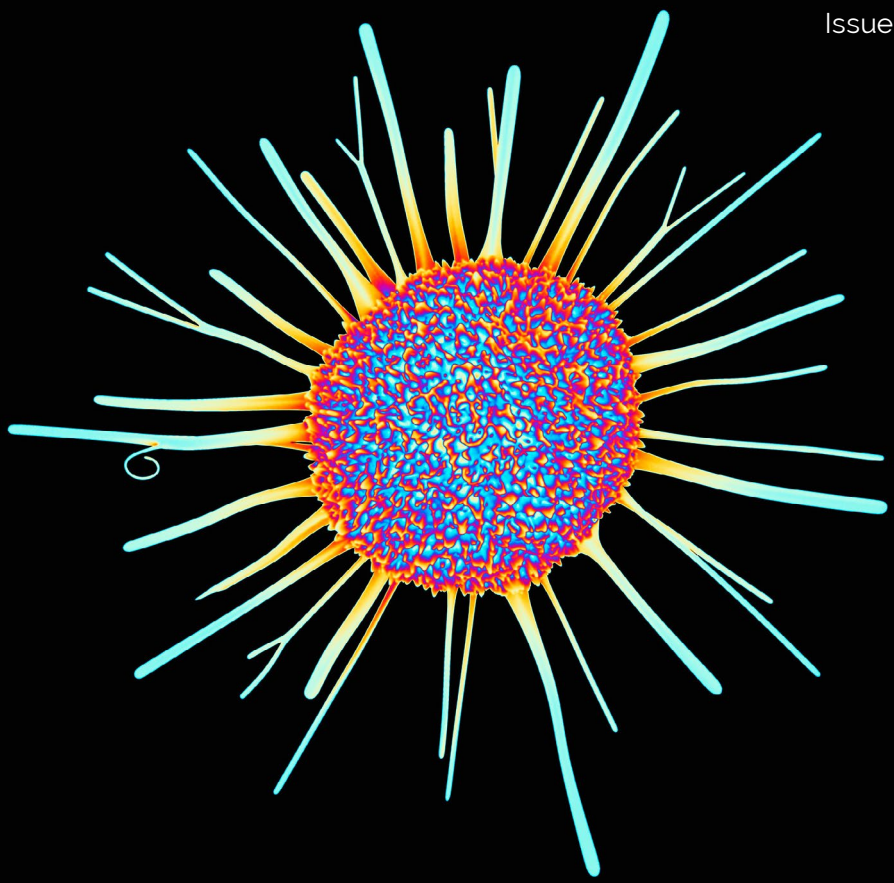
IN-PART

Showcasing university research for industry collaboration

Issue 1 | May, 2015



IN-FOCUS: ONCOLOGY

INDUSTRY INSIGHTS

IP TRENDS IN ONCOLOGY

Assessing the European and US patent landscape

Withers and Rogers LLP

DIAGNOSTICS

FUTURE FORECASTING

Predictive biomarkers for prostate cancer treatment outcomes

University of Strathclyde

THERAPIES

TARGETING CANCER

Antibody therapy successfully locates 80% of melanomas

King's College London

PATIENT CARE

TAMING RADIATION

Toll-like receptor inhibitor suppresses GI-syndrome

University of Tokyo

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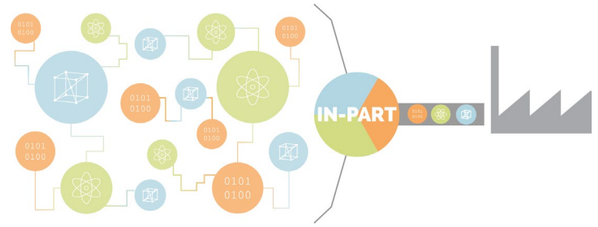

Welcome to IN-FOCUS

This issue marks the inauguration of IN-FOCUS: a digest of the latest opportunities from universities seeking commercial partners within an industry sector. As the first publication of its kind, IN-FOCUS is designed to centralise and contextualise the latest university technology for a commercially minded audience.

In our first issue of IN-FOCUS, we showcase some of the most innovative research being performed across the globe within oncology. Cancer represents not just one disease but a multitude, each with shared characteristics but ultimately requiring different approaches to treatment and patient care. It should therefore be noted that this short publication has not been designed as an all-encompassing review, rather, it is our vision to provide an informative aid to facilitate the commercialisation of research featured within the following pages.

Our overriding goal is to further aid the translation of academic research into usable treatments and technologies, ultimately for the benefit of the general public. We would like to thank all of the universities we work with as well as the sponsors of this publication, whose interaction represents a company mind-set geared towards the generation and maintenance of university-industry partnerships.

The universities we work with invite interested readers to contact them. All the technologies featured within this publication can be found at *www.in-part.com*, alongside a facility to contact the relevant technology transfer professionals at each university.

The IN-PART team hope you enjoy our first issue of IN-FOCUS, a publication that contains a plethora of exciting and innovative university research, much of which will no doubt impact our own lives in the near future.

