Oncology and Haematology

Current Research Opportunities

- Cancer and imaging – Professor Glyn Johnson
- Angiogenesis and solid cancers – Dr Stephen Robinson
- Prostate cancer genetics – Professor Colin Cooper and Dr Dan Brewer
- Melanoma and neural crest development – Dr Grant Wheeler
- Microtubule an epithelial cell differentiation in health and cancer – Dr Mette Mogensen
- Proteases and breast cancer metastasis – Professor Dylan Edwards
- Chemopreventive agents in the diet – Professor Dylan Edwards and Professor Cathie Martin

Cancer and imaging

Conventional magnetic resonance imaging (MRI) is superb at identifying the presence of lesions in the body but much less accurate at distinguishing between different types of lesion. However, MRI acquisitions can be adapted to give estimates of parameters that are either directly related to, or provide surrogate markers for, important aspects of underlying tissue biology.

We are particularly interested in two techniques: perfusion MRI which provides estimates of blood flow, blood volume and vascular permeability; and diffusion MRI which provides information on cellular density and complexity. These techniques can be used to determine tumour aggressiveness, monitor treatment and for surgical planning (Figure). Our current goals are:

- To determine whether diffusion measurements can be used to assess infiltration of tumour cells into apparently normal white matter in brain tumour patients.
- To determine whether a combination of diffusion and perfusion methods predicts outcome in brain tumour patients.
- To determine whether diffusion measurements can distinguish between aggressive and indolent prostate cancer.

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Angiogenesis and solid cancers

The recruitment of a blood supply is critical for solid cancers to grow beyond a very small size. Once this vasculature is established (by a process called angiogenesis) tumours become much more aggressive, they begin to invade nearby tissues, and they may eventually spread to distal sites throughout the body (metastasise). Thus, angiogenesis presents itself as a key target for cancer therapeutic development.

To date, the drugs that have been developed as anti-angiogenic agents are showing only limited effect in the clinic. The Robinson group works on understanding how cells of the blood vasculature respond to angiogenic signals derived from the cancer, in an effort to develop better anti-angiogenic therapies. Current goals are:

- To understand how movement of the vasculature toward a growing tumour is orchestrated; who are the essential molecular players that might serve as drug targets?
- To determine the short- and long-term impacts of current angiogenic interventions that are designed to ameliorate cancer growth and spread; are they good targets?
- To develop better anti-angiogenic strategies.

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Prostate cancer genetics

Cooper and Brewer are helping to run the Cancer Research UK International Cancer Genome Consortium Prostate Cancer Project (www.icgc.org). This group has collected and analysed whole genome DNA sequence data from 250 prostate cancer leading to new insights into the mechanism of development of prostate cancer and to the model of cancer development shown here (Nature Genetics 47, 367–372, 2015; Nature 520, 353–357, 2015).
A critical problem in the management of prostate cancer is that it is not possible to distinguish reliably aggressive from non-aggressive disease at the time of diagnosis. This results in considerable overtreatment of this disease such that many men with indolent disease are given radical treatments (surgery, radiotherapy) unnecessarily and made impotent. Our current work focuses on identifying novel biomarkers that can identify aggressive disease. To achieve this we are examining both patient urine and cancer tissue and utilizing a range of genomic technologies from RNAseq analysis to targeted DNA sequencing. Our work has strong components of both data generation and bioinformatics analysis.

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Melanoma and neural crest development

The Wheeler group works on the molecular events that govern the origin and migration of different cell types within developing embryos. We use tadpoles from Xenopus laevis (African Clawed Frog) as our model system. To investigate these processes we are using a combination of embryological, molecular developmental biology, imaging and chemical genetic approaches.

We are also interested in developing Xenopus as a potential tool in the drug screening and discovery process. We are mainly focused on looking at the differentiation and migration of Neural Crest cells especially with respect to pigment cell development and melanoma growth. Current projects include:

- Using chemical genetic screens to determine a role for epigenetic modifiers in neural crest development and migration.
- Screening small molecule libraries for inhibitors of pigment cell development to gain insight into neural crest and also to identify inhibitors of melanoma growth.
- Developing in vivo toxicity assays for small molecules and nanoparticles.

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Microtubules an epithelial cell differentiation in health and cancer

Microtubules are tubular filaments that are vital for cell survival with many critical functions including cell division and intracellular transport being dependent on them. They are also important for cell differentiation with dramatic reorganization of the microtubule network driving changes in cell architecture and supporting specialised functions. For example, the formation and maintenance of polarised transport epithelia such as that lining the gut is dependent on microtubules. The correct alignment of the microtubules is critical for normal tissue function with defects in polarisation leading to loss of function, cell invasion and cancer. Microtubules are therefore often targets of cancer drugs with the stabilising taxanes being classic examples.

Our aim is to identify the molecules and mechanisms involved in microtubule organisation and maintenance. Funding from BigC and Breast Cancer Now is helping us to better understand the mechanisms responsible for loss of epithelial polarity and progression to an invasive cancer state. We use 3D in vitro gut organoids that closely mimic the in vivo gut architecture and organogenesis as well as cancer cell lines in combination with GFP- and RNAi technology and immuno-localisation and confocal, multi-photon and live time-lapse microscopy to pursue these aims. Developing in vivo toxicity assays for small molecules and nanoparticles.

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Proteases and breast cancer metastasis

Metastasis is the main cause of death for cancer patients. Our group is studying the roles of extracellular proteases in regulation of the tumour microenvironment, and how these enzymes contribute to tumour growth and metastasis.

It had previously been thought that these enzymes promoted cancer by acting as molecular scissors to cut a path for the invading cells through the extracellular matrix (ECM) but we have found that they work in many different and subtle ways – essentially, they control the microenvironment within tumours, influencing growth, cellular organization, immune function, angiogenesis (blood vessel formation), invasion and metastasis. Indeed - as we have found - some proteases such as matrix metalloproteinase-8 (MMP8) actually stop cancers from spreading. We have developed a number of tools to evaluate the “degradome” – the repertoire of proteases and related molecules that cells and tissues deploy during normal and pathological tissue remodeling processes. We are interested in how these degradome genes act, how they are controlled, and their development for diagnosis and for novel therapies.
Particular projects underway at present include:

- Studies of the interplay between ADAMTS metalloproteinases and Syndecan proteoglycans in signalling and adhesion mechanisms in breast cancer.
- Regulation of the innate immune system by the anti-metastatic protease MMP8.
- Protease involvement in angiogenesis
- Use of nanoparticles for delivery of cancer therapeutic agents.

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Chemopreventive agents in the diet

This work is undertaken in collaboration with Prof Cathie Martin at the John Innes Centre, who has engineered strains of tomato that are enriched in particular plant polyphenolic compounds. We have demonstrated that extracts from these plants cause selective apoptosis of cancer cells. We are interested in the mechanisms by which these dietary polyphenolic compounds influence cancer cell survival and apoptosis

The research would primarily be wet lab-based but there are opportunities for bioinformatic studies related to analysis of cancer gene and gene expression databases. For further details on the work of the lab go to the following links:

http://www.uea.ac.uk/biological-sciences/People/Academic/Dylan+Edwards

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