



White Rose HIP Health Technology Bulletins

The White Rose Health Innovation Partnership (WRHIP) aims to accelerate new health-related technologies by facilitating interactions between academia, industry and the NHS using an *open innovation* approach.

The new projects funded as part of this initiative are built upon a foundation of excellence in health innovation by the Partnership's members. This series of Health Technology Bulletins offer an introduction to this research excellence and cover a broad range of clinical and technology areas.

Each bulletin is written to give a general introduction to the topic area along with short case studies of clinical applications of new knowledge. Information is also presented on where to learn more about these new technologies and health challenges, and how to access the network of health innovation professionals established by the Partnership.

Cancer Research

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Cancer is a group of diseases characterised by the uncontrolled growth of the patient's own cells. These abnormal cells usually multiply to form a lump of tissue called a tumour. Malignant cancer is when the abnormal cells acquire the ability to invade and spread to other parts of the body, which is known as metastasis. There are over 200 different types of cancer, each with different causes, symptoms and treatments.

Over a quarter of a million new cases of cancer are diagnosed each year in the UK, and it is estimated that more than one in three people will develop some form of cancer in their lifetime. Cancer is predominantly a disease of the elderly, with two thirds of all cases occurring in people over 65. Although the overall cancer incidence rate has risen by 25% since 1975, it has remained fairly constant over the last 10 years. The good news is that overall cancer mortality has fallen by nearly 20% since 1975, and around half of all people diagnosed with cancer now survive more than 5 years. However, cancer remains an important health problem, being responsible for 24% of all deaths in the UK, which corresponds to the death of over 150,000 people every year. There is therefore a need for earlier diagnosis

and better treatment, which is where cancer research comes in.

Cancer research is the study of cancer, from its basic biology to the effects of treatment. This includes research into the causes of cancer, studying how cancers form, finding new ways of diagnosing and treating cancer, developing more effective treatments, identifying cancer risk factors, finding how cancer can be prevented, and understanding the psychological and social impacts of cancer.

These topics broadly fit into five main areas of cancer research: basic research, translational research, clinical research, behavioural and population research, and psychosocial research. The ultimate goal of cancer research is to produce effective diagnosis, treatment and prevention for the many different types of cancer.

A large number of groups within the White Rose Health Innovation Partnership (WRHIP) are involved in different aspects of cancer research (summarised in final section 'Regional Centres of Expertise'). However, this Health Technology Bulletin will focus on just three case studies, where new technologies are being developed and applied to the field of cancer research.



Figure 1: Mass Spectrometry
A new mass spectrometry facility at the University of York has been created thanks to a major capital investment of £1.6 million through Science City York, supported by Yorkshire Forward and with funds from the Northern Way Initiative. It will help scientists to tackle some of their most testing analytical challenges, and provide a highly specialised technical service to industry. Figure provided by Dr John Pillmoor, Director of the Technology Facility, Department of Biology, University of York.



Case study 1: Human Designer Cells for Cancer Research, University of York

Our understanding of carcinogenesis, the sequential steps involved in the development of malignant cells from their normal counterparts, has advanced considerably over recent years. We now know that a number of genes in the same cell need to be altered before a cell becomes cancerous, and we have identified many of the key oncogenes (genes that in cancer become permanently switched on) and tumour suppressor genes (regulatory genes that are lost in cancer) that are involved. However, many questions remain unanswered, and work in the field is complicated by the emerging notion that the precise molecular events involved in carcinogenesis are not only unique to every tissue type, but are influenced by the individual's genetic makeup or genotype. Elucidating the molecular genetic pathways implicated in malignant progression is important for discovering new targets for anti-cancer drugs, as well as for the identification of markers of disease prognosis.

The group headed by Professor Jenny Southgate at the Jack Birch Unit for Molecular Carcinogenesis at the University of York is interested in the process of human bladder carcinogenesis. They have developed systems to first isolate normal human bladder epithelial cells from surgical specimens and then to grow the cells under safe and controlled laboratory conditions. The bladder epithelial cells can be propagated and even used to form normal bladder tissues – with exciting possibilities for tissue engineering of replacement bladders. For cancer research, the bladder cells are infected with engineered retroviruses, to introduce bladder cancer-specific gene alterations. This approach has generated “para-malignant” human bladder epithelial cells that carry the key molecular changes involved in the development and progression of early-stage bladder cancer. The engineered “designer” human cells with defined genetic alterations represent a useful tool not only for gaining a better understanding of carcinogenesis, but also for investigating how response to chemotherapeutic agents is influenced by specific cancer-related changes. In the future, this will inform the development of therapies on a patient tumour-specific basis.