Dr Robin Knight
IN-PART Co-founder

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IN-FOCUS

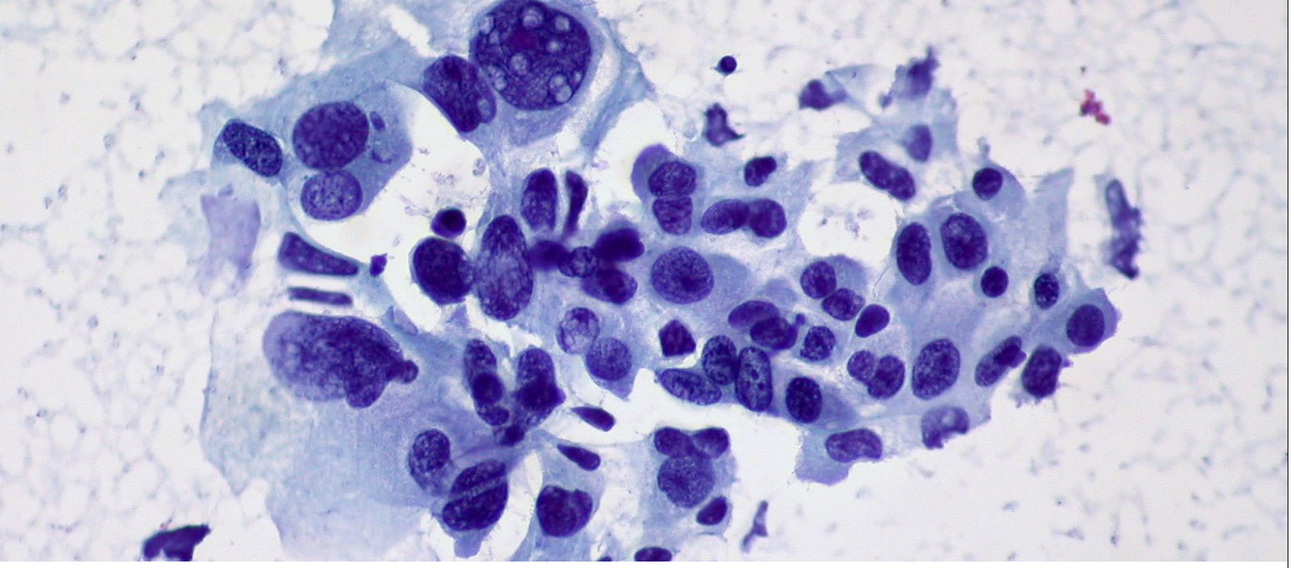
Issue 1 | Oncology | May, 2015

OPPORTUNITIES

FEATURES

[= **IN-PART** collaboration opportunity]

FEATURING RESEARCH FROM:



NON-SMALL CELL CARCINOMA OF THE LUNG: ED UTHMAN / CC BY 2.0

Diagnostics

The ability to quickly and accurately diagnose cancers at their earliest stage of development often means more effective and simpler treatment for patients. This not only requires early-stage participation from individuals for screening, but also the development of sophisticated diagnostic techniques for early-stage cancer detection. Advancing diagnostic technology is an area of active and innovative research within universities, and within this section are several novel opportunities seeking industry partners to develop them further.

BIOMARKERS

Biomarkers represent a quantitative or quantifiable biological readouts used to indicate the disease status of an individual. The discovery of biomarkers that accurately indicate disease is crucial. Below we discuss some current developments within biomarker diagnostics for lung cancer, and developing patient stratification regimes which enhance the efficacy of treatment.

Lung cancer is currently the main cause of cancer mortality amongst men, second only to breast cancer in women.[1] One explanation for lung cancer's high mortality rate is the lack of effective tools for accurate, non-invasive detection of early-stage disease.

Researchers at the University of Strathclyde have developed ribonucleic acid (RNA)-nanoprobes that bind to specific complementary genetic sequences of RNA found in tumour cells. These sequences act as biomarkers of disease, and when bound by Strathclyde's novel gold nanoprobe, their presence can be detected using laboratory techniques based on the detection of a fluorescent signal.

Strathclyde's nanoprobe technology uses a unique combination of RNA sequences for detecting disease. However the discovery of these sequences is not the only novel aspect of their technological offering; the inventors have also addressed the issue of invasive sampling. Their gold-nanoprobe technology can be used to detect genetic signatures in a very small amount of patient material - only a single Circulating Tumour Cell (CTC) is required, and can be found circulating within the blood of patients.

The University of Strathclyde is currently seeking partners to develop a prototype diagnostic tool to utilise their nanoprobe technology and unique set of molecular biomarkers for the early detection of lung cancer.

Researchers at Aberystwyth University have developed another innovative technology within the diagnostics field for lung cancer. Scientists at Aberystwyth have created an inexpensive and high-throughput screening method for diagnosis based upon the comparative detection of bacterial species within sputum samples.

By analysing the quantity and type of bacterial species present in a subject's sputum, Aberystwyth's technology is not only able to diagnose cancer by virtue of a bacterial environment, but also the stage of cancer development.

This type of technology is especially pertinent for *en-masse* detection regimes, providing a much needed solution for high-throughput screening. This is of particular need in isolated locations, and in countries not well served by healthcare services.

Aberystwyth University is currently searching for partners to develop their technique which could have a major impact on the early detection, and consequently successful treatment of lung cancer.

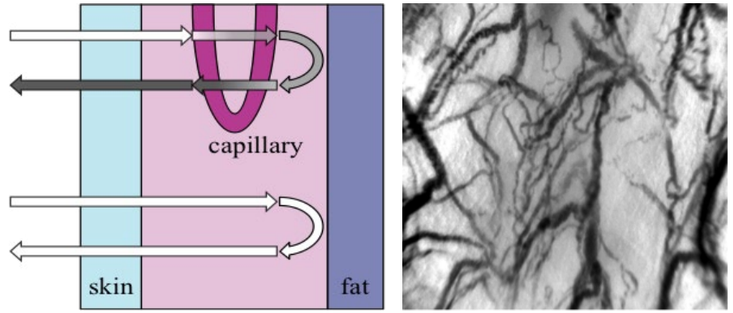


Figure 1. Left: an illustration of KCL's vascular imaging technique; green light is reflected by the sub-cutaneous fat layer, and absorbed in locations where it passes through capillaries. Right: an image showing common vasculature of the lower lip mucosae. | *King's College London*

PATIENT STRATIFICATION

The last decade has seen an increasing number of novel cancer therapies proving successful in clinical trials and making their way into the clinic. However one major challenge oncologists still face is predicting which patients will benefit most from different treatment modalities. Why are some individuals within patient groups non-responsive to treatments, whilst others are?

