The Society for Medicines Research

NEWSLETTER

September 2016

Editorial

Welcome to the third edition of the SMR Newsletter, which the committee hopes you will find useful in keeping up to date with the activities of the Society. This newsletter includes announcements of our upcoming meetings including the SMR award 2016; a precis of the last two meetings, and our gallery of recent literature highlights as recommended by 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 LinkedIn and Twitter with all contributions welcome.

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

Announcement of the SMR award 2016

After considerable deliberation The Society for Medicines Research is pleased to announce that the 2016 SMR Award for Drug Discovery is awarded to the Bristol-Myers Squibb team responsible for OPDIVO® (Nivolumab), a fully human anti-programmed death receptor-1 (PD-1) antibody approved to treat several cancers. Immunotherapies such as Nivolumab have revolutionized the treatment of cancer in recent years.

The SMR Award will be received by Dr Francis Cuss, Executive Vice President & CSO R&D, Bristol-Myers Squibb on 1st December at the National Heart and Lung Institute, London, UK at the 'Recent Disclosures of Clinical Candidates' SMR meeting. Dr Cuss will also deliver the SMR Award Lecture entitled 'The discovery, development and delivery of Opdivo'. For the meeting details please see here.

Nivolumab is an immune checkpoint inhibitor that acts by blocking PD-1, a negative regulator of T-cell activation and response, thereby releasing the immune system to attack the tumour. It is a fully human monoclonal, immunoglobulin G4 antibody to PD-1, originally discovered by Medarex and brought to market by Bristol-Myers Squibb (which acquired Medarex in 2009) and Ono Pharmaceutical Co. Nivolumab was the first PD-1 inhibitor to gain marketing approval worldwide in July 2014 when it was approved in Japan as monotherapy for unresectable melanoma. It has subsequently been approved by the US FDA in December 2014 for metastatic melanoma and more recently for treatment of metastatic squamous non-small cell lung cancer, renal cell carcinoma and classical Hodgkin lymphoma after previous treatments have failed.

About the SMR Award

The SMR Award recognises outstanding research in the multi-disciplinary field of drug discovery and development. The award has been presented every 2-3 years since 1983 and is decided by the SMR Organising Committee. A distinguishing feature of the award is a demonstration of scientific innovation and excellence leading to the launch of a new therapy to the market. Recipients are individual scientists, or teams of scientists, duly acknowledged for their contribution by the scientific and medical community.

Future SMR meetings

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Rare Diseases, Extraordinary Aspirations
Thursday 13th October 2016
Grand Connaught Rooms
London, London, WC2B 5DA
UK

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

Gene therapy: right here, right now
Thursday 9th March 2017,
London, UK

Our next meetings

Our October meeting 'Rare Disease, Extraordinary Aspirations' will be held on the 13th October at the Grand Connaught Rooms London WC2B 5DA. Please note the change of venue from that originally advertised.

Orphan drugs are designated drug substances that are intended to treat rare or 'orphan' diseases which are classified as < 200,000 total individual cases in the US and a rate of <5 in 10,000 individuals in the EU. More than 7000 rare diseases are known that collectively affect some 6-7% of the developed world's population. 75% of patients are children, a third of whom will die before they reach the age of 5 years. In the case of

cancer, all but the four most common indications fall under the orphan disease definition. Given this, the cancer community normally classifies "rare cancers" as those with an incidence of < 6 per 100,000 persons per year. Individually any single rare disease may only affect a handful of people making them a relatively unattractive prospect for the biopharmaceutical industry to target. However, groundbreaking legislation, starting with the Orphan Drug Act that was passed in the US in 1983, now provides financial incentives to develop orphan drugs, sparking ever increasing interest from biopharmaceutical companies to tackle rare diseases.

Today, rare diseases and the drugs that treat them are sufficiently attractive that many companies and research institutes now have research units dedicated to this area. It is therefore timely to review the area of orphan drugs and some of the basic science, drug discovery and regulatory factors that underpin this important, and growing, area of biomedical research.

This meeting brings together experts from academia, industry and disease advocacy organisations to present their experiences and thoughts on tackling rare diseases through case studies and opinion pieces. This promises to be an exciting and interesting meeting with in depth discussions of how the drug discovery and development community has approached rare disease research in the past and how this will evolve in the future to allow broader access to rare disease therapeutics. It will provide an excellent networking environment for anyone interested in this important research area.

Please note the new option on registering and paying for the meeting registration in a single operation.

Confirmed sponsors of this meeting are Vertex, Charles River Laboratories and Pharmidex and it is also supported by EFMC. Please register soon for this meeting.

Our final meeting of the year will be 'Recent Disclosures of Clinical Candidates and SMR Award lecture', 1st December, London - see the article above announcing the award winner. Registration is open.

