

## Editor's choice

### Day 2: Protein Kinase Targets, Boston, 24 June 2008

25-Jun-08

The second day of the Cambridge Healthtech Institute's 6<sup>th</sup> [Protein Kinase Targets](#) conference was chaired in the morning by Dr Michael Yaffe ([Massachusetts Institute of Technology](#), USA) and kicked off with the keynote presentation by Dr Robert Copeland ([GlaxoSmithKline](#), USA) followed by a series of talks focusing on screening and lead optimization.

#### Morning session

Dr Robert Copeland started the session with a brief overview of GSK's strategic vision towards molecularly targeted cancer drug discovery. Dr Copeland noted that the days of compounds with indiscriminate cytotoxicity are over and that successful drug discovery programs must produce compounds that selectively target well-validated proteins with a full understanding of the mechanism involved. The implications of this view for GSK has led to time being invested to understand the biochemistry of target proteins and the signaling pathways in which they function. While this approach increases time at the early stages, it reduces compound attrition post-candidate selection. The presentation went on to cover the development of GSK690693 (GSK), a first generation pan-AKT ([AKT1](#), [AKT2](#), [AKT3](#)) inhibitor now in Phase I trials for lymphoma and solid tumors. An interesting point was raised in the discussion: one of the key features of GSK690693 is the long residence time that enables the compound to remain active in tissues even after complete clearance from circulation; Dr Copeland stated that compound residence time was one of the most important parameters for selecting GSK690693.

Dr Stephen Burley ([SGX Pharmaceuticals](#), USA) spoke about the SRC family receptor tyrosine kinase [MET](#) and SGX's fragment-based approach to drug discovery. The latest MET inhibitor, SGX126 (SGX), was reported to address the problems that caused the previous MET inhibitor SGX523 (SGX) to show dose-limiting toxicity. Dr Burley went on to describe SGX393 (SGX), an effective inhibitor of wild-type and all four major drug-resistant mutant forms of BCR-ABL, including T315I. An investigational new drug application will be filed this week with the FDA for the use of SGX393 in CML-relapse patients with resistance to imatinib (Gleevec, [Novartis](#)), dasatinib (Sprycel, [Bristol-Myers Squibb](#)) and nilotinib (Tasigna, [Novartis](#)).

Dr Michael Yaffe (Massachusetts Institute of Technology, USA) gave an excellent summary of his finding for the role of [MAPK2](#) (MAPKAP-K2) in response to DNA damage. He first summarised how p38 is thought to be activated by DNA damage agents [135387] and went on to describe how disruption of MAPK2 was able to greatly sensitize p53 null cells to cytotoxic drugs, such as cisplatin and doxorubicin, by eliminating cell cycle checkpoints. The take home message was that by targeting MAPK2, lower chemotherapy doses could be used in patients with p53-null tumors. Dr Yaffe stated that while both [CHK1](#) and MAPK2 target the checkpoint phosphatase CDC25 at the same site, MAPK2 is a safer target, since CHK1 heterozygous mice are highly cancer prone but MAPK2 knockout mice are relatively normal.

Dr Ming-Q Zhang ([Biotica](#), USA) described a fascinating synthetic biology approach that has been taken by Biotica to generate analogues of the naturally occurring [FRAP](#) (mTOR) inhibitor, rapamycin. The method comprises a series of genetically engineered bacteria with alterations to the genes responsible for rapamycin biosynthesis. Over 50 derivatives have been prepared and have been used for a systematic structure-activity relationship study, the first ever to be performed for analogues of rapamycin.

### Afternoon session

The afternoon session was chaired by Dr Robert Liskamp ([Utrecht University](#), Netherlands) and continued the morning's focus on compound screening and lead optimization.

Dr Raymond Matting ([Wayne State University](#), USA) gave an interesting presentation about altered drug sensitivity observed for cells growing in three-dimensional tissue culture systems in comparison to traditional two-dimensional tissue culture. Mutant Ras-transformed breast cancer cells showed increased sensitivity to MEK inhibition by PD184352 (C11040, [Pfizer](#)), while normal wild-type MCF10A (non-cancerous breast tissue) cells showed increased resistance to PD184352 when grown in 3D culture.

Dr Robert Liskamp discussed a novel assay format by PamChip and how this technology has enabled his research group to identify several peptide pseudosubstrates for PKC family kinases. Dr Liskamp went on to describe how a PKC pseudosubstrate had been linked to generic ATP competitive inhibitors to generate a [KPCT](#) (PKC-theta) isoform-specific inhibitor. It was acknowledged that this kind of large non-drug-like compound would probably not be useful for medicinal purposes but could be used in the laboratory setting to help dissect kinase pathways by inhibiting specific kinase isoforms.

The concept of increased residence time touched on at the start of the day was further extolled by Dr Doris Hafenbradl ([Proteros Biostructures](#), Germany). After a review of the binding data for current marketed kinase inhibitors, Dr Hafenbradl noted that drug-target residence time should be an integral part of every structure-activity relationship study. Dr Hafenbradl went on to describe the probe-based reporter assay system that Proteros has developed and their fragment-based screening program to identify novel candidate kinase inhibitors.

The day was rounded off by Michael Eck ([Harvard Medical School](#), USA) who spoke about the [EGFR](#) mutations that alter the response to the ATP competitive inhibitor gefitinib (Iressa, [AstraZeneca](#)). L858R causes increased EGFR sensitivity to gefitinib due to moderately increased drug binding affinity and greatly reduced ATP binding affinity. This combined effect opens a therapeutic window whereby gefitinib is able to inhibit mutant EGFR, present in tumor cells, many times more effectively than wild-type EGFR or other wild-type kinases. However, a second mutation, T790M, found together with L858R, causes resistance to gefitinib. It was thought that this gatekeeper residue mutation was preventing gefitinib binding, but this was not the case. The T790M mutation, in fact, does not affect gefitinib binding affinity but instead restores EGFR's normal ATP binding affinity, thus closing the therapeutic window. The take home message was the importance of using physiological concentrations of ATP (1mM) in screening assays.