Researchers are increasingly trying to address this question, investing time to discover how clinicians can tell which patients will be responsive to which drug. This type of fine-tuning for the treatment of cancer at the patient-level comes under the banner of personalised medicine, where genetic and proteomic differences within individual cancers can be detected and exploited to select the most effective therapy.

Advances made within the field of sequencing have enabled this approach to be both feasible and high-throughput for patients. The sensitivity and speed of next-generation sequencing (NGS) technologies continues to increase, resulting in its use becoming commonplace in diagnostic laboratories[2].

A personalised approach to cancer therapy enables the stratification of patients into sub-groups for different types of treatment based on best-predicted therapeutic outcomes. The first footholds of personalised medicine are being made in clinics, enabling healthcare professionals to administer tailored treatment. As well as saving patients from unnecessary treatments, which often come with undesirable side-effects, it will also reduce the wastage of expensive treatments which may, ostensibly be ineffective, or even harmful in certain patients.

Two universities in particular are seeking commercial partners to further develop their work in stratifying patients for optimal treatment regimes.

King's College London (KCL) have discovered new biomarkers present in Acute Myeloid Leukaemia (AML) patients that have the potential to identify individuals who have sensitivity to highly effective PARP (poly-(ADP-ribose)-polymerase) inhibition treatment.

AML treatment programs vary but often utilise long-standing chemotherapeutic regimens with a predicted five-year survival rate of around 25%. The requirement for alternative, safe and clinically effective treatments is therefore paramount.

PARP inhibition (PARPi) therapy is used in breast and ovarian cancers with mutations of BRCA1/BRCA2, two well-known mediators of Homologous Recombination (HR) DNA damage repair.[3] The PARP family of proteins are also involved in genomic repair, working to correct single-strand breaks in DNA. The inhibition of PARP in tumours also carrying a defect in the DNA damage repair mechanism associated with BRCA1/BRCA2 leads to death of that cell. Normal cells subjected to PARPi are able to overcome their inability to repair single-stranded DNA breaks through redundancy in the DNA repair machinery, ultimately utilising alternative mechanisms such as those associated with functioning BRCA1/BRCA2 genes. PARPi is therefore a highly selective and effective treatment that impacts compromised DNA damage repair in cancer cells with defective HR machinery. The use of PARPi shows anti-tumour activity in cancers associated with the BRCA1 or BRCA2 mutation[3].

Researchers at KCL have identified novel markers for PARPi sensitivity in AML, and the underlying mechanisms accounting for the sensitivity. The researchers propose the selective use of PARPi treatment in targeted AML subgroups identified using their technology. In total, this subgroup of AML patients accounts for about 10-15% of all cases.

If utilised strategically, KCL's technology could have important implications on the design and execution of effective clinical trials using PARPi on targeted AML patients. Currently they are seeking to discuss this prospect with interested industry parties.

The University of Strathclyde is also working towards developing biomarkers to predict patient responses to treatments, in this case for prostate cancer.

Continued research efforts within the prostate cancer field are translating into new and promising therapeutic agents to treat the disease. Several of these new treatments are now being provided for patients unresponsive to first-line therapies such as androgen-deprivation.

In order to maximise the benefits and minimise the side-effects of these new treatments, researchers at Strathclyde are establishing a bank of patient-derived cancer cell lines and tissue samples to test responses to therapies. Of note, Strathclyde researchers have identified a panel of biomarkers that are associated with a poor clinical outcome. These biomarkers can be monitored to predict responses to therapeutic interventions, and assess the efficacy of second-line therapies at the patient level.

Strathclyde researchers are currently seeking partner organisations interested in utilising their research and advances within the biomarker field, for the treatment and diagnosis of prostate cancer.

IMAGING

As academic researchers develop more ways to accurately target and destroy cancerous tissues, our ability to visualise and monitor the growth and spread of tumours must keep pace. Whilst detecting biomarkers from patient samples can indicate the presence of malignant cells, determining the location of tumours and monitoring the expression of significant biomarkers from biopsies is the gold-standard for diagnosing cancer and metastases.

Determining the location of a tumour is regularly performed through non-invasive imaging techniques using X-rays and MRI. Now, a revolutionary technology developed at KCL may also be added to a clinician's imaging arsenal.

Employing a state-of-the-art reflective optical technique, researchers from KCL are able to analyse blood vessels and blood flow via non-invasive, direct microscopic examination.

Real-time assessment of the blood supply to a particular tissue, without the use of staining or contrast agents, can enable the direct visualisation of a tumour. Similarly, key hallmarks of malignancy such as new blood vessel growth (angiogenesis) can be assessed, enabling more effective monitoring of suspicious lesions *(see figure 1)*.

Multiple other applications exist for this new and inexpensive imaging technology, such as determining optimal biopsy locations, and when required, real-time precision guidance for excision during surgery.

