

Editor's choice

Day 3: Protein Kinase Targets, Boston, 25 June 2008

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The third and final day of the Cambridge Healthtech Institute's 6th [Protein Kinase Targets](#) conference was chaired in the morning by Dr John Doukas ([TargetGen](#), USA) and was host to round table discussions followed by presentations focusing on therapeutic kinase inhibition beyond the scope of cancer

Morning session

The roundtable session comprised five tables, each with a different topic for discussion that delegates were free to participate in. See below for a summary of the topics discussed and main conclusions reached by each table.

Table 1: Multi-targeted versus selective kinase inhibitors, chaired by Dr Dorano Fabbro ([Novartis](#), Switzerland). It was noted that for cancer therapy, multi-target selectivity might be of benefit, but outside of cancer therapy, selectivity will be of greater importance to retain a satisfactory therapeutic window. However, multi-targeted approaches may also be viewed in terms of targeting wild-type and mutant kinases with a single compound.

Table 2: Drug-kinase binding kinetics, chaired by Doris Hafenbradl ([Proteros Biostructures](#), Germany). The discussion started with opinions of the current methods used. Surface plasmon resonance (SPR) and isothermal titration calorimetry (ITC) are currently the techniques of choice to determine accurate kinetic profiles but are not yet suitable for high throughput screening. The question of using specific kinase conformations (e.g. active or inactive) to screen for potential hit compounds was addressed. It was noted that early hit compounds that only target one specific conformation of a kinase would almost always eventually bind all conformations after greater potency is built in. Discussion over what is the best residency time for a compound concluded that this could not be specified, as it would depend on many variables relating to the target compound. The majority of delegates at the table agreed that testing compound residency is of great importance and such kinetic analyses will be included in future screening programs

Table 3: Screening compound collections for kinase inhibitors - focused, subset or HTS, chaired by Rob Bradbury ([AstraZeneca](#), USA). Topics discussed included the screening of fragment libraries and the screening of subsets. It was noted that by only screening subsets, the potential for novel hit compound detection would be limited. The main conclusion was that for any screening approach, informative functional biological assays are essential.

Table 4: Maximizing the therapeutic window, chaired by John Doukas (TargetGen, USA). The main theme of this discussion focused on the importance of the therapeutic window as the ultimate goal of any drug discovery program and not just drug-compound affinity. The discussion went on to cover how different delivery methods (systemic versus compartmentalized) could help increase the therapeutic and safety windows.

Table 5: Potential roles for companion diagnostics in clinical development, chaired by

Stephen Burley ([SGX Pharmaceuticals](#), USA). The main driving force for personalized medicine will come from patients and medics, but more importantly third parties such as insurance companies. Even now, certain health insurance policies limit payout if prescribed therapeutics do not provide an adequate response. This will ultimately force pharmaceutical companies to tighten prescription indications based on the analysis of patient samples for pre-specified drug efficacy-predictive biomarkers

The first presentation of the day was given by Dr Elliot Drobetsky ([Maisonneuve-Rosemont Hospital](#), Canada). After a review of current thinking on global genomic nucleotide excision repair (GG-NER), Dr Drobetsky went on to describe his research in this area relating to the role of ATM in DNA repair during cell cycle S-phase. Previous research in this field has always ignored S-phase cells but Dr Drobetsky was able to show that GG-NER during S-phase is highly dependent on ATM and not MAPK signaling, as was previously thought [135867]. Furthermore, several cancer cell lines, but not wild-type cells, were shown to be completely defective for GG-NER activity during S-phase.

Dr John Doukas gave the final invited presentation of the morning's session and covered the use of kinase inhibitors to treat inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD). TG100115 (TargetGen) is a PI3K inhibitor that selectively targets PK3CD (PI3K delta) and PK3CG (PI3K gamma) isoforms. The compound has completed Phase I safety trials and will soon enter Phase II testing. Pre-clinical data was also presented for the use of TG100115 in mouse models of asthma and COPD. In both diseases, the compound showed remarkable results. TG101348 (TargetGen) a [JAK2](#) inhibitor was also touched on briefly; this compound is currently in a Phase I dose escalation trial for patients with myelofibrosis [2]. [135868].

Afternoon session

The afternoon session was chaired by Gregg Siegal ([ZoBio](#), The Netherlands) and featured presentations focusing on structure-based drug design (SBDD).

Dr Stefan Knapp ([Oxford University](#), UK) gave an interesting overview of the Structural Genomics Consortium ([SGC](#)) and its continuing mission to publish human kinase crystal structures. The consortium has deposited over 600 human structures in the protein data bank (PDB) between 2004 and 2007. Dr Knapp went on to describe the structure-based drug design efforts that are underway at SGC for inhibitors of FES (C-Fes), a receptor tyrosine kinase. Other drug discovery programs were briefly mentioned, including the targeting of HASP (haspin) and isoform-selective PIM1 and PIM2 inhibitors.

The next two talks discussed the difficulties of crystallizing PLK1 (Polo-like kinase-1) and how these were overcome by two independent methods. It was noted that PLK1 can be purified and concentrated to 18 mg/ml and would seem like an ideal protein for crystallization. However, it has taken many years to discover the conditions in which the protein will crystallize. Dr Roman Hillig ([Bayer](#), Germany) was able to solve the PLK1 structure by co-crystallizing the protein in the presence of an antibody-like ankyrin repeat protein (DARPin). This artificial binding partner stabilized a region of the PLK1 protein that contained many large 'floppy' residues. These residues were thought to be the reason why no pure PLK1 crystals could be grown. Dr Michael Kothe's platform used by Dr Kothe also helped, in that the system was contaminated with a very low concentration of zinc ions, the addition of which was essential for PLK1 crystals to form. Both Bayer and Pfizer have programs underway utilizing a structure-based drug design approach to developing inhibitors of PLK1.

Dr Michael Harte ([Cytopia](#), Australia) reported the initial results of Cytopia's CSF1R (FMS) drug discovery program. Over 100 lead compounds have recently been published in a worldwide (PCT) patent [130879]. Dr Harte noted that the structure-activity relationship studies for these compounds will also be published soon. Other developments from Cytopia include a potent JAK2 inhibitor for which an investigational new drug application will be filed soon

The very last talk of the conference was given by Dr Gregg Siegal and focused on his company's unique approach to fragment-based screening. ZoBio has developed a method they call target immobilized nuclear spectroscopy (TINS). This method can rapidly screen the protein-binding properties of fragment compounds. The protein of interest is immobilized on sepharose beads that are then exposed to buffer containing the fragments. Nuclear resonance is used to measure the presence of the fragments in solution; when fragments bind the protein and enter the solid phase, this change can be detected. ZoBio functions primarily as a contact screening company but also has it's own in-house drug discovery program for receptor tyrosine kinase inhibitors.