Speaker Abstracts

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Integrating complex genomic datasets and high-throughput cancer cell lines

Human cancer genome sequencing projects currently underway will soon provide a systematic, comprehensive, and unbiased catalogue of the genes and transcripts that are altered in human cancer. Early data from these worldwide efforts are already identifying high-frequency genetic alterations in specific cancer types that are potential therapeutic targets. There is a compelling body of evidence, both clinical and scientific, that for an increasing number of drugs in the clinic the likelihood of a patient's cancer responding to treatment is strongly influenced by alterations in the cancer genome. We have established a high-throughput screen of >1000 human cancer cell lines against 400 cancer compounds (either as single agents or as 2-drug combinations) and have developed a computational platform to identify statistically robust correlates of drug response with genomic/transcriptomic data. This collection of cell line represents the spectrum of common and rare types of adult and childhood cancers of epithelial, mesenchymal and haematopoietic origin. We have used this large panel of cell lines in order to better capture the high degree of genomic diversity in cancer and to identify rare mutant subsets with altered drug sensitivity. All cell lines have been subjected to systematic genomic and transcriptional profiling, including sequencing of the full coding exons of 21,416 protein-coding genes and 1,664 microRNA, genome-wide analysis of copy number gain and loss, and expression profiling of 14,500 genes. We have selected a panel of 400 agents that covers all FDA-approved cancer drugs, chemotherapeutics, pre-clinical and early phase drugs as well as tool compounds specifically targeting pathways implicated in cancer biology. Effects on cell viability are measured and a curve-fitting algorithm is applied to the raw intensity values to derive a multi-parameter description of drug response, including the half maximal inhibitory concentration (IC50) and the slope of the dose response curve. We have confirmed that this screen is able to detect previously identified gene-drug interactions in an entirely unbiased manner, and have already begun to identify entirely novel genomic markers of drug response. The drug response data is analysed using both a MANOVA of IC50 values/slope or curve as well as a logic model approach developed in collaboration with The Netherlands Cancer Institute. In addition, we have begun to screen the cell line panel against approx. 600 2-drug combinations. We propose to build computational models to explain perturbation phenotypes as logic combinations of mutations, copy number alterations and gene expression.

This analysis is capable of identifying statistically significant drug-sensitizing mutations as well as capturing combinatorial gene interactions that confer resistance to compounds in the screen and may indicate potential 2-drug combinations within specific genetic contexts. Single drug or combinatorial strategies identified from this screen will be validated using 3D cancer cell models, early passage primary tumour cultures as well as genetically engineered mouse models in specific cancer types.

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Reconstructing Cellular Networks from Chromatin State

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Mutations and epimutations that drive malignant transformation

Distinguishing the epimutations that drive tumorigenesis and malignant progression from the much larger span of alterations that are functionally inconsequential is a major challenge. While the characteristics of true driver epimutations are not fully defined, a major group will show evidence of natural and/or therapy-induced selection in vivo, and will exhibit quantifiable effects on the target gene transcript and downstream gene networks. Low-grade gliomas (LGG) may remain indolent for more than a decade after initial surgery, or unpredictably, may undergo malignant progression to anaplastic astrocytoma (AA) or Glioblastoma (GBM). Elucidating the genetic and epigenetic drivers of malignant progression is a critical step in preventing progression and positively impacting overall survival for LGG patients. On the epigenome level, despite the successful translation of MGMT methylation as a clinical biomarker of temozolomide response in GBM, the clinical relevance of this epigenotype in LGG is uncertain. There are no widely accepted guidelines for whether or not to use temozolomide, or when to use it, in treating low grade glioma patients. I plan to discuss how such an epigenotype may drive tumor progression through a genetic mechanism, depending on whether or not chemotherapy is administered. I will also discuss insights gained from the integration of these sequencing based genomic and epigenomic profiles with clinical histories.

