The Society for Medicines Research

NEWSLETTER

April 2016

Editorial

Welcome to the second 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. This edition includes: a brief obituary for one of our founding members Dr. Alma Simmonds who died days before our December meeting, alerts for our meetings for the rest of the year; a precis of the last two meetings, a reminder about membership fees which are now due, a brief history of the Society and finally our gallery of recent literature highlights from the committee. We hope that you will find the diversity of topics covered valuable in your own work and in your continuing professional development.

Don't forget to follow us on Linked-In, Facebook and Twitter with all contributions welcome.

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

Membership

This is the time of year for renewing membership of the SMR. Hopefully everyone will have received an reminder e-mail about renewal. Remember membership fees can be offset against tax if paying yourself.

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 (secretariat@smr.org.uk).

As discussed at the AGM we have been looking at ways of encouraging people to become members of the Society. As of the October meeting we will introduce an additional means of re-registering for a meeting: Alongside the existing registration for an existing member (£85.00) and non-member (increased to £130.00) will be a combined registration plus membership of £110.00, which will be carried out as a single transaction. This will be a simpler way for non-members to become members and hopefully lead to an increase in membership numbers.

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.

Our next meeting

Alzheimer's Disease Therapeutics: Are we making progress towards a disease modifying therapy for patients? 10th June 2016

This meeting is being held at the 'Living Tomorrow' Conference Centre, Indringingsweg 1, 1800 Vilvoorde, Brussels, Belgium.

Future SMR meetings

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Alzheimer's Disease Therapeutics: Are we making progress towards a disease modifying therapy for patients?
Friday 10th June 2016
The 'Living Tomorrow' Conference Centre, Indringingsweg 1,
1800 Vilvoorde, Brussels, Belgium

Rare Diseases, Extraordinary Aspirations
Thursday 13th October 2016
NHLI, London, UK

Recent Disclosures of Clinical Candidates and SMR Award Lecture
Thursday 1st December 2016
NHLI, London, UK

It is sponsored by Janssen and Astex Pharmaceuticals.
Alzheimer's disease is arguably the largest healthcare issue of our time, with over 45 million people currently diagnosed with dementia worldwide. With the single biggest risk factor being age, this number is only going to increase as our populations age. The human impact of this is huge for patients and their families, but the financial impact to our health care systems is also going to be enormous. In the US alone, Alzheimer's disease is the 6th leading cause of death, with over 5.4 million people affected and health care costs in excess of $400 billion and expected to rise to over $1 trillion by 2050. Alzheimer's disease pathology is

highly complex, but is believed to be principally the result of an inter-play between the toxic proteins beta-amyloid and tau and driven by several genetic and environmental risk factors.
Current treatments focus on treating cognitive and behavioural symptoms but have only modest effects and duration of efficacy. Alzheimer's disease has no cure or even therapeutics which slow disease progression, although a number of promising agents are currently in clinical development. So it is clear that there is a huge need to find treatment options.
While considerable resources by multiple pharmaceutical and biotechnology companies have been directed towards finding "disease modifying" drugs, the results from several large clinical trials have been mixed. This symposium will look at the progress that the field has made over recent years in attempting to target different aspects and stages of Alzheimer's disease pathology and what lessons have been learned. It will also look at the current biological mechanisms under clinical and pre-clinical evaluation, together with exploring how new genetic insights into the disease are directing us to novel mechanisms for potential new treatment options.
Leading experts from industry and academia have been brought together for an exciting symposium to review, challenge and debate this complex disease biology and to address the critical question - "Are we making progress towards a disease modifying treatment for patients?"

Our October meeting **'Rare Disease, Extraordinary Aspirations'** will be held at the National Heart and Lung Institute (NHLI), London, 13th October. More details on this meeting will be appearing shortly on the website.

Our final meeting of the year will be **'Recent Disclosures of Clinical Candidates and SMR Award lecture'**, 1st December, also at the NHLI in London. Your committee is currently working hard to select the recipient of the Society's award. The award is given for the most innovative medicine to be approved over the last two years.