This symposium will feature an international line up of speakers presenting on the discovery and development of novel therapeutic agents that have recently progressed towards or into clinical trials. The symposium will start with the 2016 Society of Medicines Research Award Lecture followed by presentation of the award. The programme will also cover a variety of mechanistic approaches for novel therapeutics including small molecules, monoclonal antibodies and a drug repurposing presentation. Talks will address a range of therapeutic areas including oncology, anti-infectives, inflammation and anaemia.

This meeting is, so far, sponsored by Liverpool Chirochem

Our first meeting of 2017 'Gene therapy: right here, right now', 9th March 2017, London is now on the web and registration is open.

Whilst the concept, application and enormous potential of gene therapy to repair the direct cause of genetically driven diseases 'at source' has tantalised and fascinated the scientific community over recent years, the development of suitable treatments using this technology has encountered many challenges. Only few gene therapy trials reported clear clinical benefits and in some, severe adverse events including lethality were observed. Overall, concern and scepticism rose over the further deployment of these strategies. However these attitudes are changing with the introduction of new delivery approaches and gene technologies. Several trials in inherited diseases as well as cancers have demonstrated evidence of efficacy and safety. Additional precision gene editing technologies, in particular CRISPR, are now nearing the clinic, further increasing the possibilities of altering the human genome to treat serious diseases.

This meeting brings together experts from academia and industry to discuss the promise, challenges and reality of gene therapy as a therapeutic approach. This promises to be an exciting and interesting meeting with in depth discussion of how the drug discovery and development community has approached gene therapy in the past, how this will evolve in the future to benefit patients and provide an excellent networking environment for everyone interested in this important and rapidly emerging research.

A new meeting for young scientists

Planning for our Autumn meeting next year - October 5th 2017 is now underway. It will be a joint meeting with the British Pharmacological Society and will be of a different format to our usual meetings. It is strongly targeted at third year undergraduate through to post doctoral students and to industry workers in their early careers. There will be three keynote speakers who will be supporting talks by student and early career industry speakers accompanied by a poster session. While the focus will be on early career scientists the committee is hoping that many more "mature" colleagues will also participate, as this will be a great networking opportunity for these young scientists with those who already have significant experience in drug discovery. Not to forget the high quality talks and posters that delegates will also be able to enjoy. The meeting will be held at Charles Darwin House, London WC1N 2JU.

Please do keep an eye open for more information about this exciting new meeting and do let interested colleagues know about it. Remember we are able to offer limited numbers of travel bursaries to students - for more details see the side panel elsewhere in this newsletter.

Previous meetings

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

This meeting was held in Brussels and was sponsored by Janssen and Astex Pharmaceuticals. It attracted over 100 researchers from across Europe to listen to a wide ranging discussion about this disease.

Dr. Simon Ridley, Director of Research, Alzheimer's Research UK, opened the meeting with a survey of the landscape of the dementia research environment, initiatives/investments and our progress towards therapeutic interventions for Alzheimer's Disease (AD). Dr. Samantha Budd Haeberlein, VP Alzheimer's Discovery and Development, Biogen Idec, provided an insight into the progress we have made in the development of amyloid-focused therapeutics. Professor Julie Williams, MRC Centre for Neuropsychiatric Genetics & Genomics, University of Cardiff, summarised where the genetics of Alzheimer's has taken us in terms of genetic vulnerabilities and the biological pathways implicated in the development of AD.

Dr. O'Neill from Eli Lilly discussed the role of tau isoforms and phosphorylation and their role in the formation of neurofibrillary tangles and neurite plaques, followed by a discussion of some of the biological models and therapeutic strategies to target tau. Dr. Marc Mercken from Janssen also discussed the role of tau, now focusing on some of the issues with tau as a target, concluding with a discussion of immunotherapy as an approach to manage tau pathology.

In a section surveying the role of inflammation in AD Dr. David Brough, from University of Manchester, discussed the role of the inflammasome. Finally, Dr. Fiona Menzies described the research of the David Rubinsztein lab based at the University of Cambridge, looking at autophagy upregulation as a therapeutic target for neurodegenerative diseases.

Published meeting reports

The full meeting reports of our March and June meetings have now published

'Alzheimer's disease therapeutics - are we making progress towards a disease-modifying treatment for patients?'
A meeting held on 10th June 2016.
Ward, S.E., Dawson, L.A., Konneh, M., MacDonald, G.

Drugs Fut 2016, 41(7): 461

'New Developments in Translational Technologies'
Meeting held on March 17th 2016.
Dawson, L.A., Alderton, W.K., Alavijeh, M.S., Weber, P.