<http://www-users.york.ac.uk/~biol32/>

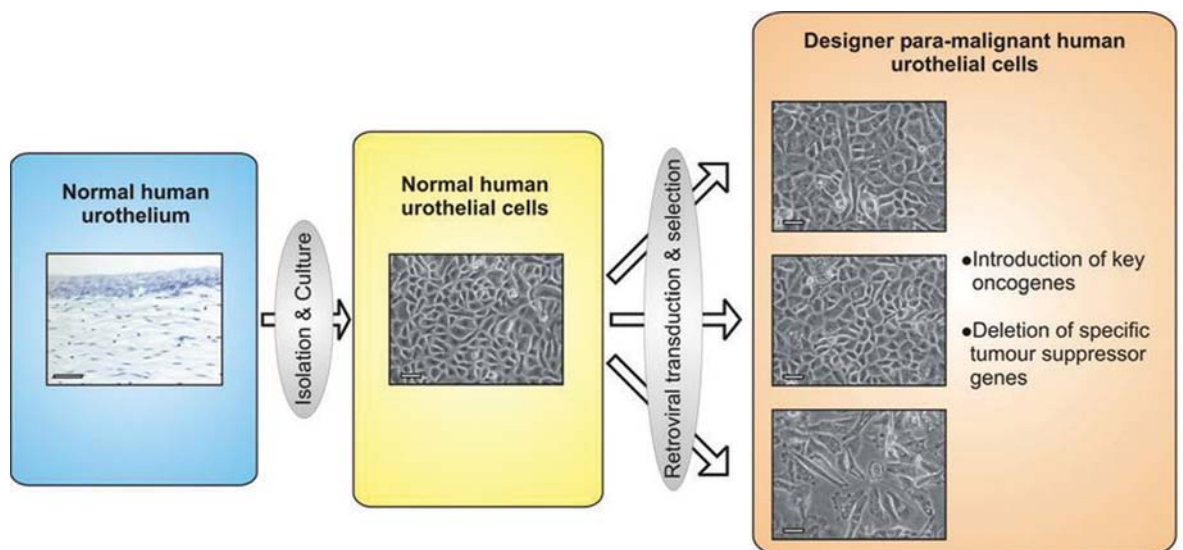


Figure 2: Designer cells for cancer research.

Schematic to illustrate how bladder epithelial cells are isolated from human surgical tissues and grown in the laboratory. Viruses are engineered to deliver cancer genes to the cells, generating so-called “paramalignant” sublines for cancer research.

Case study 2: The Epitheliome, University of Sheffield

Whereas predictive modelling has been applied for many years in the physical sciences, biological systems are inherently more complex and difficult to model. Recent advances in computational and mathematical modelling techniques are being applied in order to understand and predict important aspects of the behaviour of biological systems. This is achieved by building realistic and useful models of biological phenomena.

Working with a team in the Computational Systems Biology group at the University of Sheffield, Professor Rod Smallwood and Dr Dawn Walker have led development of the Epitheliome, which is an agent-based computational model of epithelial tissues. In the Epitheliome, biological cells are represented as individual virtual entities or software agents that are controlled by a number of rules governing behaviour, such as cell cycle and proliferation, migration and interactions with other cells. This model is realistic in that it considers the structure of biological tissue as an outcome of the physical and chemical interactions between individual cells and with their environment. The Epitheliome can also help in interpreting how cells are influenced by different environments – for example comparing normal and malignant tissues.

The Epitheliome has already been used to simulate the growth and wound-healing characteristics of a monolayer of epithelial cells in low and physiological calcium environments. The model has also been used to predict how the growth of epithelial cells is dependent on the concentration and availability of growth factors. The aim of ongoing work is to improve the existing Epitheliome to include three-dimensional physical interactions between cells and to incorporate rules representing more complex aspects of cell behaviour. Ultimately, the Epitheliome will represent the three-dimensional interactions of millions of individual cells, incorporating details down to the level of the genome. Such a tool will be invaluable in improving our

understanding of how the tightly-regulated controls on cell proliferation and migration can go wrong, causing uncontrolled tumour cell growth and invasion. Eventually, the Epitheliome will also be able to make predictions about the result of changing factors in the tissue environment, or manipulating individual cells at the genetic level. Such a model would be an extremely useful addition to the cancer research tool box, for example by predicting which anti-cancer therapies are likely to be effective under a given set of environmental or genetic circumstances. This “virtual” tissue model could ultimately provide an environment for screening potential drugs more quickly and cheaply, helping to focus the time and resources devoted by laboratory and clinical researchers on the most promising treatments.