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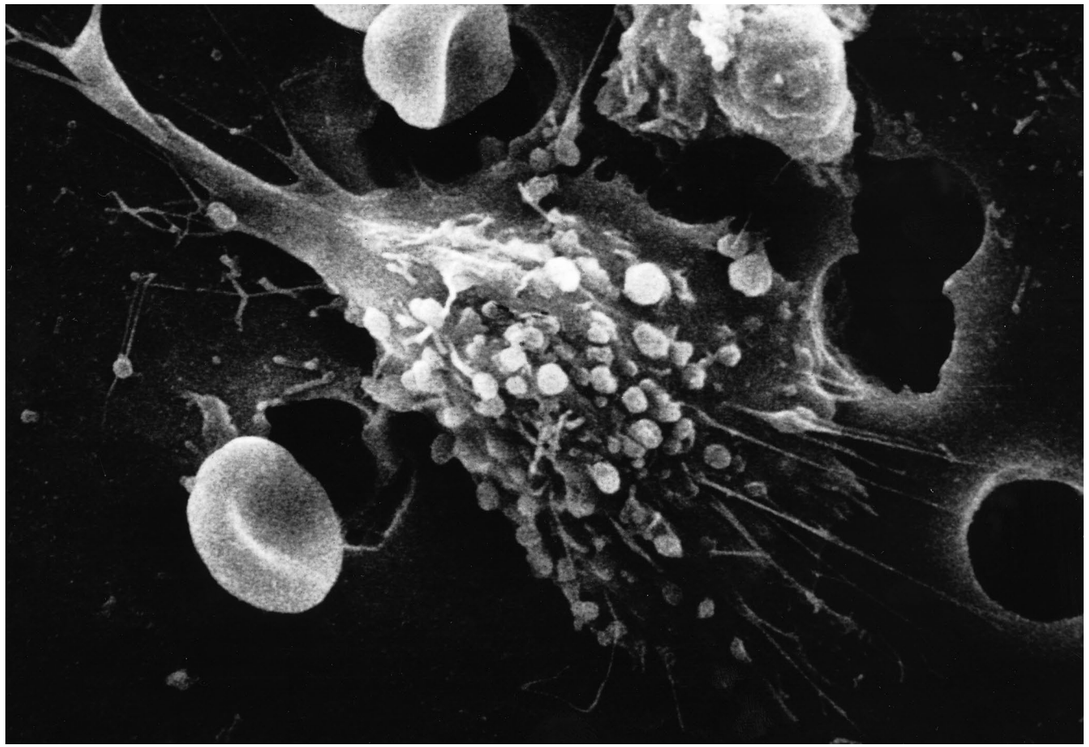
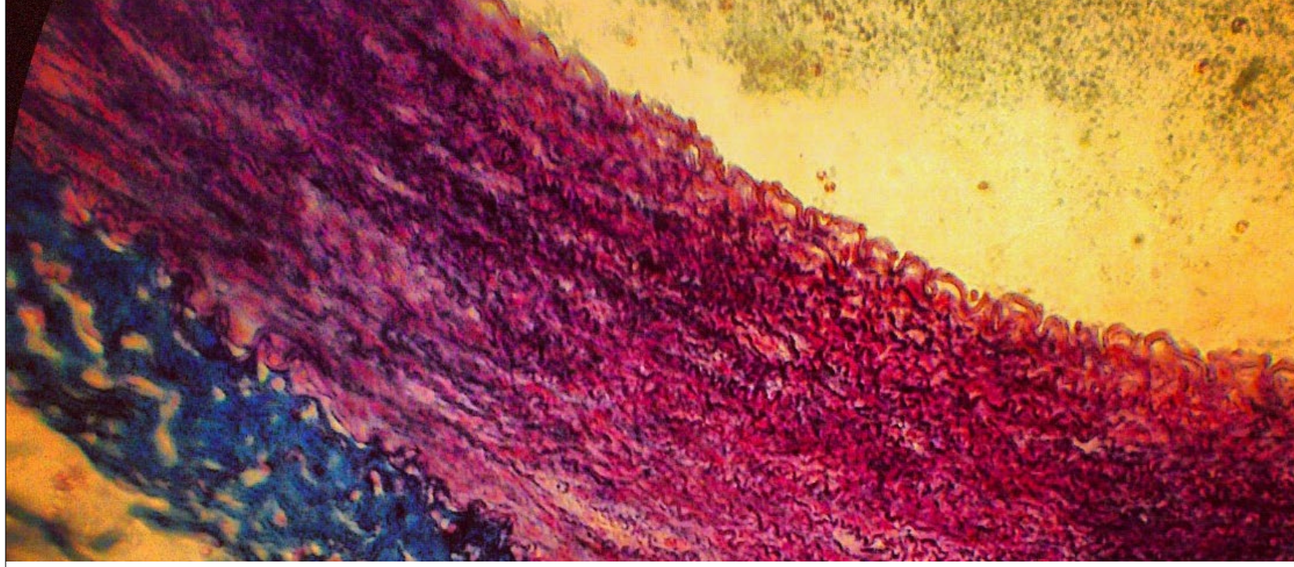


Step one of a six-step cancer cell death sequence of an invading cancer cell | *Susan Arnold / Dr. Raowf Guirguis / National Cancer Institute*



ARTERY HISTOLOGY : IYAD LAYKAH / FLICKR / CC BY 2.0

Therapies

Our knowledge about cancer and the number of high-tech treatments available has significantly improved since the disease was first described 5000 years ago[1]. Major advances in therapy have largely occurred within the 20th century, with the implementation of radiotherapy at the turn of the century, followed by the birth of modern chemotherapeutics and their accrual through preceding years. We are now living in an age in which cancer survival rates are at their highest[2], with new treatments becoming increasingly innovative and sophisticated, leading to successful patient outcomes.

ANTIBODY IMMUNOTHERAPY

Monoclonal antibody therapy represents an off-the-shelf treatment for specific types of cancer. Prescribing these treatments on a case-by-case basis in accordance with patient-specific parameters can optimise successful outcomes.