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

Previous meetings

'New Developments in Translational Technologies' Royal Veterinary College, London 17th March 2016

Hosted by Transpharmation sponsored by Pharmidex

Our spring meeting was 'New Developments in Translational Technologies' held on 17th March 2016 at the Royal Veterinary College, London. An area of drug discovery and development that has seen a great increase in focus in recent years has been the need for more translational approaches in many if not all therapeutic areas. This has stemmed from the increasing appreciation that many of the cellular and animal models, traditionally used for the assessment of efficacy, have limited predictive validity for human diseases. The meeting brought together experts from a variety of imaging and preclinical model backgrounds across both neuroscience and oncology to discuss how the drug discovery community can better target disease processes, more optimally test novel therapeutics in appropriate populations and ultimately enhance clinical success in producing efficacious therapeutics for patients. Talks covered a review of biomarkers for Alzheimer's disease, electrophysiological markers of cognitive dysfunction and patient derived tumour xenografts. Spontaneous (non evoked) pain models were also discussed as well as the use of stem cell technologies to assess neuropathy associated the familial Alzheimer's disease and Down's syndrome.

Keep an eye out for the full meeting report appearing in 'Drugs of the Future', which we will announce on LinkedIn and Twitter

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The ever popular December meeting **'Trends in Medicinal Chemistry'** Thursday 3rd Dec 2015 NHLI, London attracted some 100 delegates who heard presentations on how medicinal chemistry has responded to the rapid and significant changes drug discovery has undergone in recent years. Themes discussed included how the discipline has adapted through organizational change and application of new technology. Areas of new opportunities for medicinal chemistry were also discussed, specifically the role of chemical biology and the application of medicinal chemistry in stem cell research.

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
- Apply early - there are five available for each meeting

The meeting was sponsored by Astex Pharmaceuticals.

Meeting reports

A full report of the December 2015 meeting has now published Davenport, R., Jeffrey, P., MacDonald, G., Porter, R.

Drugs Fut 2016, 41(1): 59 and will be made available on the SMR website in approximately 3 months.

The Drugs of the Future meeting reports from our October 2015 Biotherapeutics - Innovative Future Medicines. and June 2015 Opportunities and Challenges in Cancer R&D meetings are now available on the SMR website.

Obituary of Alma Simmonds

Sadly the committee have to announce the death of Dr Alma Simmonds. She passed away on Tuesday 24th November 2015 aged 95. Dr. Simmonds was one of the founders of the Society for Drug Research in 1966 which later changed its name to the Society for Medicines Research.

It was Dr. Simmonds together with Norman J Harper, Professor at Aston University, who approached the Pharmaceutical Society in 1966 to let them know about their intention to create this new Society. They were greatly encouraged by the response they got including permission to use the Pharmaceutical Society's Hall for meetings and access to the membership list to publicise the new Society.

Dr Simmonds served as Honorary Secretary 1966-75 and it is likely that without her hard work in promoting the Society it might well have had only a short life. In a token recognition of Dr. Simmonds' major contribution to the Society she became the first person to be made an honorary life member of the Society in the 1980's.

The 2015 Christmas meeting was dedicated to Dr. Simmonds' memory.

