Targeting Epigenetics for Cancer Therapy: Recent Breakthroughs to Accelerate Drug Discovery

**Location:** NDM Research Building, University of Oxford, Old Road Campus, Headington, OX3 7FZ

**Date:** Wednesday 17th September 2014

**Time:** 9:00 AM - 5:00 PM

**Chairman:** Steve Rees, VP Screening Sciences and Sample Management AstraZeneca, UK

### Agenda

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<td>9:00 – 9:30 AM</td>
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<td>9:30 – 9:40 AM</td>
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| 9:40 – 10:20 AM  | Stefan Knapp, Oxford University, Nuffield Department of Clinical Medicine, Structural Genomics Consortium (SGC) and Target Discovery Institute (TDI)  
**Towards a comprehensive chemical probe set targeting the human bromodomain family**  
Bromodomains (BRDs) are evolutionary conserved protein interaction modules that specifically recognize ε-N-lysine acetylation motifs, a key event in the reading process of epigenetic marks. The human proteome encodes 61 of these highly diverse domains present in 46 mainly nuclear proteins. During the recent years we have established a family wide platform of reagents, assays and crystal structures enabling the rational design and comprehensive selectivity screening of bromodomain inhibitors. Using this platform we and our collaborators have developed highly selective chemical tool compounds for most bromodomain subfamilies. In this talk I will present recent data on the developed tool compounds including their in vitro characterization and phenotypic responses observed in cellular model systems. |
| 10:20 – 11:00 AM | Katherine Jones, Investigator, Epinova DPU, GlaxoSmithKline          
**The discovery of I-CBP112, a specific inhibitor of the CBP/p300 bromodomain, that suppresses self-renewal in leukaemia**  
The closely related histone acetyl-transferases CBP (CREB binding protein) and p300 are key regulators of gene transcription. Both proteins have a number of domains in common, including a bromodomain that binds acetylated lysine residues. Deregulation of CBP/p300 has been reported as a causative factor in a large variety of human diseases, including leukaemia, suggesting that specific targeting of functional domains in CBP/p300 may lead to new therapeutic strategies. A collaborative medicinal chemistry programme between GlaxoSmithKline and the Structural Genomics Consortium, University of Oxford, will be described which developed the specific and potent acetyl-lysine competitive inhibitor I-CBP112. Further investigation using I-CBP112, by collaborators at the University of Cambridge and University of Basel, will be discussed. These studies suggest that using I-CBP112 to target the CBP/p300 bromodomain impairs self-renewal in leukaemia. |
| 11:00 – 11:30 PM | Coffee                                                                |
**11:30 – 12:10 PM**  
**Dr. Kilian Huber, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences.**

**Disruption of nucleotide pool homeostasis as a new and selective way to target cancer**

Activated Ras GTPase signalling is a critical driver of oncogenic transformation and malignant disease. About 20-30% of human cancers contain mutations in one Ras isoform which is accompanied by poor prognosis and low overall survival, highlighting the urgent need to develop new targeted approaches. Phenotypic screens have been used to identify active small molecules, however, elucidating the molecular mechanism of action of these compounds often provides a substantial challenge. Using a chemoproteomic approach we have recently identified the human mutT homologue MTH1, a nucleotide pool sanitizing enzyme, as the mechanistic target of compounds that are active against cells transformed by mutant Ras. Consistent with expectations, transient or stable knockdown of MTH1 abolished colony formation of KRAS tumour cell lines whereas MTH1 overexpression mitigated sensitivity toward the inhibitors. Screening for more potent and drug-like compounds we identified the dual ALK/c-Met kinase inhibitor crizotinib as a selective, first-in-class nanomolar inhibitor of MTH1. We solved the co-crystal structure of MTH1 and crizotinib, providing a basis for inhibitor development in this new target class. Due to suppression of MTH1 activity, the inhibitors induced an increase of DNA single strand breaks, activated DNA repair in KRAS positive human colon carcinoma cells, and effectively suppressed tumour growth in colon carcinoma animal models. Our results suggest small molecule inhibitors of MTH1 are a promising novel class of drugs to treat cancer.