Pioneering advancements were made in the field of cancer therapy last year, where the latest range of immunotherapies designed to "take the brakes off" the anti-cancer immune response showed the most promising clinical successes[3]. Classified as checkpoint blockade therapy *(CBT, see box 1)*, antibodies have been produced to bind and block molecules expressed on tumours that help evade the immune system's anti-cancer response, and could herald the next generation of cancer immunotherapy[4].

Checkpoint blockade is now an established treatment regimen with proven efficacy in the clinic, and with huge potential to further increase the effectiveness of cancer treatment regimens. However, the applications of antibodies within oncology are myriad, and their acute specificity allows them to target different tumour types effectively. As is such, tumour targeting antibodies can be harnessed to highlight such tumours, targeting them for downstream clearance by secondary agents. Numerous targeted therapies utilising antibodies are currently under development.

Researchers at King's College London are seeking partners to further develop a monoclonal antibody that targets melanoma. The targeted molecule (chondroitin sulphate proteoglycan-4) is over-expressed on the surface of >80% of melanoma cells. Proof-of-concept studies regarding the efficacy of the antibody have been achieved in a human xenograft model *in vivo*.

The further novelty of this technology is the use of an immunoglobulin E-isotype (IgE) antibody, opposed to the usual IgG class. Mechanistically, antibodies bound to a tumour activate its clearance by in turn being bound by cells of the immune system which target the cancer for destruction. IgE antibodies have additional benefits

***Box 1.* CHECKPOINT BLOCKADE THERAPY:** The tumour microenvironment induces a 'regulatory' setting which dampens the anti-tumour immune response; checkpoint blockade therapeutics aim to counter this effect. Blockade of CTLA-4 has so far been the most successful example of this treatment type. CTLA-4 is a molecule expressed on some types of tumour that hinders the activation of a subset of immune cells called 'T-cells'. The activation of T-cells provides a crucial cellular component in the response against cancer. Use of a monoclonal antibody treatment targeting CTLA-4 (called Ipilimimab, produced by Bristol-Meyer Squib), led to a significant increase in the survival of patients with metastatic melanoma in a phase III trial[4]. Another notable therapeutic agent utilising this idea of 'releasing the brakes' of the immune system, is Merck's PD-1 blockade drug MK-3475 (Lambrolizumab), which has shown promising results in a phase I expansion study[8]. Current and prospective trials are ongoing with this class of drugs, and several drug combination studies are currently in the pipeline.

over IgG isotypes because of their increased affinity for immune cell receptors, which when engaged, mediate the clearance of the antibody bound tumour. This high affinity binding of IgE results in enhanced clearance of IgE antibody-bound tumours[5].

The potential for antibody therapy extends further than highlighting cancerous cells to the immune system. Antibodies have the potential to also specifically direct toxic drugs to cancerous cells, in complexes known as antibody-drug conjugates (ADC). Often the process of delivering a toxic molecule into a cell by ADC relies upon internalisation of the complex. Due to the need for internalisation, antibodies used in ADCs often target cell surface receptors, mimicking the usual complementary signalling molecule by binding and interacting at the same critical points on the receptor. This leads to activation and internalisation of the receptor complex - usually the starting point in a biological signalling cascade – resulting in uptake of the toxic drug bound in the ADC, which when inside the cell becomes active, destroying the cancerous target[6].

One of the most recent antibodies proposed for use in ADC, targets the Thyroid Stimulating Hormone Receptor (TSHR) and has been developed by scientists at King's College London.

The TSHR is primarily found on the surface of healthy thyroid epithelial cells but is also highly expressed in Differentiated Thyroid Cancers (DTC). As is such, KCL's anti-TSHR antibody has been generated for use in DTC;

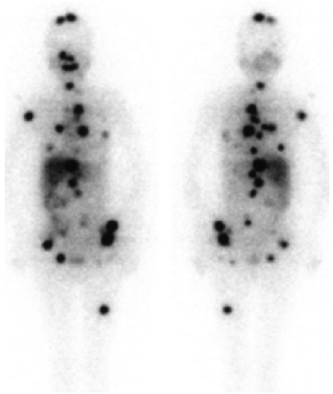
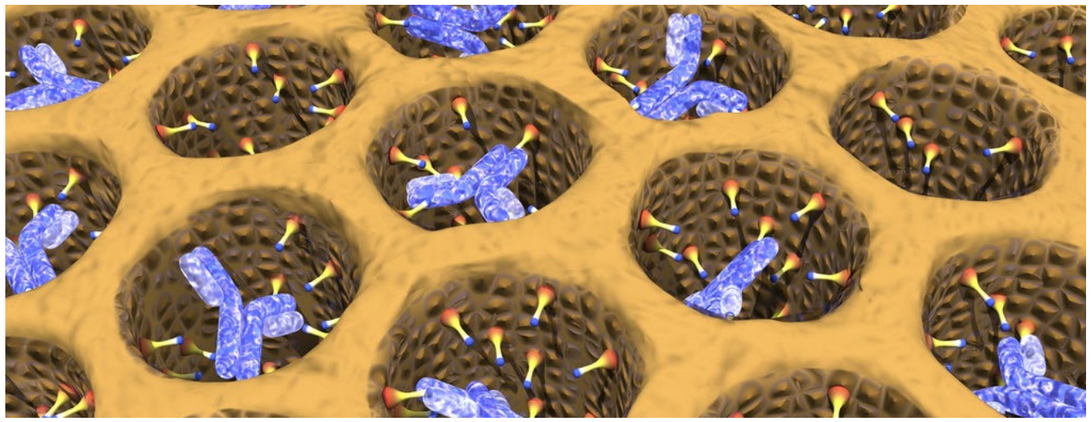


Figure 2. SPECT imaging showing extent of metastases in a patient with Differentiated Thyroid Cancer | *King's College London*

while currently treated by removal of the thyroid gland, 10-30% of patients suffer from recurrent, usually fatal, metastatic disease[7].