Celebrating 50 years of the SMR

It is almost 50 years since the inaugural meeting of the Society for Drug Research was held in September 1966 in the Hall of the Royal Pharmacological Society, London to establish an organization dedicated to encouraging interdisciplinary approaches to drug research. The first major residential meeting held in London in 1969 entitled simply 'Medicinal Chemistry' attracted nearly 300 delegates. The Society gained charitable status in 1977 and changed its name to the Society for Medicines Research in 1994. Since 1996 the Society has held 3 or 4 one day symposia a year on subjects diverse as the Chemotherapy of nematode infections (1966); Peptic ulceration (1971); Drug intervention in the ageing process (1977); Computers in drug design (1985); Fertility control in the 21st century (1982); Oral cavity diseases and treatment (1979); Burns and drug action (1978) as well as covering a wide range of therapeutic areas and the ever popular Case Histories and Trends in Medicinal Chemistry meetings. Joint meetings have been held with other organisations such as the British Pharmacological Society, The London Biotechnology Network, IUPHAR, The Italian Chemical Society and the British Association of Cancer Research. Pharmaceutical companies have regularly supported the SMR by hosting conferences at their facilities. Meeting reports have been published since 1997 by Thomson Reuters in 'Drugs News and Perspectives' and later in 'Drugs of the Future' journals. In 1981 the biennial SMR Award for Drug Discovery was established (as featured in the November 2015 SMR newsletter), and has been awarded to an illustrious list of recipients. The multi-disciplinary nature of the achievement of successfully bringing an innovative medicine to market is inherent in this award. The SMR has a broader purpose than professional development and also seeks to strengthen the life science sector in the UK for future careers in drug discovery. A student bursary fund, with a cornerstone donation of £5,000 from AstraZeneca, to facilitate wider student participation at meetings has been established. The membership of the SMR has always been multi-disciplinary in nature and with both industry and academic participants. It has evolved over the years to now include many biotech and contract research organization members in addition to the traditional pharmaceutical industry members. The Society continues to adapt to face the challenges of an ever-changing landscape of medicines research in the UK.

Some recent literature references highlighted by the SMR committee

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

B. C. Doak et al **How Beyond Rule of 5 Drugs and Clinical Candidates Bind to Their Targets** *J Med. Chem.,* 2016, 59, 2312

Considers how perceptions of what constitutes druggable may need to change along with how efficiency metrics should be applied to such targets

PMID: 26457449

N. A. Meanwell **Improving Drug Design: An Update on Recent Applications of Efficiency Metrics, Strategies for Replacing Problematic Elements, and Compounds in Nontraditional Drug Space** *Chem. Res. Toxicol.,* DOI: 10.1021/acs.chemrestox.6b00043

Relating back to our December meeting a consideration of the impact of compound metrics on attrition in drug discovery

PMID: 26974882

S. Jasial et al **Assessing the Growth of Bioactive Compounds and Scaffolds over Time: Implications for Lead Discovery and Scaffold Hopping** *J. Chem. Inf. Model.,* 2016, 56, 300. Highlights increasing diversity of scaffolds identified for targets over time and is supportive of computational scaffold hopping

PMID: 26838127

T. Lassila et al **Toxicity of Carboxylic Acid-Containing Drugs: The Role of Acyl Migration and CoA Conjugation Investigated** *Chem. Res. Toxicol.,*

DOI: 10.1021/acs.chemrestox.5b00315

PMID: 26558897

P. Schyman et al **General Purpose 2D and 3D Similarity Approach to Identify hERG Blockers**, *J. Chem. Inf. Model.,* 2016, 56, 213.

PMID: 26718126

K. M. Page **Validation of Early Human Dose Prediction: A Key Metric for Compound Progression in Drug Discovery** Mol. Pharmaceutics, Article ASAP. DOI: 10.1021/acs.molpharmaceut.5b00840

Validation of a method to predict human dose using only in vitro and predicted parameters incorporated into a PK model was undertaken by predicting human dose and free Cmax for a number of marketed drugs and AZ Development compounds. 92% dose prediction were within 10 fold and 68% within threefold of marketed compound dose

PMID: 26696327

R.F. Sweis et al **Analysis of Impact of Post-Treatment Biopsies in Phase I Clinical Trials** J. Clin. Oncol., 2016,34, 369
Despite the increasing use of pre- and post-treatment tumour biopsies being included in Phase I cancer clinical trials, the authors of this article perhaps surprisingly demonstrate, that their impact on dose or schedule selection for future clinical development has been minimal. Use of more traditional dose selection criteria such as maximum tolerated dose are still proving to be the default option for this purpose, even for targeted small molecules or biotherapeutics.

