Editor's choice

Day 1: Protein Kinase Targets, Boston, 23 June 2008

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The first day of the Cambridge Healthtech Institute's 6th Protein Kinase Targets conference was host to presentations focusing on non-ATP competitive inhibitors, cell cycle kinase inhibitors and the targeting of solid tumors.

Morning session

The first morning session was chaired by Dr Jeffery Ohren (Pfizer, USA) and saw some excellent presentations from leading biochemists and medicinal chemists.

The non-ATP competitive session was kicked off by Dr Doriano Fabbro (Novartis, Switzerland) with a presentation on what had been learned during the development of imatinib (Gleevec, Novartis) and how this affected the follow up development of allosteric inhibitors. Imatinib (Gleevec, Novartis) and nilotinib (Tasigna, Novartis) target the ATP binding pocket of ABL, but also fill space in the DGF-out region of the kinase regulatory site, beyond the gatekeeper residue. This approach allows exquisite target selectivity but is susceptible to drug resistant mutations. Discussion of non-ATP competitive targeting focused on the myristylate pocket of ABL. Several compounds designed to bind the myristylate pocket were presented with particular focus on the use of NMR to determine protein conformations in solution. Finally, it was noted that other kinases, such as SRC, contain similar myristylate pockets and that these could be exploited by non-ATP competitive inhibitors. However, the primary protein sequence alone is unable to predict the existence of a myristylate pocket; at present this feature can only be determined by X-ray crystallography.

Dr Jeffrey Ohren (Pfizer, USA) discussed CI1040 (Pfizer), a non-ATP competitive MP2K1 (MEK1) and MP2K2 (MEK2) inhibitor. Initial *in vivo* experimentation demonstrated reduced tumor size in mouse models of cancer treated with this compound. However, early clinical Phase I/II studies were disappointing, with an overall low outcome. In hindsight, it was noted that only patients positive for mutations causing over-activation of the MEK pathway should have been selected for these trials. The take-home message was that the use of validated biomarkers and genetic screening for over-activation of the target pathways will be essential to improve the outcome of future clinical trials.

Dr Marcie Glicksman (Brigham and Women's Hospital, USA) introduced the Laboratory for Drug Discovery in Neurodegenerative Diseases (LDDN) at the Harvard NeuroDiscovery Center and spoke of its mission to pursue diseases less attractive to mainstream pharmaceuticals. Drug discovery programs currently underway include the targeting of LRRK2, EPHB3 and STEP, as well as other non-neurodegenerative targets, such as HASP (haspin). The presentation went on to cover the current development of CDK5 inhibitors. CDK5 is overexpressed in the brains of Alzheimer's disease patients and is thought to be responsible for the phosphorylation of TAU. It was revealed that a large library screen had resulted in several hit compounds but that these were all ATP competitive.

Afternoon session

The afternoon session was chaired by Dr Jurgen Mol (Nerviano Medical Sciences, Italy) and focused on chemical lead optimization of compounds for the treatment of solid tumors. The session started with the first of the selected poster presentations.

Dr Michael Kaufman (Deciphera Pharmaceuticals, USA) presented data for two pre-clinical compounds designed to target the switch pocket of ABL. Both compounds potently inhibited wild-type and mutant forms of BCR-ABL, including the drug resistant T315I mutant form. The short presentation went on to detail the mouse models (BaF3 cell injection and retroviral transduced bone marrow transplant chronic myelogenous leukemia) that were used to screen candidate compounds.

Dr Xi-De Wang (Bristol-Myers Squibb, USA) spoke of the multi-target kinase inhibitor dasatinib (Sprycel, Bristol-Myers Squibb) and its efficacy in solid tumors from a biomarker perspective. Dr Wang also specified predictive biomarker genes that can be used to identify prostate cancer patients with a high risk of developing dasatinib resistance.

The afternoon session was rounded off with two excellent presentations from medicinal chemists. Dr Johan Oslob (Sunesis Pharmaceuticals, USA) described the lead optimization process and selection of SNS314, a novel Aurora kinase inhibitor about to enter the clinic. This was followed by Dr Rob Bradbury (AstraZeneca, UK) who gave a detailed account of the screening, selection and optimization process of a novel ERBB2 inhibitor.