and a lot of networking during the breaks. Herbie Newell's personal perspective of his distinguished career in oncology drug discovery set the scene to explore past lessons and new horizons for this field. The meeting gave a mix of academic and industry perspectives and projects were discussed at the cutting edge of cancer R&D including rationally designed targeted drugs, combination therapies and effective immunotherapies.

A report from this meeting is now published see *W. Alderton et al Drugs Fut 2015, 40(8): 535* and will be available from the SMR website in the next few months. Talks were varied with medicinal chemistry accounts of early stage hit and candidate identification through to discussion of immunotherapy (preclinical and clinical), the changing genomic aberrations in tumours, application of clinical pharmacology and finally developing radiotherapy combinations.

Our Spring meeting **Effective and Emerging Strategies for Utilising Structure in Drug Discovery** was sponsored by Astex and held at Astex (Cambridge UK) on Thursday 19th March.

Perhaps not surprising considering the venue and theme of the meeting was the emphasis of several talks on fragment based drug design (FBDD) with application to a range of targets. Particularly highlighted was FBDD in combination with crystallography in modulating protein-protein interactions with approaches to RAD51/BRCA2 inhibition and inhibitors of IAP discussed – amongst others. FBDD was also used for more conventional targets such as branched chain amino acid transferase.

Student Bursaries

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Do you know a student who could benefit from attending one of our SMR conferences?

They can apply for a bursary.....

- Bursaries cover registration fee and can make a contribution towards travel costs.
- Applicants are eligible for one bursary per year.

How to apply:

- Visit http://www.smr.org.uk/smr/StudentBursaries/default.asp to download the application form.
- Complete form and appropriate registration document with a signature confirm student status e.g. head of department and send to secretariat@smr.org.uk or post to the secretariat - details at the end of this newsletter.
- Decisions on student bursary eligibility are made by the SMR committee and are final

Technology platforms were not neglected with description of the Schrodinger FEP platform to analyse multiple crystal structures of ligand bound EphB4 to support prediction of binding free energy, the SGC platform for determining membrane bound protein structures and finally the application of cryo-EM in drug discovery. Finally an account of the identification of selective pan-Trk inhibitors was given which exploited determinants of selectivity for ATP competitive protein kinase inhibitors and both apo and substrate bound

structures coupled with an analysis of the role of water in determining binding of ligands.

To see a full report on this meeting see K. A. *Brown et al.,*
Drugs Fut 2015, 40(4): 251

Some literature references highlighted by the SMR committee over the last few months

PubMed ID links to abstracts at http://www.ncbi.nlm.nih.gov/pubmed

Dennis A. Smith, et al., **Volume of Distribution in Drug Design** J. Med. Chem. 2015, 58, 5691

Volume of distribution is one of the most important pharmacokinetic properties of a drug candidate. This paper reviews design strategies against volume of distribution and pitfalls to avoid. PMID: 25799158

Mark E Bunnage et al., **Know your target, know your molecule** Nature Chem. Biol., 2015, 11, 368

This paper looks at some of the important characteristics of targets and drugs that may be important to increase chances of success. PMID: 25978985

R. K. Wolff **Toxicology Studies for Inhaled and Nasal Delivery** Mol Pharm. 2015, 12, 2688

A review examining the challenges and complexities related to the toxicological testing of pharmaceuticals delivered by the inhalation or nasal route. PMID: 25915006.

A useful blog post from the University of Sussex Drug Discovery Centre: "**Not all LogP's are calculated equal**"

https://sussexdrugdiscovery.wordpress.com/2015/02/03/not-all-logps-are-calculated-equal-clogp-and-other-short-stories/

C. H. Arrowsmith et al., **The promise and perils of chemical probes** Nature Chem. Biol., 2015, 11, 536

An important initiative to improve the quality of chemical probes – vital for us all in drug discovery. PMID: 26196764

J. Kaiser., **The Cancer Test** Science. 2015 348, 1411

Following Bayer and Amgen's disclosure on problems of reproducibility of academic studies this is an initiative to check reproducibility of the top 50 high impact cancer studies. PMID: 26113698

Michael J. Waring *et al*., **An analysis of the attrition of drug candidates from four major pharmaceutical companies** Nat Rev Drug Discov. 2015, 14, 475.

Describes the combined data on the attrition of drug candidates from AZ, Eli Lilly, GSK and Pfizer, reaffirming that control of physicochemical properties during compound optimization is beneficial in identifying compounds of candidate drug quality and indicates for the first time a link between the physicochemical properties of compounds and clinical failure due to safety issues. PMID: 26091267

Eric P. Gillis et al., **Applications of Fluorine in Medicinal Chemistry**
J. Med. Chem.,

A very good medicinal chemistry perspective on the use of fluorine in medicinal chemistry, from basic properties through to applications in drug discovery programmes and the range of properties that the introduction of fluorine can modulate. PMID: 26200936

Antoine Louveau et al., **Structural and functional features of central nervous system lymphatic vessels** Nature 2015, 523, 337

The discovery of the central nervous system lymphatic system may call for a reassessment of basic assumptions in neuroimmunology PMID: 26030524