Drugs Fut 2016, 41(5): 311

As usual these will be placed on the SMR website approximately 6 months after first publication.

Published meeting reports on the SMR website

The December 2015 meeting report Davenport, R., Jeffrey, P., MacDonald, G., Porter, R.

Drugs Fut 2016, 41(1): 59 is now available on the SMR website.

Membership

Hopefully everyone has now had a chance to renew their membership. If you haven't why not take advantage of the new registration/membership option when booking your place for October's meeting?

Remember membership fees can be offset against tax if paying yourself.

It is a great help to our secretariat if, when moving between jobs, you can provide your new contact details to secretariat@smr.org.uk.

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 panel.

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 the SMR website to download the application form.
- Complete form and appropriate registration document with a signature, confirm student status e.g. by 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 three available for each meeting

Some recent literature references highlighted by the SMR committee

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

A Mullard
EMA rewrites Phase I guidelines in aftermath of FAAH tragedy
Nat. Rev. Drug Disc., 2016, 15, 595
PMID: 27573225

A Mullard
FDA approvals for the first 6 months of 2016
Nat. Rev. Drug Disc., 2016, 15, 523
The FDA approved 13 new drugs in the first 6 months of this year the CDER approvals included 8 small molecules and 5 biologics
PMID: 27469224

G. Patlewicz and J. M. Fitzpatrick **Current and Future Perspectives on the Development, Evaluation, and Application of in Silico Approaches for Predicting Toxicity**
Chem. Res. Toxicol., 2016, 29, 438
This review proposes a workflow for how non-testing approaches could be practically integrated within testing and assessment strategies in drug discovery
PMID: 26686752

D. M. Dambach, et al
Safety Lead Optimization and Candidate Identification: Integrating New Technologies into Decision-Making
Chem. Res. Toxicol., 2016, 29, 452
PMID: 26625186

E. A. G. Blomme, Y. Will
Toxicology Strategies for Drug Discovery: Present and Future
Chem. Res. Toxicol., 2016, 29, 473
PMID: 26588328

R. A. Thompson et al
Reactive Metabolites: Current and Emerging Risk and Hazard Assessments
Chem. Res. Toxicol., 2016, 29 , 505
PMID: 26735163

ACS Epigenetics collection
A wide ranging selection of papers discussing many aspects of epigenetics research from the ACS
http://pubs.acs.org/page/vi/2015/epigenetics.html

P. Lassalas et al
Structure Property Relationships of Carboxylic Acid Isosteres
J. Med. Chem., 2016, 59, 3183
often a challenge to move to more user friendly acid alternatives this article may help.
PMID: 26967507

Y. Miyaji, et al
Advantage of the Dissolution/Permeation System for Estimating Oral Absorption of Drug Candidates in the Drug Discovery Stage
Mol. Pharmaceutics, 2016, 13, 1564
PMID: 27031624

J. Schiebel et al
Six Biophysical Screening Methods Miss a Large Proportion of Crystallographically Discovered Fragment Hits: A Case Study
ACS Chem. Biol., 2016, 11, 1693
Reinforces the value of X-ray crystallography as a frontline approach for fragment screening
PMID: 27028906

T. T. Wager et al
Central Nervous System Multiparameter Optimization Desirability: Application in Drug Discovery
ACS Chem. Neurosci., 2016, 7, 767
Assesses the impact of application of the Pfizer MPO approach reported 5 years ago in CNS drug discovery, estimating a significant positive effect - open access
PMID: 26991242

M. Pettersson et al
Quantitative Assessment of the Impact of Fluorine Substitution on P-Glycoprotein (P-gp) Mediated Efflux, Permeability, Lipophilicity, and Metabolic Stability
J. Med. Chem., 2016, 59, 5284
PMID: 27228214

C. J. Dickson et al
Uncoupling the Structure-Activity Relationships of β2 Adrenergic Receptor Ligands from Membrane Binding
J. Med. Chem., 2016, 59 (12), pp 5780-5789
PMID: 27239696

G. Milligan et al,
Complex Pharmacology of Free Fatty Acid Receptors
Chem. Rev., Article ASAP Publication Date (Web): June 14, 2016
This recently deorphanized receptor class is receiving a lot of interest despite the complex pharmacology
PMID: 27299848

A. Jazayeri et al,
Structurally Enabled Discovery of Adenosine A2A Receptor Antagonists
Chem. Rev., Article ASAP
Discusses key developments in enabling GPCR structural studies and the application of this information to the design of potent selective adenosine A2A receptor antagonists
PMID: 27333206

