Conference Report

The 1st Israeli-UK Medicinal Chemistry Conference

22-23 April, 2012

Weizmann Institute of Science

Rehovot, Israel

The first Israeli-UK Medicinal Chemistry Conference took place at the Weizmann Institute of Science in Rehovot, Israel on 22-23 April 2012. This meeting came about after an initial approach from the Medicinal Chemistry Section of the Israel Chemical Society to the Biological and Medicinal Chemistry Sector of the Royal Society of Chemistry. Both societies were keen to promote interactions between the groups and so with sponsorship from the European Federation of Medicinal Chemistry the meeting was planned. The Weizmann Institute is a superb venue with a heritage of outstanding science, an atmosphere to encourage great discussion and a newly refurbished lecture complex to allow the participants the best opportunity to interact.

Session 1 (22 April)

The meeting began with a presentation from Dr Justin Bower from the Beatson Institute in Glasgow describing some of their most recent approaches using fragment-based methods to modulate protein-protein interactions. The merits of a fragment based approach were expounded and the uses versus this typically undruggable target class demonstrated. The importance of ligand efficiency was emphasised and some efficient bioisosteres described.

The morning continued with a talk from Dr Ayelet David (Ben Gurion University) who described some fascinating methods for drug targeting and cell penetration. Cell-penetrating peptides were covalently linked to drugs to facilitate their cellular penetration. This can lead to non-specific effects and so photo-cleavable masks were attached to the peptides which could be cleaved at a specific location generating the active entity. A second strategy used polyanions to prevent cell penetration until it was required; permeation was then “switched-on” by administering a polycationic counterpart.

After the break Dr Gordon Saxty from Astex described further work on the use of fragment based approaches to lead generation. This included a detailed demonstration of how the availability of many protein-ligand crystal structures and other biophysical methods have been used to build in specific intermolecular interactions and optimise ligand efficient leads into equally efficient preclinical and clinical candidates.

The final fascinating presentation of the morning was from Professor Abraham Nudelman (Bar-Ilan University), where he described exuberantly how the use of co-drugs and pro-drugs has led to therapeutic agents which have reached the later stages of clinical development. This included linking an anti-schizophrenic and an anti-depressant agent with gamma-aminobutyric acid to produce promising agents for schizophrenia and neuropathic pain. Also, interesting anti-tumour activity was demonstrated from the combination of an anti-epileptic/HDAC inhibitor with an antiviral.

After lunch the organisers were delighted to welcome HE Matthew Gould, the British Ambassador to Israel, who shared some of his thoughts on the importance of collaboration in science and his ideas on strengthening interactions between our scientific communities.

Session 2 (22 April)

Following the address of the British Ambassador, which embodied the spirit of the conference and the hopes of the organizing committee, the scientific programme of the first afternoon was launched by Micha Fridman, who described the work of his research group at Tel Aviv University on synthetic strategies to overcome resistance to aminoglycoside antibiotics. Through a series of extremely challenging synthetic targets Dr Fridman demonstrated the feasibility of designing inhibitors for aminoglycoside modifying enzymes with potent antibacterial activity.

Contract research organizations have become a sizable part of the chemistry-focussed SME sector in the UK and the second speaker, Trevor Perrior from Domainex, highlighted the quality and impact of collaborative ventures with expert CROs. The lecture described Domainex's work with Ark Therapeutics on the development of the first small-molecule inhibitors of the protein-protein interaction between neuropilin-1 receptor and its endogenous ligands. The intricacy of the design and the understanding of the target were abundantly evident as the story unfolded.

The conference was marked as much for the fascinating mix of academic and industrial research as it was for the bi-national programme, and the final presentation of the day drew again from the depth of academic medicinal chemistry research in Israel. Avital Shurki, from the Hebrew University of Jerusalem, presented work from her group that unveiled some of the secrets of copper-chaperones. Regulation of copper ions has been implicated in the aetiology of a number of diseases, and Dr Shurki described, with notable clarity and beauty, how theoretical chemistry has contributed to the understanding of nature's response to binding Cu (I).