Problems surrounding the diagnosis of metastases in thyroidectomised DTC patients, and the lack of specific therapeutics, may now be overcome using these monoclonal IgG antibodies which have demonstrated efficacy both for imaging metastasised DTC *(see Figure 2)* and for specifically targeting the delivery of chemotherapy to tumour sites.

The dysregulation of a family of structurally related transmembrane signalling molecules, called ErbB, is linked with tumour formation and growth. Under normal



An artists' depiction of anti-cancer antibodies being held by chemically functionalized mesoporous silica | *US Government / Department of Energy*

conditions ErbB receptor signalling plays a fundamental role in the regulation of key cellular processes including survival, proliferation and differentiation. In cancerous settings, mutations within ErbB receptor genes leads to an increased level of receptor expression on cell surfaces, and as a consequence, hypersignalling and increased activation of the pathway. This results in increased tumour growth and the rise of tumours more resistant to routine chemotherapies[9].

Antibody therapies targeting family members of ErbB have resulted in major clinical success. The most commonly known drug, Trastuzumab, targets the HER2 receptor which is over-expressed in some forms of breast cancer. Trastuzumab, more commonly known as Herceptin (as marketed by Genentech), disrupts HER2 signalling and thereby arrests unchecked cellular growth[10].

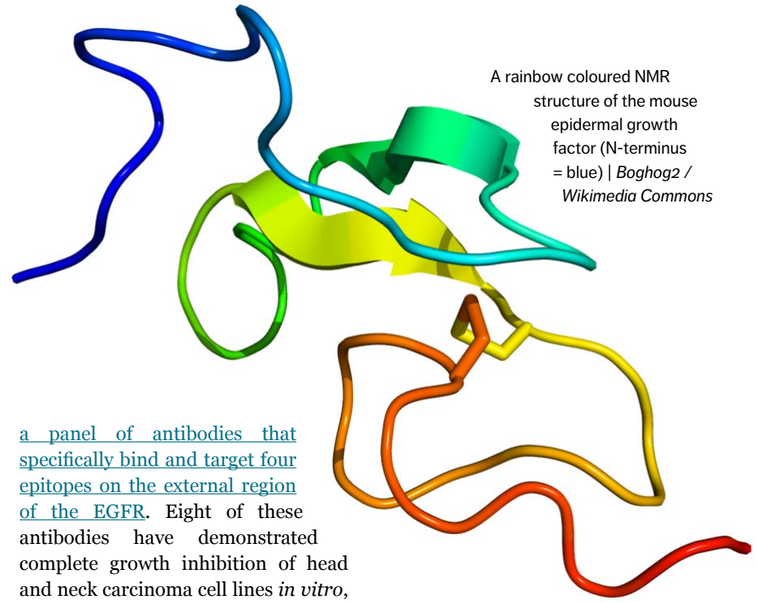
High levels of HER2 overexpression are found in approximately 20-30% of metastatic breast cancers, and it is based on this anomaly that significant efforts in drug discovery have been focused[11].

The Institute of Cancer Research (ICR) have developed and raised a panel of seven monoclonal antibodies that recognise HER2. These antibodies have been characterised extensively *in vitro*, and their therapeutic potential has been demonstrated *in vivo* using breast cancer xenograft models. Pilot clinical studies have also been carried out, which demonstrate effective localisation of radiolabelled antibody to tumours in patients with breast cancer.

The ICR is currently seeking an industrial partner interested in one or a selection of these antibodies for further development for a multitude of potential applications.

Another member of the ErbB family is Epidermal Growth Factor Receptor (EGFR, also known as HER1), the over-expression of which has been linked to a number of human malignancies including cancer of the breast, brain, bladder, head and neck, pancreas and lung[9].

The ICR have also developed a panel of antibodies that specifically bind and target four epitopes on the external region of the EGFR. Eight of these antibodies have demonstrated complete growth inhibition of head and neck carcinoma cell lines *in vitro*, and restrict the growth of breast and vulval carcinoma cell lines over–expressing the EGFR.



A rainbow coloured NMR structure of the mouse epidermal growth factor (N-terminus = blue) | *Boghog2 / Wikimedia Commons*

In addition, the ICR also have impressive *in vivo* data showing that three of the antibodies cause complete regression of established head and neck tumour xenografts, with one antibody inducing the complete regression of a breast carcinoma xenograft.

The institution is currently seeking to license or develop these antibodies further with an industrial partner for EGFR targeted therapies or diagnostic applications.

CELL THERAPY

Adoptive Cell Transfer *(ACT, see box 2)* has seen a rise in popularity amongst biotech companies in recent years. There are several ways in which ACT can be utilised in an oncology setting. One technique is to isolate a patient's T-cells, identify those that specifically recognise a tumour, and greatly expand their numbers in the lab before re-infusing them back into the patient in an activated state, enabling them to destroy their tumour target[12].

A major stepping-stone for researchers is maintaining the characteristics of isolated T-cells (and other immune cell types) once they have been isolated and expanded *in vitro*. Technologies are now emerging that will allow ACTs to overcome these barriers and thereby increase the efficacy of the treatment and its therapeutic potential.

Researchers at The University of York have developed a technique to overcome the maintenance of cellular characteristic *in vitro* cell culture. Their method enables simple production of lymphoid stromal cells *en-masse*, resulting in the creation of a 3D cellular-network of stromal cells which can support the scale-up of immune cells, and crucially maintain their essential functions *in vitro*. This technology has applications for the expansion of T-cells for ACT, as well as for expansion of 'antigen-presenting cells' in ACT, which, when infused back are responsible for activating tumour specific T-cells *in vivo (box 2)*.

