Newsletter
May 2014

Welcome to the May 2014 SMSdrug.net Newsletter, a regular update on some of the initiatives within the Network. If you would like to highlight any news to our industrial and academic network please contact the network administrator helen.feilden@strath.ac.uk

ChEMBL Update -2014 Tour Dates

Following the success of the 2013 ChEMBL Tour SMSdrug.net supported last year, Dr Gerard van Westen (EMBL –EBI) is going to be doing a 2014 ChEMBL tour. This year's tour will be going to mainland Europe and some dates will include a presentation on Allosteric Modulators which will refer to this recent publication: van Westen GJP, Gaulton A, Overington JP (2014) Chemical, Target, and Bioactive Properties of Allosteric Modulation. PLoS Comput Biol 10(4): e1003559. doi:10.1371/journal.pcbi.1003559.

Dates are as follows:

19th of May – Maastricht University- Host Egon Willighagen / ChEMBL + Allosteric modulators
20th of May – Maastricht University- Host Jos Kleinjans / ChEMBL + Advanced ChEMBL
20th of May – KU Leuven - Host Pieter Annaert / ChEMBL
22nd of May – Universiteit Antwerpen - Host Koen Augusteyns / ChEMBL
26th of May – VU University Amsterdam - Host Rob Leurs & Universiteit van Amsterdam - Host Willem Stiekema / ChEMBL + Allosteric modulators
28th of May – University of Groningen - Host Alexander Domling / ChEMBL + Advanced ChEMBL
6th of June – Utrecht University - Host Roland Pieters / ChEMBL
6th of June – Universiteit Leiden - Host Ad IJzerman / ChEMBL
17th of June – Erasmus Medical Centre, Rotterdam - Host Roland Kanaar / ChEMBL
18th of June – Radboud University Nijmegen - Host Tina Ritschel / ChEMBL + Allosteric modulators

Please contact gerardvw@ebi.ac.uk if you want to find out more about any of these meetings.

Chemical Biology Grant Success

A grouping from University of Strathclyde and University of St Andrews, established through SMSdrug.net, has secured £575K from BBSRC to investigate the *S*-acylation of proteins.
The cells in our body contain a diverse array of different proteins that coordinate and drive specific pathways, such as cell growth and division. These proteins are subjected to strict modes of regulation to ensure that they are able to perform their specific functions as and when required. One prominent mechanism of protein regulation is via chemical modification and a variety of different molecules are added to proteins that affect their activity. One modification that is receiving increasing interest is "S-acylation", the attachment of fatty acids onto proteins, which is catalysed by a family of twenty-four "DHHC" enzymes. Dysfunction of DHHC enzymes has been linked with many important disorders, including diabetes, Huntington's disease, schizophrenia, intellectual disability and cancer.
This project will capitalise on the collective expertise of the applicants in chemical synthesis, lipid biochemistry and cell biology to define features of DHHC enzymes that control fatty acid specificity and how different fatty acids impact on functional properties.

CRUK Grant Success

Recent studies implicate the involvement of the non-canonical NFκB pathway in the development of a number of cancers, including CLL, prostate and pancreatic cancer, and a key role for the upstream regulatory kinase, IKKα. Over the last six years, the SMDD group at Strathclyde has successfully prosecuted a program to establish the first ever series of selective IKKα inhibitors, generating novel compounds with promising pharmacodynamic properties that have considerable clinical potential. The group have recently demonstrated that a compound from our lead series has in vivo activity in a xenograft model of prostate cancer.

In a collaborative project with Peter Storz at the Mayo Clinic, USA, the group have shown for the first time that inhibition of IKKα reduces the proliferation of a number of pancreatic cancer cell lines. Pancreatic cancer is one of the most intractable and untreatable cancers in the UK. Death rates are unacceptably high and despite considerable research, the survival rate for both men and women over five years remains less than 4%. The group has now been awarded funding by Cancer Research UK (£200K) to pursue a proof-of-concept drug discovery project to establish whether selective IKKα inhibitors offer a new therapy for the treatment of pancreatic cancer. In addition to working with the Mayo Clinic, Strathclyde researchers teamed up with Andrew Biankin and David Chang at the Wolfson Wohl Cancer Research Centre at Glasgow University, who will examine compounds emerging from our lead optimization programme in primary patient-derived pancreatic cancer cells. These samples have been genetically profiled, which will be crucial for future stratification studies should a pre-clinical drug candidate from our lead series reach clinical trials.

This project is another example of the SMS-Drug network facilitating successful collaborations between biologists, clinical scientists and chemists in drug discovery at the national and international level. In a similar vein, the recent publication in the Journal of Medicinal Chemistry of new compounds inhibiting the cancer target sphingosine kinase 1 exemplifies further collaborations between chemists and biologists from across the pond between the University of Strathclyde and the City University of New York [Dongjae Baek, Neil MacRitchie, Nahoum Anthony, Simon Mackay, Susan Pyne, Nigel Pyne and Robert Bittman (2013) Structure activity relationships and molecular modelling of sphingosine kinase inhibitors. *J. Med. Chem*., 56, 9310-27.

This Newsletter highlights some of the efforts within SMSdrug.net
For more information and full details of our initiatives to bridge the gap between Chemistry and Biology please visit our website, or contact the network administrator helen.feilden@strath.ac.uk