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Heterochromatin assembly and epigenetic genome control by non-coding and coding RNAs

Heterochromatin assembly involving posttranslational modifications of histones is critical for various chromosomal processes including the regulation of gene expression and the maintenance of genomic integrity. Defective heterochromatin formation has been linked to cancer. Our previous work has shown that non-coding RNAs and the RNAi machinery, involved in the processing of non-coding RNAs, play prominent roles in the assembly of heterochromatin structures. Indeed, the loss of factors involved in RNAi such as Argonaute, Dicer and RNA-dependent RNA polymerase cause severe defects in centromeric heterochromatin formation, leading to missegregation of chromosomes during cell division. An Argonaute-containing RNAi effector complex named RITS has been identified that facilitates the loading of a conserved histone methyltransferase Clr4/Suv39h, which is essential for heterochromatin assembly. We have recently discovered an unexpected role for heterochromatin factors in the RNA quality control. Heterochromatin factors localize broadly across the genome and collaborate with RNAi machinery to suppress potentially deleterious RNAs, the uncontrolled accumulation of which can cause DNA damage and modify epigenetic genomic profiles. I will present our recent findings showing that non-coding RNAs and heterochromatin play important roles in dynamic regulation of genomes, which has important implications for human health and disease.

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BRG1 versus Polycomb - a new battle site

BRG1, part of the SWI/SNF complex, and the Polycomb Repressive Complex 2 (PRC2) are epigenetic regulators that are typically tumor suppressive and oncogenic, respectively. These activities have been attributed to their effects on cell cycle, survival, differentiation and stemness. We have found that these proteins regulate IFNgamma signaling, an essential component of immune surveillance. In view of the high frequency of BRG1 and PRC2 defects in human tumors our work suggests a general mechanism by which tumors evade immune surveillance, and a novel function for these chromatin modifiers in cancer. Overcoming PRC2 mediated silencing of IFNgamma targets offers a new strategy to reactivate immune surveillance in human cancer.

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Novel macromolecular and small molecule inhibitors of DNMT1

Dnmt1 is the major maintenance DNA methyltransferase in vertebrates. Dnmt1 activation is promoted by multiple oncogenic pathways and opposed by multiple tumor suppressor pathways. In turn, because Dnmt1 silences tumor suppressor genes, this molecule is a major epigenetic target in cancer. Moreover, genetic analysis in mouse indicates that Dnmt1 activity is limiting in models of hereditary and environmental carcinogenesis, suggesting that Dnmt1 may constitute a target in cancer prevention. Recently, we showed that deletion of the replication foci targeting sequence (RFTS) domain activates enzymatic activity by 640-fold and that the isolated RFTS domain behaves like a DNA-competitive inhibitor. This allowed us to correctly predict that the RFTS domain occludes the DNA active site (1). In addition, development of a restriction enzyme-coupled fluorigenic assay enabled a high throughput screen (HTS) that has facilitated inhibitor characterization and discovery. Our data indicate that the vast majority of compounds reported in the literature to inhibit Dnmt1 do not inhibit Dnmt1. However, we have confirmed one previously reported Dnmt1 inhibitor and discovered five new inhibitors by HTS. Each of these compounds has been confirmed as a direct binder by differential scanning fluorimetry with potencies as low as 100 nM. We will report our progress in establishing the specificity of these hits in biochemical and cellular assays.

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Enhancer-mediated gene dysregulation in cancer

Cancer is a disease involving gene expression aberrations that result in altered cell identity and function. Studies have largely focused on coding sequences and promoter regions, despite the fact that distal regulatory elements play a central role in controlling gene expression patterns. We utilized the method of ChIP-seq to map the genome-wide distribution of mono-methylated lysine 4 of histone H3 (H3K4me1), the epigenetic signature of gene enhancer elements, in primary cells derived from human colon tumors. We have identified thousands of loci that have either gained or lost the H3K4me1 signal in colon cancer compared to normal colon crypts. We call these regions variant enhancer loci, or VELs. Thousands of VELs are shared at high frequency across multiple colon cancer samples and thus provide an epigenomic signature of colon cancer. The VEL signature is highly predictive of the in vivo colon cancer transcriptome. Furthermore, VELs are significantly enriched in haplotype blocks containing colon cancer genetic risk variants, which validates the importance of these genomic regions in colon cancer pathogenesis. Our data demonstrate that reproducible changes in the epigenome at enhancer elements drive a unique transcriptional program to promote colon carcinogenesis.