Session 3 (23 April)

The morning session of the second day of the meeting began with a presentation from Dr Chris Newton, Managing Director of BioFocus, who described a novel approach to the treatment of Huntingdon's Disease (HD) prosecuted in partnership with the CHDI Foundation. Although HD is a genetic, neurodegenerative disorder for which there is current cure or even palliative treatment, recent studies have suggested the involvement of the HDAC gene in this disease. The identification of a prototype, selective HDAC Class IIa inhibitor using a HTS-based approach was described as well as some early pre-clinical data in rodent models

At the other end of the drug discovery timeline, Prof. Irun Cohen then presented an overview of his research showing that the HSP peptide fragment, DiaPep277, arrests the destruction of beta cells in Type 1 diabetes. Despite the fact that DiaPep277 does not contain unnatural amino acids or amino acid surrogates, positive data on disease progression has been obtained with this agent in phase III clinical trials

The morning continued with a talk from Dr Darren McKerrecher of AstraZeneca who outlined the search for the next generation of Glucokinase Activators for the potential treatment of Type 2 diabetes. Using property-based design, this work led to the identification of the prototype development candidate AZD1092 which unfortunately was associated with testicular toxicity liabilities. However, using rational analysis of the physical and structural parameters responsible for solubility, permeability and hERG activity, a phase II clinical candidate AZD1656 was identified

The final talk of the morning session was delivered by local speaker Dr Avihai Yacovan of Dynamix Pharmaceuticals, who presented his work on activators of the tumour-specific M2 isoform of Pyruvate Kinase (PKM2). PKM2 modulates the metabolism of cancer cells by switching between a low activity monomeric form and a high activity tetrameric form; stabilisation of the latter may normalise cancer cell metabolism. Using their proprietary DynamixFit™ structure-based technology, he identified novel series of allosteric PKM2 activators, one of which was optimised to a potent compound which was selective against other PK isoforms.

Over lunch, there was another opportunity to look at the 40 or so posters, which covered a whole range of therapeutic targets and approaches.

Session 4 (23 April)

The afternoon session commenced with the announcement of the two recipients of the 2012 Chorev awards for innovative research in drug discovery. Ezequiel Wexselblatt (School of Pharmacy, Hebrew University) and Anat Levit (Faculty of Agriculture, Hebrew University) were chosen this year and presented a short talk that summarized their PhD achievements. Anat described her work on understanding and predicting GPCR-mediated signalling. Her insights have led to the discovery of potential GPCR antagonists for a variety of modalities as well as using FDA approved drugs for treating novel indications.

Ezequiel then described the design and synthesis of novel ppGpp analogues that were shown to inhibit bacterial growth by a novel mechanism of action, namely, inhibiting the RelA protein that triggers the stringent response. One of the most promising analogues was then shown to inhibit sporulation in Gram positive bacteria (*Bacillus Subtilis*) as well in the pathogenic bacterium *Bacillus anthracis* that causes the acute Anthrax disease.

Two poster prizes were also announced in this session: Lital Zilbershtein from Bar-Ilan University (Prof. B. Fischer) and Michal Shavit from the Technion (Prof. T. Baasov).

The next speaker was Dr Ged Giblin (Convergence Pharmaceuticals, UK) that described efforts in drug design of a novel orally given and highly specific Ca blocker for treating neuropathic pain. As such a drug is given today via infusion directly to the spinal cord, there is a great need to develop an orally available drug for treating chronic pain with minimal side effects. One such candidate has reached clinical trials (Phase I) and seems very promising.

The final speaker of the conference was Prof. Timor Baasov from the Technion (Haifa, Israel). In his talk, Timor detailed the efforts in his group to design and synthesize novel aminoglycosides that cause translational read-through of in-frame stop mutations by binding to the A-site of the ribosome. The newer generation of aminoglycoside derivatives was shown to be more specific to human vs. bacterial ribosomal RNA, a phenomenon which might shed light on the reduced cytotoxicity of these analogues.