TARGETED MOLECULAR THERAPY

Successfully halting the production of proteins associated with tumour growth, immune evasion or cell death is a major goal in treating cancer. When RNA interference (RNAi) was

first described it earned the paper's authors, Fire and Mello, a Nobel prize[13], such is the promise of their technique in reducing, or entirely switching off the expression of specific genes. In the context of oncology, the clinical use of RNAi has the capability to switch off tumour-promoting oncogenes.

There are three different types of RNAi, each of which utilises double-stranded or single-stranded RNA to interrupt the production of a specific protein. However, RNAi faces many barriers to its successful deployment in clinical settings[14].

Currently there are two major barriers to successful RNAi therapy; i) Accurate delivery of therapeutic molecules to specific tumour targets; and ii) their evasion from degrading-enzymes following cellular uptake[15]. Current innovations available for industry collaboration aimed at increased accuracy of RNAi delivery are discussed in the Drug Delivery section of this issue.

RNAi based therapies which have successfully targeted tumours, find themselves subject to the cell's proteolytic machinery, and are quickly degraded before they have elicited their desired effects.

To overcome this, researchers from the University of York have developed a 'crook' modification for siRNA. York's additional 'crook' sequence for siRNA confers resistance to degradation following cellular uptake, significantly increasing the half-life of the molecule and thus the efficiency of the targeted protein's inhibition.

In addition, this technology provides a mechanism to detect the siRNA within tissues, enabling resolution of individual cells containing the siRNA. The ability to gather this type of information is invaluable for the accurate assessment of RNAi biodistribution, showing researchers and clinicians if the treatment is reaching the target site.

Several other universities pursuing drug candidates for cancer therapy featured on IN-PART are also seeking partners to further develop their potential. These therapies do not provide the same molecular targeting as RNAi, nor the degree of tumour specificity conferred by antibody-based therapies, but instead elicit their anti-cancer properties from targeting signalling pathways which are over-activated in tumours.

Box 2. **ADOPTIVE CELL THERAPY (ATC):** The use of T-cells for ATC is now a widely studied field with multiple clinical trials ongoing, many of which are showing encouraging results and patient outcomes[12]. T-cells are an essential part of the immune system's cellular response to cells infected by invading pathogens, or undergoing cancerous transformation, and are responsible for destroying them and supporting other immune cells with the same task. The destruction of cancerous cells by T cells is often hindered by the tumour microenvironment and the intrinsic mechanism for the body's immune system not to target 'self'. By taking a tumour biopsy, researchers are able to isolate underactive tumour specific T-cells within the cancerous tissue. A variety of techniques can then be employed, and are still in development, that can re-engage these cells to identify and destroy cancerous cells; whether by genetic manipulation or providing a stimulating/activating environment in vitro. These cells now primed to destroy the cancer, are expanded before re-infusion into the patient. Similarly, other cells of the immune system crucial for provoking a strong immune response can be extracorporeally manipulated before being administered back into a patient to generate an immune response sufficient to destroy the tumour - such as antigen-presenting cells.

Apoptosis is the process of regulated cellular death. During normal cellular development cells die via apoptosis through age, and as a mechanism to control cell populations. Similarly, if damage occurs to cells through the action of invading organisms or as collateral damage resulting from an immune response, apoptotic pathways will be activated[16]. Cancers may often use the expression of anti-apoptotic proteins to promote unchecked cellular growth, preventing programmed cell death.

The University of York is seeking to target the enhanced activation of anti-apoptotic proteins in cancer cells in a bid to exploit this over-activation to kill tumour tissues, while healthy cells remain unaffected.

Using molecular approaches to inhibit the production of anti-apoptotic proteins is one potential route to halting tumour growth. Two targets of particular interest are Sirtuin 1 (SIRT1) and a c-Jun N-terminal kinase (JNK) gene member. The University of York is currently seeking industry partners to further explore the possibility of targeting cancer in this novel way, and welcomes contact from interested parties.

An additional molecular pathway exploited by cancers results in the activation of the enzyme, autotaxin (ATX). ATX controls the level of lysophosphatidic acid (LPA), an important phospholipid used for normal cell signalling. However, it's activity is also strongly linked to abnormal cell migration in disease settings[17].

The University of Strathclyde has produced a library of candidate compounds that inhibit the action of ATX (showing efficacy *in vitro),* which could have a profound effect on lung disease progression, including cancer growth and metastases. Currently, the university is seeking partners to further explore the potential of these novel compounds in disease settings.

Other research performed at the University of Strathclyde has revealed high levels of Sphingosine Kinase 1 (SK1) in tumours from breast cancer patients. Furthermore, their work has also shown the ability of SK1 to induce resistance in breast and androgen-independent prostate cancer cells, highlighting its potential role in generic cancer resistance.

When cancer-resistance to chemotherapy occurs in the absence of effective second-line therapies, the tumour inevitably progresses to disseminated metastatic disease. It is therefore an area of great therapeutic interest to understand how resistance develops and whether it can be prevented.

Investigators at Strathclyde have developed novel sphingosine kinase inhibitors for the treatment of cancer. This represents an exciting prospect, as this action has the ability to enhance the efficacy of current chemotherapeutics, namely by overcoming the significant problem of the development of resistance.

The University of Strathclyde's SK1 inhibitors have been developed to promote the enzyme's degradation, enabling a prolonged effect on reducing enzyme activity. Contact from companies and organisations interested in developing or licensing this technology are encouraged.