S. V. Frye et al., **Tackling reproducibility in academic preclinical drug discovery**

Nat. Rev. Drug Disc., 2015 Proposes that academic drug discovery groups can help address the issue with their translational focus on using generated data PMID: 26388229

T. Nagahara et al., **Design and Synthesis of Non-Peptide, Selective Orexin Receptor 2 Agonists** J. Med. Chem. 2015 Describes the synthesis of small molecule agonists of the Orexin-2 neuropeptide hormone GPCR PMID: 26267383 (see also commentary from A. Heifetz et al J. Med. Chem. 2015 DOI: 10.1021/acs.jmedchem.5b01394 with some speculation on ligand binding modes)

A Bortolato et al., **Model Decoding the Role of Water Dynamics in Ligand–Protein Unbinding: CRF1R as a Test Case** J. Chem. Inf. Mode, 2015, 55(9), 1857 An investigation of the influence of water on off-rates of ligands from proteins PMID: 26335976

An Assay Guidance Manual on the NCBI bookshelf. As an academic researcher, I find it provides guidance on drug development in a more structured and directed manner:
http://www.ncbi.nlm.nih.gov/books/NBK92015/

Early Drug Discovery and Development Guidelines: For Academic Researchers, Collaborators, and Start-up Companies. M. Hughes, J. Inglese, A. Kurtz, et al..

'This chapter contains guidelines to develop therapeutic hypothesis, target and pathway validation, proof of concept criteria and generalized cost analysis at various stages of early drug discovery. Various decision points in developing a New Chemical Entity (NCE), description of the exploratory IND and orphan drug designation, drug repurposing and drug delivery technologies are also described geared toward those who intend to develop new drug discovery and development programs

S. Schatz et al, **Minimizing DILI risk in drug discovery - a screening tool for drug candidates** Toxicol in vitro 2015,

The authors suggest a combination of in vitro assays to help DILI risk mitigation during lead optimization particularly after PK/PD has been established . PMID: 26407524

J. Bisson et al **Can Invalid Bioactives Undermine Natural Product-Based Drug Discovery?**

J. Med. Chem., Oct 27 2015 A reminder that natural products are not free of PAINS like molecules.
DOI:10.1021/acs.jmedchem.5b01009

B. C. Doak et al **How Beyond Rule of 5 Drugs and Clinical Candidates Bind to Their Targets** J. Med. Chem. Oct 12 2015 Discussing how larger molecules can still ake drug candidates with appropriate care in their design
DOI:10.1021/acs.jmedchem.5b01286

The Society of Medicines Award

The Society for Medicines Research believe that outstanding contributions, achievements and inventions in the world of drug discovery and development should be recognised and celebrated. To achieve this goal the SMR instigated its own symbol of recognition, the SMR Award for Drug Discovery. Recipients are individual scientists, or teams of scientists, duly acknowledged for their contribution by the scientific community. The multidisciplinary nature of the achievement is inherent in this award. With members from all disciplines of drug research, we are proud to recognise the successes of others in order to help the individuals and their host institution gain the reward and acclaim they deserve from within the pharmaceutical world. There are still very few prizes of this kind in the drug discovery area and we believe that the multidisciplinary nature of the SMR adds to the recognition status of this award, making it significantly different from those awards that recognise achievements within a single discipline.

If any reader has a suggestion for a candidate for the next award scheduled for December 2016 please contact the secretariat. Nominations should be of novel drugs with first marketing approval post 2013, that demonstrate novel modes of action and are likely to have major impact on disease treatment.

Recipients of the award on behalf of the drug discovery team have been:

- 2014 Dr. Betty Chang (Pharmacyclics) Ibrutinib
- 2012 Dr Peter Mueller (Vertex Pharmaceuticals) Telaprevir
- 2009 Dr Emma Parmee (Merck) Januvia
- 2006 Napoleone Ferrara (Genentech) Bevacizumab
- 2003 Dr Juerg Zimmermann, Dr Elisabeth Buchdunger, Dr Ulrike Pfaar, Dr Peter Graf, Dr John Ford and Dr Renaud Capdeville (Novartis) Imatinib
- 2001 Dr Michael Cawthorne, Dr Stephen Smith, Dr Barrie Cantello, Mr Richard Hindley and Dr David Haigh (GlaxoSmithKline) Rosiglitazone
- 1999 Dr David Tupper, Mr Terence Hotten and Dr Nicholas Moore (Eli Lilly) Olanzapine
- 1997 Drs Duncan, Redshaw and Roberts (Roche) Saquinavir
- 1995 Prof Pat Humphrey (Glaxo) Sumatriptan
- 1993 Dr Ken Richardson (Pfizer) Fluconazole
- 1991 Drs Dutta, Furr and Hutchinson (ICI) Zoladex
- 1989 Prof Sir James Black, in association with Dr Albert Crowther & Prof Robin Ganellin (ICI and SK&F) Beta-blockers and H2 antagonists
- 1987 Prof John Stenlake (University of Strathclyde) Atracurium
- 1985 Dr David Jack (Glaxo) Salbutamol
- 1983 Mr Peter Doyle (Beecham) Augmentin

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