embedded within *PPARGC1b* which encodes PGC-1β and that their expression is co-regulated by ERBB2 in breast cancer cells. We will show that miR-378 performs this function by inhibiting the expression of ERRγ leading to a reduction in tricarboxylic acid cycle gene expression and oxygen consumption as well as an increase in lactate production and in cell proliferation. *In situ* hybridization experiments also show that miR-378 expression correlates with progression of human breast cancer. These results thus identify a novel molecular mechanism governing the Warburg effect in breast cancer cells and demonstrate the important roles played by the ERRs in the etiology of cancer.

5 A role for mutant p53 in promoting invasion

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The p53 tumour suppressor protein restrains malignant progression through a number of mechanisms, and most cancers show loss of the normal functions of p53. In many cancers this is due to a mutation in the p53 gene that leads to the expression of a mutant p53 protein. Interestingly, these tumour associated mutant p53s not only lose wild type p53 activity but can also acquire the ability to promote cell motility and migration, and so contribute to the development of metastases. We have found that tumour associated mutant p53s can promote invasion and loss of directionality when cells migrate *in vitro*. These activities are independent of the loss of wild type p53 function, and reflect activation of integrin and EGFR trafficking that depends on Rab-coupling protein and which results in constitutive activation of EGFR/integrin signalling. These findings open the possibility that blocking alpha5/beta1 integrin and/or the EGF receptor will have therapeutic benefit in mutant p53 expressing cancers. We are now proposing to extended these observations by testing whether this activity of mutant p53 is restricted to the EGFR, or may also promote the activity of other cell surface receptors too. Simultaneous loss of p53 and p63 recapitulates the phenotype of mutant p53, suggesting that this function of mutant p53 reflects, at least in part, the inhibition of p63. However, mutant p53 is likely to have additional functions that contribute to the ability to induce an invasive phenotype, and we are presently investigating the activity of other mutant p53 binding proteins.

Saturday 26 June 2010 14:30–16:30

Symposium
Animal models

6 Mouse models for lung cancer and mesothelioma

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The mouse is used as a model organism for establishing the role of oncogenes and tumour suppressor genes in tumour development. By exploiting Cre/Lox mediated cell-type-specific switching and by taking advantage of somatic gene transfer methods, the expression of multiple oncogenes and tumour suppressor genes can be controlled in a tissue-specific and spatial-temporal fashion. This permits a more accurate modeling of tumourigenesis as it occurs in man, and therefore provides the opportunity for establishing more relevant genotype-phenotype correlations. These models also provide an excellent experimental tool to test prevention and intervention strategies especially when combined with sensitive in vivo imaging techniques. Finally, these models permit us to identify new oncogenes and tumour suppressor genes involved in tumour progression using a variety of techniques, such as array CGH, expression profiling and proviral and transposon-based insertional mutagenesis. Some of the gene families identified in our models are being studied in more depth.

We utilize mice carrying combinations of different oncogene and conditional tumour suppressor gene alleles to model a range of tumours. Our current focus is on several lung cancers subtypes and mesotheliomas. To achieve (sporadic) activation of oncogenes and inactivation of tumour suppressor genes we use Adeno-Cre or Lentivirus-mediated gene transfer to switch the conditional oncogenes and tumour suppressor gene alleles. Subsequently, tumour initiation and progression is monitored in longitudinal studies in which noninvasive imaging techniques are used.

Lung tumours: We focus on small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC). When *Rb* and *p53* are inactivated specifically in lung, SCLC ensues after a relatively long latency period. The marker profile of these tumours is very closely resembling that of human SCLC. The tumours also metastasize to the same organ sites as observed in human SCLC. Array CGH showed frequent amplification of *L-Myc* further supporting their resemblance with the human counterpart. The tumours are heterogeneous and are composed of different cell types. Cloning of the different cells from a single tumour showed very different marker profiles. Both cells with neuroendocrine and progenitor marker profiles were found. Interestingly, these phenotypically highly diverse cell lines shared some highly distinct genetic aberrations indicating that they were derived from a common progenitor. We show by co-culture and co-grafting experiments that these clonally-related cells influence each other through paracrine mechanisms providing a basis for their maintenance during tumour progression.

To gain more insight into the cell of origin of these tumours, we have designed a series of cell-type specific Adeno-Cre viruses that enable us to switch oncogenes and tumour suppressor genes in distinct lung cell types in vivo. Using promoters specific for Clara cells, Alveolar type I and II cells, and neuroendocrine cells to drive Cre expression upon Adeno-Cre infection we are defining the marker profile of cells in lung that give rise to SCLC and NSCLC.

7 Signalling via the ALK receptor tyrosine kinase – insights from the fruitfly

No abstract received.

8 Investigating the tissue specific functions of tumour suppressor genes and oncogenes in vivo

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Colorectal Cancer is the third most common cancer in the western world and the second most common cause of cancer mortality. Germline heterozygosity of the Apc (Adenomatous Polyposis Coli) gene leads to Familial Adenomatous Polyposis (FAP), a disease characterised by patients developing 1000's of colorectal adenomas by the time they are 30.Importantly, Apc loss is also the key initiating event in sporadic colorectal cancer with up to 80% of sporadic colorectal cancers having an Apc mutation.

I will discuss my groups latest attempts to find key regulators downstream of Apc loss in vivo. I will focus on the importance of mTOR and Rac1 on mediating hyperproliferation following Apc loss.

Moreover I will discuss our recent work on developing murine models of invasive and metastatic colorectal cancer and will focus on the role of p53 mutation.

9 Studying the p53 pathway using Zebra fish models

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While many thousands of studies on the regulation of the p53 pathway have been reported the majority use tissue culture cell systems and there are relatively few reports of the tissue specific nature of the response. To examine these questions we have begun to develop tools and reagents that allow an examination of the p53 response in the Zebrafish vertebrate model system. New monoclonal antibodies to Zebrafish p53 have established the tissue restricted nature of the p53 protein accumulation response to be measured. Reporter transgenic fish, where a GFP reporter gene is induced by p53 have allowed activity measurements in response to kinase inhibitors and DNA damaging drugs to be discerned and studies using p53 mutant fish have allowed the accumulation of p53 protein in response to stress to be shown to be independent of its transcriptional activity negating some feedback theories of p53 control. Mutations in p53 inactivate the apoptotic response to many agents to a dramatic extent underlining the importance of p53 in these whole tissue systems. Genetic experiments establish that mutant p53 is recessive to wild type p53 which helps to explain the Li-Fraumeni phenotype. Using a variety of approaches the clear role that p53 plays in inducing the phenotype of many developmental mutants has been established and finally the detection of p53 isoforms in this species confirms that these isoforms have been conserved through 400 million years of evolution supporting their biological importance. These early results suggest that the Zebrafish system could be a powerful addition to existing models for the study of the role of p53.

Saturday 26 June 2010 14:30–16:30

Symposium
Cancer systems biology

10 The HER2 and EGFR alliance in cancer: defects in system control

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Growth factors and their transmembrane receptors contribute to all steps of tumour progression, from the initial phase of clonal expansion (cell proliferation), through recruitment of blood vessels to growing tumours (angiogenesis), and, eventually to migration and colonization of distant organs (metastasis). Hence, the information relay system involved in growth factor signaling provides potential site for signal interception and tumour inhibition.