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**12:10 – 12:50 Andrew Baxter, Ph.D., MBA, Director BioSeek® Services Europe**

**Profiling compounds in primary human cell BioMAP® systems for drug discovery and therapeutic development in inflammation and cancer.**

The emergence of novel targets such as epigenetic modulators shows considerable promise but remain poorly understood from a clinical perspective. The ability to test new agents, alone or in combination, in predictive human models would support the identification, optimization and development of compounds for the clinic. Human primary cell-based BioMAP Systems are designed to recapitulate the complex signals and phenotypic responses of diseased tissues and thus provide broad biological coverage of inflammation, wound healing, tissue remodeling, vascular and epithelial biology. We have recently expanded the platform to include oncology systems employing co-cultures of primary human fibroblasts or endothelial cells with PBMCs and a cancer cell line. Profiling in BioMAP enables better understanding of the human pharmacological and toxicological properties of compounds, including on- and offtarget effects, dose responses, discrimination of closely related compounds and indication selection. This proven predictive approach provides an unsupervised, structure-independent measure of overall phenotypic impact of compounds under disease-like conditions and identifies clinically relevant activities across a broad protein biomarker panel. Profiling compounds for new targets, such as BET family epigenetic readers, revealed target-specific phenotypic signatures that confirm mechanism of action. In addition BET inhibitor activities in the Oncology systems showed efficacy related anti-inflammatory effects, matrix-remodeling activities and reduced expression of a tumor-restricted marker. BioMAP Systems thus provide a highly useful platform to (1) identify anti-inflammatory and anti-cancer effects of various target inhibitors and (2) identify different phenotypic outcomes of these agents that influence cancer progression and disease resolution. Together these BioMAP data will support the discovery and development of safer and more effective therapies in cancer and other diseases.

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**12:50 – 13:50 PM**  
**Lunch & Networking**
### 13:50 – 14:30 PM

**Niall Igoe, UCL School of Pharmacy, London, UK**

**Epigenetic Drug Discovery: Small Molecule Inhibitors of Class IV Bromodomains**

The human BRPF (bromodomain and PHD finger containing) family of histone acyl-lysine reader proteins, BRPF-1, -2, -3, are important regulators of epigenetic signalling. These proteins recognise specific acyl lysine residues on histones, leading to changes in chromatin structure, multi-protein complex formation and transcriptional regulation. This drug target is relatively early wrt target validation although there is an emerging understanding of its potential role in acute myeloid leukemia (AML). The activation of the BRPF1/HOX pathway through MOZ histone acyl transfer is critical for MOZ-TIF2 to induce AML. In collaboration with the Structural Genomics Consortium (University of Oxford, UK), we have identified potent and selective small molecule inhibitors of BRPF1 through optimization of a fragment derived screening hit. Ultimately, these inhibitors may represent potential starting points for a drug discovery program as a new approach to the treatment of AML and possibly other cancers.

### 14:30 – 15:10 PM

**Dr. Davide Gianni, Research Laboratory Head, Boehringer Ingelheim RCV GmbH & Co KG**

**Targeting bromodomain containing proteins beyond the BET family**

Bromodomains (BRDs) are a diverse family of evolutionarily conserved protein-interaction modules that recognize acetylated lysines. BRD4, a member of the Bromodomain and Extra Terminal domain family (BET), is an important and druggable target in cancer and inflammatory diseases. Bromodomains are also found with components of multiprotein complexes such as the SWI/SNF complex, a chromatin-remodeling complex that performs fundamental roles in gene regulation, cell lineage specification and development. Nearly 20% of human cancers contain mutations that inactivate SWI/SNF subunits, suggesting that appropriate control of this complex is required to prevent tumour formation. Recent studies show that SWI/SNF-mutant cancers depend on residual SWI/SNF complexes for their aberrant growth, thus revealing synthetic lethal interactions among bromodomain-containing subunits of this complex that could be exploited for therapeutic purposes.

### 15:10 – 15:40 PM

**Coffee**

### 15:40 – 16:20 PM

**Dr. Joëlle Rüegg, Swedish Toxicology Science Research Center (Swetox)/Karolinska Institutet, Stockholm, Sweden**

**Mechanisms underlying epigenetic effects of endocrine disruptive compounds**

**Endocrine disruptive compounds (EDC) are substances interfering with our hormone systems.**

Exposure to EDCs during critical windows in development has been associated with a number of diseases, such as infertility, metabolic disorders, and some forms of cancer. EDCs are able to induce epigenetic changes, however, the underlying mechanisms are unknown. By investigating the interaction between regulators of DNA methylation and EDC targets, such as the estrogen receptors, we aim to unravel the molecular events underlying epigenetic effects of EDCs, and thus to better understand and assess the risks posed by these compounds.
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| 16:20 – 17:00 PM | **Karen Roberts, Ph.D., AstraZeneca**<br>The Use of BROMOscan® and BioMap® to Identify and Help Annotate a Potent TAF1(2) Inhibitor
AstraZeneca have a library of compounds targeted towards bromodomains. As this is an emerging target class, 200 compounds from this library were profiled against the full BROMOscan® panel at DiscoveRx to look for potential probe molecules for established or novel targets. Profiling data highlighted a number of compounds that showed potency and selectivity against other bromodomains, and this presentation focuses on the identification and annotation of one of these compounds, active against TAF1(2). |
| 17:00 PM       | **Closing Remarks**                                         |