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Remodeling of the chromatin landscape underlies endocrine response in breast cancer

The estrogen receptor alpha (ER) drives the growth of over two third of all breast cancers. Endocrine therapy, which antagonizes ER activation by estrogen, significantly improves survival rates. Unfortunately, 50% of ER-positive primary breast tumors ultimately are endocrine therapy-resistant (ETR). Here we demonstrate that changes to the chromatin landscape typified by epigenomic reprogramming underlie the transcriptional changes associated with ETR. Genomic region enrichment of annotation analysis identifies the Notch pathway within epigenomic maps of regulatory elements and transcripts specific to ETR breast cancer cells. In agreement, blocking Notch signaling using gamma-secretase inhibitors or through the depletion of PBX1, a target effector of Notch signaling, abrogates growth of these ETR cells. The epigenomic reprogramming also favors the expression of PBX1 and Notch signaling dependent genes that define a signature stratifying a priori breast cancer patients responding or not to endocrine therapy. Overall, this work demonstrates that epigenomic mapping can identify the Notch pathway as a new therapeutic target against ETR breast cancer.

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Regulation of the Cancer Epigenome by the KAP1-SETDB1 complex

Neoplastic transformation can be characterized by the inappropriate silencing of genes that confer a differentiated phenotype. One histone modification that has been associated with gene silencing is H3K9me3. We have used genome-wide ChIP-seq to demonstrate that the histone methyltransferase SETDB1 is associated with regions of the genome enriched for H3K9me3. It has been proposed that SETDB1 is recruited to specific genomic locations via interaction with the co-repressor KAP1, which is in turn recruited to the genome via interaction with zinc finger transcription factors that contain a KRAB domain. Using ChIP-seq, we show that ZNF274 co-localizes with SETDB1, KAP1, and H3K9me3. Our studies provide the first identification of a KRAB-ZNF that is involved in recruitment of KAP1 and SETDB1 to the human genome. Surprisingly, ZNF274 recruits the KAP1-SETDB1 complex to the 3' coding exons of certain genes but not to promoter regions. In addition, we have begun investigating inter-relationships between different types of epigenetic silencing mechanisms. We have shown that treatment of cells with a DNA methylation inhibitor can have major effects on the levels and localization patterns of H3K9me3. We conclude that inhibiting one silencing mechanism can have severe consequences on target selection mediated by other epigenetic regulatory complexes.

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Renewable, recombinant antibodies to histone marks

Antibodies to histone posttranslational marks are critical important in epigenetic research, but the inherent variations of polyclonal antibodies has been a major bottleneck in establishing reliable ChIP experiments.

We developed a quantitative and sensitive assay for antibody characterization. Our method closely mimics how antibodies are utilized in ChIP experiments, and it enables the determination of the dissociation constants (Kd), the fundamental parameter defining antibody properties. We found that the Kd values of commercial "ChIP grade" antibodies varied greatly ranging from sub nanomolar to the level that is too weak to be determined. There also was substantial lot-to-lot variability in affinity and specificity. These results confirmed previously reported problems with currently available antibodies.

To fundamentally solve this “antibody bottleneck”, we set out to develop recombinant antibodies to histone marks. Recombinant antibodies, generated from large libraries in vitro, are monoclonal, well defined, highly reproducible and scalable. Also they can be further improved by protein engineering. We have identified recombinant antibodies to several methylated histone tails. Among these, an antibody to the H3K9me3 mark had levels of affinity and specificity superior to currently available ones. These results strongly suggest the feasibility of systematically generating high-quality recombinant antibodies to many histone marks.

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Leukemogenic properties of histone modifying enzymes

The ability of AML1 and AML1-ETO to function as activators and/or repressors of gene expression likely depends on their post-translational modifications, which control their ability to interact with different protein partners. Many of these modifications are catalyzed by enzymes classically thought of as chromatin remodeling proteins, including lysine methyltransferases, arginine methyltransferases, and lysine acetyltransferases. We have recently identified specific sites within AML1-ETO that are modified by p300 and sites within AML1 that are modified by PRMT4. We have found that lysine and arginine methylation affects the binding partners of these proteins and their ability to regulate self renewal and myeloid differentiation. This data will be presented.