PMID:26668350

M. Dambach et al **Safety Lead Optimization and Candidate Identification: Integrating New Technologies into Decision-Making** *Chem. Res. Toxicol.,* DOI: 10.1021/acs.chemrestox.5b00396

An extensive survey of the tools available to help evaluate possible tox liabilities early in the drug discovery process as used by Genentech

J. M. Elkins et al. **Comprehensive characterization of the Published Kinase Inhibitor Set.** *Nat. Biotech.,* 2015, 28, 370

D. E. Frail et al **Pioneering government-sponsored drug repositioning collaborations: progress and learning** *Nature Rev. Drug Disc.,* 2015, 14, 833

PMID: 26585533

D. G. Brown and J. Boström **Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone?** *J. Med. Chem.,* Article ASAP

DOI: 10.1021/acs.jmedchem.5b01409

Analysis revealing none of the commonly used reactions in medicinal chemistry was discovered in the last 20 years

PMID: 26571338

T. Cernak et al **The medicinal chemist's toolbox for late stage functionalization of drug-like molecules** *Chem. Soc. Rev.,* 2016, 45, 546 A good review of C-H functionalisation chemistries looking at functionalization of advanced stage molecules as an alternative strategy in synthetic chemistry of drug discovery. Perhaps the conclusions of the previous article will be different in years to come!

PMID: 26507237

S. G. Smith et al **The Bromodomain: A New Target in Emerging Epigenetic Medicine** *ACS Chem. Biol.,* 2016, 11, 598

PMID: 26596782

A S. Kesselheim et al **Two decades of new drug development for central nervous system disorders** *Nature Rev. Drug Disc.,* 2015, 14, 815

PMID: 26585536

Wager TT **Central Nervous System Multi-Parameter Optimization (CNS MPO) Desirability: Application in Drug Discovery** *ACS Chem Neurosci.* 2016 Apr 4. [Epub ahead of print]

Pertinent to our June meeting is a review by the Pfizer team of their MPO approach to CNS drug discovery

PMID: 26991242

H. Gunaydin **Probabilistic Approach to Generating MPOs and Its Application as a Scoring Function for CNS Drugs** *ACS Med. Chem. Lett.,* 2015, 7, 89 The utility of a new probabilistic MPO (pMPO) scoring function method and its application as a scoring function for CNS drugs are described

PMID: 26819672

T. Masuda and M. Prinz **Microglia: A Unique Versatile Cell in the Central Nervous System** *ACS Chem. Neurosci.,* Article ASAP DOI: 10.1021/acschemneuro.5b00317

Review highlighting the latest understanding of the origin to

both the physiological and pathological roles of microglia

PMID: 26844374

N. Kamei et al., **Visualization and Quantitative Assessment of the Brain Distribution of Insulin through Nose-to-Brain Delivery Based on the Cell-Penetrating Peptide Noncovalent Strategy** *Mol. Pharm.,* 2016 13, 1004

DOI: 10.1021/acs.molpharmaceut.5b00854

PMID: 26795701

M. Guirati et al **Multifunctional pH-Sensitive Amino Lipids for siRNA Delivery** *Bioconjugate Chem.,* 2016, 27, 19 This review summarizes the structure-property relationship of the multifunctional pH-sensitive lipids and their efficacy in in vitro and in vivo siRNA delivery and gene silencing.

