tumour formation and progression. We are now combining new technologies of intra-vital dynamic molecular imaging, and mouse cancer modelling, to address the important question of whether agents that target adhesion regulators have anti-invasive or anti-metastatic activity, for example how E-cadherin dynamics are affected, and if so how such activity can be monitored in cancer models and tested clinically. We will present some new findings on on a novel 'direction sensing' polarization pathway regulated by FAK at nascent integrin adhesions and on the monitoring of E-cadherin dynamics in vivo. We seek a full understanding of the molecular mechanisms by which these adhesion regulated kinases promote the malignant phenotype, and how the biological properties they perturb may be targeted for therapy.

614 Mechanisms of cell signalling in metastasis

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Rho-family GTPase signalling underlies the cytoskeletal changes that are required for cell migration. In order to delineate which Rho-family GTPases are involved in cell migration and how they are controlled we are carrying out a systematic analysis of Rho-family GTPases and their regulators. We have used RNAis targeting 22 Rho-family GTPases, 80 guanine nucleotide exchange factors (GEFs) and 73 GTPase activating proteins (GAPs) to study the requirement for cell motility and morphology in a number of different systems. Using these approaches to study migration and invasion of melanoma cells we have described pathways controlling two distinct forms of movement. Elongated, mesenchymal-type movement is driven by Rac activation mediated by a pathway containing the adaptor protein NEDD9 and the exchange factor DOCK3. Interestingly, NEDD9 has been found by others to be over-expressed in malignant melanoma. In contrast amoeboid movement, an alternative form of cell migration, is suppressed by Rac activation but driven by Rho and Cdc42 activation. In amoeboid movement of melanoma cells Cdc42 activation is driven by the GEF DOCK10 and acts through the Cdc42 effectors NWASP and Pak2. Since Rac activity suppresses amoeboid movement we have investigated how Rac activity is down regulated in melanoma cells undergoing amoeboid movement. Our studies show that Rho and Cdc42 signalling in amoeboid cells drives high levels of actomyosin contractility that activates a RAC GAP ARHGAP22, which then inactivates Rac to permit amoeboid movement. These studies therefore demonstrate a tight interplay between Rho and Rac signalling in determining modes of cell movement.

615 TGF-beta regulation of the inflammatory tumour microenvironment

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Accumulating data indicate that an inflammatory microenvironment can play a critical role in cancer initiation and progression. TGF-beta signaling in both epithelial and stromal cells appears to be a key regulator of this microenvironment. There is now compelling evidence from transgenic mouse studies and analyses of mutations in human carcinomas indicating that the TGF-beta signal transduction pathway is tumour suppressive. However, there is evidence that TGF-beta signaling can promote tumour progression in the later stages. In order to examine the roles of TGF-beta signaling in cancer more closely, we have generated mice with *loxP* sites flanking exon 2 of the type II receptor gene, *Tgfbr2,* and crossed them with mice expressing Cre driven by different epithelial specific promoters. Loss of TGF-beta signaling in six different epithelial cells gave a minimal phenotype. However, when challenged with oncogene expression or tumour suppressor gene impairment, there was rapid development of invasive and metastatic carcinomas. In an effort to address mechanisms, we have now identified gene expression signatures associated with the TGF-beta signaling pathway in mammary carcinoma cells. The results strongly suggest that TGF-beta signaling mediates intrinsic, stromal-epithelial and host-tumour interactions during breast cancer progression, at least in part, by regulating induced *Cxcl1*, *Cxcl5* and *Ccl20* chemokine expression. To determine the clinical relevance of our results, we queried our TGF-beta associated gene expression signatures in four human breast cancer data sets containing a total of 1,319 gene expression profiles and associated clinical outcome data. The signature representing complete abrogation of TGF-beta signaling correlated with reduced relapse-free survival in all patients, particularly in patients with estrogen receptor positive tumours. The functional significance of increased chemokine expression in the knockout carcinoma cells in the mouse model is recruitment of immature bone marrow derived cells that express abundant TGF-beta and MMPs in the tumour microenvironment and promote invasion and metastasis. The data indicate that TGF-beta signaling is a major regulator of chemokine secretion and resultant bone marrow cell infiltration creating the inflammatory microenvironment and suggest that targeting pathways, which inhibit bone marrow cell differentiation or chemokine receptors, could be useful in both therapy and prevention of cancer.