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Epigenetic basis and therapeutic targeting of hematologic malignancies

Epigenetic deregulation of gene expression through aberrant DNA methylation or histone modification plays an important role in the malignant transformation of hematopoietic cells. In particular, acute myeloid leukemias (AMLs) can be classified according to epigenetic signatures affecting DNA methylation or histone modifications affecting specific gene sets. Heterozygous somatic mutations in the loci encoding isocitrate dehydrogenase 1 and 2 (IDH1/2) occur in ~20% of AMLs and are accompanied by global DNA hypermethylation and hypermethylation and silencing of a number of specific gene promoters. IDH1/2 mutations are almost completely mutually exclusive with somatic loss of function mutations in TET2, which hydroxylates methylcytosine (mCpG). DNA hydroxymethylation can function as an intermediate step in mCPG demethylation. TET2 mutant de novo AMLs also display global and promoter specific hypermethylation partially overlapping with IDH1/2 mutant cases. Mutations in the IDH1/2 loci result in a neomorphic enzyme that generates the aberrant oncometabolite 2-hydroxyglutarate (2HG) using alpha-ketoglutarate (aKG) as a substrate. 2HG can disrupt the activity of enzymes that use aKG as a cofactor, including TET2 and the Jumonji family of histone demethylases. Expression of mutant IDH isoforms inhibit TET2 hydroxymethylation and Jumonji histone demethylase functions. IDH and TET2 mutant AMLs accordingly exhibit reduced levels of hydroxymethylcytosine and a trend towards reduced histone methylation. Mutant IDH or TET2 loss of function causes differentiation blockade and expansion of hematopoietic stem cells and TET2 knockout results in a myeloproliferative phenotype in mice. Hydroxymethylcytosine is abundance in hematopoietic stem cells, and displays specific distribution patterns, and yet the function of this covalent modification is not fully understood. Recent data link TET2 with the function of cytosine deaminases as a pathway towards DNA demethylation, which has implications as well for B-cell lymphomas and CML lymphoid blast crisis, which are linked with the actions of activation induced cytosine deaminase. Altogether, the available data implicate mutations in IDH1/2 and TET2 in promoting malignant transformation in several tissues, by disrupting epigenomics programming and altering gene expression patterning.

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The role of the H3K9me2 methyltransferase G9a in myeloid leukemia

Hematopoietic stem cells (HSCs) and leukemia stem cells (LSCs) often utilize the same self-renewal pathways, complicating the formulation of therapeutic strategies malignant stem cells specifically. Using conditional mutagenesis, we find that while the H3K9me2 methyltransferase G9a has a minor impact on the regenerative function of HSCs in vivo, it is required for the fast proliferation of transiently amplifying progenitor cells under stress conditions. We found that this proliferative defect also affects HoxA9/Meis1-transformed G9a-/- LSCs, suggesting that leukemic transformation is accompanied by the acquisition of a G9a-dependent proliferative program normally utilized by fast amplifying progenitor cells. As a result, lack of G9a in AML cells results in greatly delayed disease progression and significant reduction in LSCs frequency. Pharmacological inhibition of G9a and its close homolog G9a-like-protein (GLP) by UNC0638 mimics these findings in vitro, and it suppresses the growth of primary mouse and human AML cells by inducing their differentiation. Therefore, G9a inhibition may represent a potent and selective strategy to target leukemic stem cells in myeloid leukemias.

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Bromodomains: a family of druggable epigenetic effector domains

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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 41 mainly nuclear proteins. To establish a solid platform for screening and the rational design of specific inhibitors we cloned all human BRDs into bacterial expression systems, an effort that led to the development of more than 40 efficacious expression systems and the determination of more than 30 novel crystal structures. For the development of functional assays and for a better understanding of bromodomain substrate recognition we screened more than 30 representative BRDs against systematic peptide arrays covering all possible histone acetylation sites and arrays that combined acetylation sites with other histone marks. This analysis revealed that bromodomains typically recognize complex patterns of post translational modifications. High affinity sequence motifs include specific recognition of di-acetylated sites as well as combination of singly acetylated peptides with flanking phosphorylated or methylated sequences, suggesting an integrating function of BRD reader modules.
The acetyl-lysine binding pocket has been identified as an attractive binding site for the development of inhibitors. Recently, a number of highly specific and potent inhibitors for BET bromodomains have been reported by us and other laboratories. For instance, we developed the pan-BET inhibitors JQ1 in collaboration with the laboratory of Jay Bradner and PFI-1 in collaboration with Pfizer. We are now interested to develop highly specific chemical probe molecules for bromodomains outside the BET family. Evaluation of the rich body of structural information on bromodomains enabled detailed family-wide structural analysis of the human BRD family and its “druggability”. We combined a number of in silico screening approaches and fragment based screening of putative acetyl-lysine mimetic compounds to identify chemical starting points for the development of inhibitor libraries and selective lead compounds. I will discuss recent development developing selective inhibitors for a number of diverse bromodomains.