PMID: 26629982D

S. K. Soininen et al **Intracellular PK/PD Relationships of Free and Liposomal Doxorubicin: Quantitative Analyses and PK/PD Modeling** *Mol. Pharm,* 2016, 13, 1358 Cellular and nuclear concentrations of doxorubicin were quantified with LC/MS after cell exposure with free and liposomal doxorubicin (pH-sensitive and pegylated liposomes)

PMID: 26950248

S. Paricharak et al **Analysis of Iterative Screening with Stepwise Compound Selection Based on Novartis In-house HTS Data** *ACS Chem. Biol.,* Article ASAP

DOI: 10.1021/acschembio.6b00029

An efficient method for iterative screening of small subsets of compound libraries is presented. With this method, using structural information and biological activity fingerprints the retrieval of active compounds is optimized reducing the total numbers of compounds to screen

PMID: 26878899

Q.A. Huchet et al **Fluorination Patterning: A Study of Structural Motifs That Impact Physicochemical Properties of Relevance to Drug Discovery** *J. Med. Chem.,* 2015, 58, 9041-9060

PMID: 26523333

G. Cavallo et al **The Halogen Bond** *Chem. Rev.,* 2016, 116, 2478 looks at the role of the halogen bond in various fields including drug discovery

PMID: 26812185

S. Bietz et al **SIENA: Efficient Compilation of Selective Protein Binding Site Ensembles** *J. Chem. Inf. Model.,* 2016, 56, 248 SIENA is a computational approach for the automated assembly and preprocessing of protein binding site ensembles. It is available via the web.

PMID: 26759067

P. W. Kenny et al **Hydrogen Bond Basicity Prediction for Medicinal Chemistry Design** *J. Med. Chem.,* Article ASAP DOI: 10.1021/acs.jmedchem.5b01946

Molecular electrostatic potential (Vmin) is shown to be an effective predictor of hydrogen bond basicity (pKBHX), and predictive models are presented for a number of hydrogen bond acceptor types relevant to medicinal chemistry.

PMID: 26872049

J. B. Baell **Feeling Nature's PAINS: Natural Products, Natural Product Drugs, and Pan Assay Interference Compounds (PAINS)** *J. Nat. Prod.,* DOI: 10.1021/acs.jnatprod.5b00947

It turns out chemists are not the only ones who make PAINS as this paper shows nature also makes PAINS although the context of the biological readout is an important factor to consider

PMID: 26900761

D. J. Newman and G. M. Cragg **Natural Products as Sources of New Drugs from 1981 to 2014** *J. Nat. Prod.,* 2016, 79, 629 An update from 2012 and previous reviews highlighting the continued importance of natural products in drug discovery

PMID: 26852623

C. W. Lindsley et al **Practical Strategies and Concepts in GPCR Allosteric Modulator Discovery: Recent Advances with Metabotropic Glutamate Receptors**, *Chem. Rev.,* Article ASAP
DOI: 10.1021/acs.chemrev.5b00656

A comprehensive overview of the basics of GPCR allosteric pharmacology, medicinal chemistry, drug metabolism, and validated approaches to address each of the major challenges. Some of the concepts are discussed through examples of mGluR allosteric modulators

PMID: 26882314

A. A. S. T. Ribeiro and V. Ortiz **A Chemical Perspective on Allostery** *Chem. Rev.,* Article ASAP DOI: 10.1021/acs.chemrev.5b00543

Summarizes recent advances in the analysis of mechanisms of allosteric communication in proteins, and provides a perspective of allostery consistent with chemical views of molecular processes

PMID: 26741913

R. Dawaliby et al **Allosteric regulation of G protein-coupled receptor activity by phospholipids** *Nature Chem Biol.,* 2016, 12, 35-39. Characterisation of the effect of phospholipids as allosteric modulators of the 2 receptor

PMID: 26571351

M. J. C. Long et al **On-Demand Targeting: Investigating Biology**

with Proximity-Directed Chemistry *J. Am. Chem. Soc.,* 2016, 138 , 3610
Multifunctional scaffolding v. on demand targeting covers PROTACS and all those sorts of interesting linking concepts

PMID: 26907082

C. A. Hutchinson III et al **Design and synthesis of a minimal bacterial genome** *Science* 2016, 351, Issue 6280, DOI: 10.1126/science.aad6253 The title says it all!

PMID: 27013737

L. M. Jarvis **The Year in New Drugs** *Chem. Eng. News* 2016, 94, 12

A handy review of the 45 new drug approvals by the FDA for 2015

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