T. T. Talele
The "Cyclopropyl Fragment" is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules
J. Med. Chem., Article ASAP Publication Date (Web): June 30, 2016
This review focuses on the contributions that a cyclopropyl ring makes to the properties of drugs containing it and the

advantages conferred by the group's presence.
PMID: 27299736

Y-Q. Wang et al
An Update on Poly (ADP-ribose) polymerase-1 (PARP-1) Inhibitors: Opportunities and Challenges in Cancer Therapy
J. Med. Chem., Article ASAP Publication Date (Web): July 27, 2016
A timely review of an area of drug discovery generating considerable clinical excitement.
PMID: 27416328

B. R. Beno et al
A Survey of the Role of Noncovalent Sulfur Interactions in Drug Design
J. Med. Chem., 2015, 58, 4383
A review on some of the intramolecular and protein interactions Sulphur can undergo based on its two areas of positive electrostatic potential, a consequence of the low-lying ?* orbitals of the C-S bond.
PMID: 25734370

S. Christmann-Franck et al
An Unprecedentedly Large-Scale Kinase Inhibitor Set Enabling the Accurate Prediction of Compound-Kinase Activities: A Way toward Selective Promiscuity by Design?
J. Chem. Inf. Model. Article ASAP
PMID: 27482722

N. Meanwell et al
2015 Philip S. Portoghese Medicinal Chemistry Lectureship. Curing Hepatitis C Virus Infection with Direct-Acting Antiviral Agents: The Arc of a Medicinal Chemistry Triumph.
J. Med. Chem., 2016, 59, 7311
Describes the BMS work on direct acting antivirals for curing chronic hepatitis C
PMID: 27501244

H. Dolgos et al
Translational Medicine Guide transforms drug development processes: the recent Merck experience
Drug Discov Today. 2016, 21, 517
Interesting read on how Merck is approaching Translational Medicine (TxM) and have developed a "TxM Guide" which is being placed at the core of their development decision making processes.
PMID:26778693

R. A. Sharma et al
Clinical development of new drug-radiotherapy combinations
Nat Rev Clin Oncol. 2016 Jun 1. doi: 10.1038/nrclinonc.2016.79. [Epub ahead of print]
An important paper summarising consensus recommendations to increase the number of novel drugs being successfully registered in combination with radiotherapy in order to improve clinical outcomes for patients with cancer.
PMID: 27245279

D. E. Scott et al
Small molecules, big targets: drug discovery faces the protein-protein interaction challenge
Nature Rev. Drug Disc. aop, (2016)
Good review on efforts to target PPIs with useful classification scheme in an area that receives more and more attention
PMID: 27050677

M. Lek et al
Analysis of protein-coding genetic variation in 60,706 humans
Nature 2016, 536, 285
Describes the aggregation and analysis of high-quality exome DNA sequence data for 60,706 individuals of diverse ancestries generated as part of the Exome Aggregation Consortium (ExAC). A potential milestone study.
PMID: 27535533

T. P. Heffron
Small Molecule Kinase Inhibitors for the Treatment of Brain Cancer
J. Med. Chem., Article ASAP
Discusses the unmet need for Neurooncology treatments, the appeal of kinase targets in this space, and a summary of what is known about free brain penetration of clinical inhibitors of kinases that are of interest for the treatment of brain cancer.
PMID: 27414067

L. Tang et al
Structural basis for inhibition of a voltage-gated Ca2+ channel by Ca2+ drugs
Nature 2016, 537, 117-12
Finally some Ca2+ channel antagonist structures - dihydropyridines binding to the external lipid facing surface of the pore module.
PMID: 27556947

A Rialdi et al
Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation
Science. 2016, 352(6289): aad7993
Intriguing possibilities
PMID: 27127234

S. J. Andrews and J. A. Rothnagel
Emerging evidence for functional peptides encoded by short open reading frames
Nature Reviews Genetics 2014, 15, 193-204
A couple of years old now but worth a look as an insight into a perhaps underdeveloped area of research.
PMID:24514441

S Szymkuć et al
Computer-Assisted Synthetic Planning: The End of the Beginning
Angew. Chemie. Int. Ed., 2016, 55, 5904
Useful review of current state of the art in CASP
PMID:27062365

M. Wenlock
Profiling the estimated plasma concentrations of 215 marketed oral drugs
Med. Chem. Commun., 2016, 7, 706
Suggesting some guidelines on maximal free drug concentration and peak/trough ratio to reduce toxicity risks

J. W. Scannell and J. Bosley
When Quality Beats Quantity: Decision Theory, Drug Discovery, and the reproducibility crisis
PLoS ONE 11(2): e0147215
Different perspective on reproducibility crisis and a stark conclusion "The rate of creation of valid screening and disease models may be the major constraint on R&D productivity"
PMID: 26863229

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