Tuesday 29 June 2010 10:20–12:20

Symposium
CancerOmics

616 Sequencing cancer genomes

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Using massively parallel paired end sequencing, it is feasible to sequence the entire genome of cancer samples, allowing the generation of comprehensive catalogues of somatic mutations of all classes. We have developed bespoke algorithms to identify somatically acquired point mutations, small indels, copy number changes and genomic rearrangements, which have been extensively validated by confirmatory testing. The findings from our first handful of cancer genomes illustrate the potential for next-generation sequencing to provide unprecedented insights into mutational processes, cellular repair pathways and gene networks associated with cancer development.

617 Translational opportunities from genomic and chemical biology of cancer

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Cancer genomics projects, such as the International Cancer Genomics Consortium (ICGC), will in the near future provide a complete catalogue of genomic, epigenomic and transcriptomic changes in up to 25,000 different cancer samples, from up to 50 different major cancer types and subtypes. With such a comprehensive catalogue in the horizon, scientists need to consider the implications that this will have for biological and translational cancer research. This presentation will highlight different aspects of cancer research that we believe will gain in importance in the years to come as the full cancer genomic profiles start to emerge. These include: bioinformatics, genome-scale cancer biology, chemical biology, and translational research into individualized cancer medicine.

First, the availability of this massive catalogue of cancer genomics information will emphasize the central importance of bioinformatics and data mining to generate knowledge and testable hypotheses. For example, on a scale of >10,000 samples, we have created developed a transcriptomics data mining capability for the rapid bioinformatic analysis of gene expression levels in vivo in thousands of clinical samples, available at www.genesapiens.org (Kilpinen et al.. Genome Biology, 2008). The transcriptomics data have been normalized, QC-checked and annotated with clinical information to generate a fully integrated, curated and searchable database to systematically explore gene functions across the body in different cells, tissues and diseases, cancer in particular.

Second, we have developed an ultra-high-density cell-microarray screening system for siRNAs and miRNAs. The cell array technology has up to 200-fold screening throughput as compared to 384-well-based assays. In this technology, siRNAs and transfection agents are first printed as a microarray with up to 10−20,000 cell spots at a time, resulting in a highly parallel reverse transfection of siRNAs into cells. Cell phenotypes resulting from the knockdown of specific genes are read with HTS and HCS instrumentation using up to 4 parameters at a time. This technology will facilitate the genome-scale biology and will create causal data from in vitro model systems that can be linked with the descriptive cancer genomics data from in vivo specimens.

Third, many of the breakthroughs in cancer therapeutics have arisen out of coincidence, such as drugs developed for one specific indication showing promise in another disease or cancer subtype. To explore such opportunities, we have been carrying chemical biology screens covering all known drugs. For example, in prostate cancer cell lines we identified the anti-alcoholism drug Disulfiram as a nanomolar inhibitor of prostate cancer growth (Iljin et al., 2009). By investigating molecular mechanisms of these inhibitory effects, it will be possible to establish the molecular basis of chemical vulnerabilities of cancer cells as well as to create pre-clinical and clinical study designs to validate these therapeutic opportunities.

Finally, the genomic and functional tools developed for cancer research can in the near future be tested in the clinical setting in facilitating therapeutic decisions. We have investigated such opportunities in individual cancer cases where clinical decisions have not been possible with evidence-based medical guidelines. The challenges and opportunities with such future clinical "canceromics" approaches will be discussed.