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Chemical Inhibition of Bromodomains

Cellular states are maintained by coordinated gene expression programs, attributable to master regulatory transcription factors. Toward the pharmacologic control of cellular states we have undertaken a chemical biological approach to inhibit chromatin-dependent transcriptional signaling.
Transcriptional activation by master regulatory proteins is facilitated by chromatin remodeling at promoter/enhancer regions, in particular side-chain acetylation of lysine residues on nearby histone tails. Context-specific lysine acetylation prompts molecular recognition by transcriptional co-activator proteins possessing acetyl-lysine recognition modules, or bromodomains. Perhaps owing to perceptions regarding the feasibility of abrogating protein-protein interactions, research toward the direct inhibition of human bromodomains (or epigenetic reader proteins, in general) has received comparatively little attention. Based on the above rationale, we have developed chemical and biochemical platforms for the development and characterization of novel bromodomain inhibitors. Recently, we reported the first potent, small-molecule inhibitor of human bromodomains, JQ1, which exhibits selectivity for the BET family of bromodomain-containing transcriptional co-activators. Of broad relevance to cancer, we will present research demonstrating that c-Myc expression is critically dependent on BRD4 function and localization to discrete upstream regulatory regions. Exposure of cancer cells to JQ1 prompts immediate down-regulation of c-Myc expression leading to suppression of a transcriptional program associated with proliferation, survival and metabolic adaptation. In translational models of Myc-dependent hematologic malignancies, the efficacy of
JQ1 treatment establishes a mechanistic rationale for the leveraged clinical development of drug-like JQ1 derivatives. Toward this objective, we have completed chemical optimization of novel, drug-like inhibitors of BET bromodomains as reagents capable of supporting human clinical investigation.
This research has established the feasibility of inhibiting epigenetic reader proteins with efficient, cell-permeable, small molecules. In support of an open-innovation model of chemical biology, we have created a chemical probe allowing the broad study of chromatin biology, which has already been provided to more than 150 academic, governmental and industrial laboratories worldwide.
Together, we have rapidly identified mechanism-based opportunities for clinical translation in cancer, inflammation and fertility.

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EZH2, Inhibitors and Cancer

Enhance of Zeste Homolog 2 (EZH2) is the biochemical activity of the Polycomb Repressive Complex 2 (PRC2) that transfers a methyl group from the cofactor S-adenosyl methionine (SAM) to histone H3 on lysine 27 (H3K27), resulting in epigenetic silencing of target gene expression. Activity of the multi-component PRC2 complex is crucial for normal development and differentiation. However, dysregulation of H3K27 methylation is implicated in tumorigenesis and occurs through multiple mechanisms. Elevated levels of EZH2 correlate with poor prognosis in a number of solid tumors including prostate, breast, kidney and lung. The increased EZH2 expression observed in many solid tumors has been linked to loss of one or more miRNAs including mir-101, mir-26A, and mir-214; aberrant E2F activity and chromosomal amplification. Inactivating mutations in UTX, an H3K27 demethylase which acts in opposition to EZH2, have been described in several tumor types including transitional cell bladder carcinoma, esophageal squamous cell carcinoma, renal cell carcinoma and multiple myeloma. Recently, somatic activating mutations in EZH2 have been identified in follicular lymphoma (FL) and GCB diffuse large B cell lymphoma (DLBCL). The frequency of the most prevalent mutation, Y641, is reported to be 7-12% in FL and as high as 22% in DLBCL. In view of the above, biochemical inhibitors of EZH2 may have therapeutic utility and herein we report on the identification and characterization of potent and selective small molecule EZH2 inhibitors with in vitro antiproliferative activity in cancer cell lines. The studies provide a compelling rationale for the clinical evaluation of appropriate EZH2 inhibitors in EZH2 driven human cancers.

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Where are we in understanding the origins of the cancer epigenome and realizing the translational potential of the concept?