<http://www.shef.ac.uk/dcs/research/groups/compbio/personnel1.html>

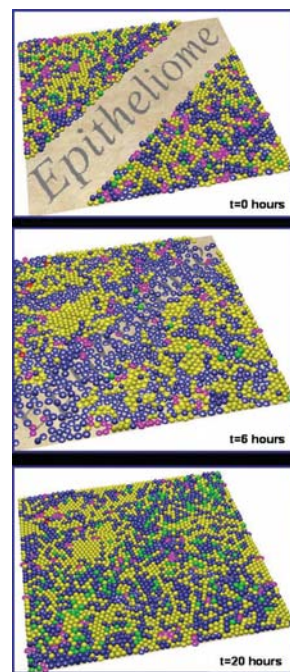


Figure 3: Computational simulation of epithelial wound repair.

A wound is made in a confluent sheet of epithelial cells to reveal the words “Epitheliome”. The cells are represented by software agents and repair of the wound occurs over 20 hours as the cells divide and move into the wound. The cells change colour from yellow (inactive) to blue (preparing for division) to pink (as cells actively divide). Figure provided by Dr Dawn Walker, Department of Computer Science, University of Sheffield.

Case study 3: Proteomic Studies, University of Leeds

Proteomics involves the identification and characterisation of the protein complement, or proteome, of a given cell type, tissue or organism under a defined set of conditions. Any proteome is therefore dynamic and will vary depending on both genetic and environmental influences. Large-scale proteomic studies have become possible in recent years due to technological developments and advances in genomics, such as the completion of sequencing of various genomes. The main advantage of proteomics over genomics is that it studies what our bodies are made of (the proteins) rather than the set of instructions (the genes). Indeed, protein quantity, structure and protein activity are not readily predicted from genomics; this is at least in part due to protein modifications that are influenced by the cellular environment.

The Clinical and Biomedical Proteomics group, led jointly by Professors Roz Banks and Peter Selby at the University of Leeds, uses proteomic-based approaches for the identification of new markers for the diagnosis, prognosis or response to treatment of

renal and ovarian cancers. This is achieved by comparing overall protein profiles under different conditions, such as in normal and malignant tissues, or before and after anti-cancer therapy. The results of such studies also provide invaluable information about the underlying biological processes. The group has identified new biomarkers for renal and ovarian cancer, as well as potential new targets for therapy.

Central to all these proteomic approaches is mass spectrometry (MS), with protein identification being achieved on the basis of the masses or amino acid sequences of small protein fragments called peptides. All MS techniques result in the generation of large amounts of complex data, which requires robust bio-informatic and statistical analysis strategies. Large-scale and high-throughput proteomic studies have only recently become possible thanks to developments of MS technology itself, but also due to increases in computer data processing capacity and storage. In the long term, the continued analysis of proteomes should ultimately yield highly individualised information, with potentially significant impact on cancer diagnosis and patient treatment.

http://www.limm.leeds.ac.uk/research_sections/oncology_and_clinical_research/groups/banks.htm

**Founding partners in
the Programme include:**

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for Industrial Collaboration
Wireless Technologies Centre for
Industrial Collaboration
Particles Centre for Industrial
Collaboration

Regional Centres of Expertise

University of York

Department of Biology

<http://www.york.ac.uk/depts/biol/>

The Department of Biology is an integrated, multidisciplinary Department with cancer biology featuring as one of its major biomedical research areas. The Department has three associated cancer research units: the Jack Birch Unit for Molecular Carcinogenesis supported by York Against Cancer and directed by Professor Jennifer Southgate, the YCR Cancer Research Unit directed by Professor Norman Maitland and the Yorkshire Cancer Research P53 Unit directed by Professor Jo Milner.

Other cancer-related research is carried out by Professor Eve Roman (Department of Health Sciences) and Professor Paul Walton (Department of Chemistry).

University of Leeds

Leeds Institute of Molecular Medicine (LIMM)

<http://www.limm.leeds.ac.uk/>

LIMM is a research institute based in part at St James's University Hospital that is dedicated to defining the molecules involved in human diseases and using this knowledge to develop novel therapies and new drugs. The section of Experimental Oncology is directed by Professor Margaret Knowles and the section of Oncology and Cancer Research is directed by Professor Peter Selby.

University of Sheffield

Institute for Cancer Studies

<http://www.shef.ac.uk/medicine/research/sections/oncology/ics/leaders.html>

The Yorkshire Cancer Research Institute for Cancer Studies is headed by Professor Mark Meuth. The Institute provides an interactive environment for basic and translational cancer research with a focus on genetic instability in cancer.

Further relevant research activity takes place in the Academic Departments of Clinical Oncology and of Surgical Oncology.

University of Bradford

Institute of Cancer Therapeutics

<http://www.cancer.brad.ac.uk/>

The Institute of Cancer Therapeutics is part of the School of Life Sciences at the University of Bradford and incorporates the Tom Connors Cancer Research Centre. Research themes at the Institute encompass the development of new molecules across three broad stages of medicine development: discovery, pre-clinical evaluation and clinical application.



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