While the dysregulation of signalling within cells can lead to tumour development through unchecked-cellular growth, reciprocal interactions between the cancerous cells and the surrounding cells and tissues, dubbed the 'tumour microenvironment', co-evolve to promote the growth, invasion and metastasis of the tumour.

Large-scale studies have identified numerous key proteins and molecular pathways that are overexpressed in malignant cells, a number of which have been described previously in this issue (ErbB, Sirtulin1). Another pathway overexpressed within the tumour microenvironment is inflammatory in nature, relying on NF-κB/IKK activation and signalling[18].

The University of Strathclyde have also developed a series of first-in-class IKKα inhibitors; a protein of increasing importance in prostate cancer. These inhibitors are effective at nanomolar concentrations, and have been shown to induce the arrest of cancer cell growth.

The University of Strathclyde is now seeking industry partners to further develop these technologies for therapeutic use.

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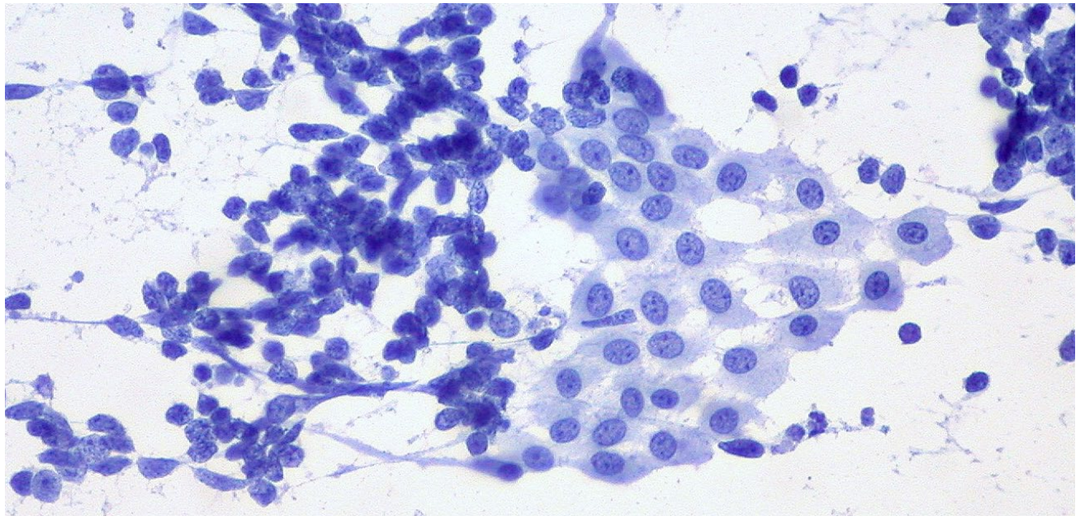
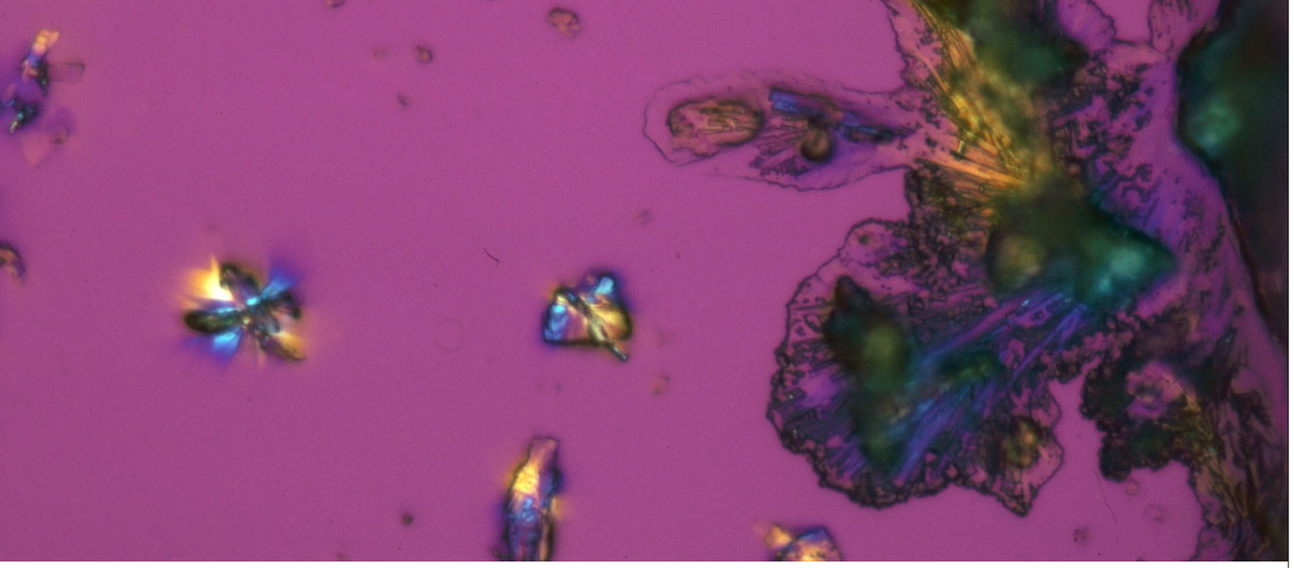


Small cell lung carcinoma vs. benign mesothelial cells, showing fine-needle aspirate of a pleural-based lung mass | *Ed Uthman / Flickr / CC BY 2.0*



CIS-PLATIN CRYSTALS: LARRY OTSBY / NATIONAL CANCER INSTITUTE

Drug Delivery

Cancer represents a host of diseases, each with different requirements for successful treatment. Whilst the development of new drugs for specific cancer types is vital, just as important is the ability to specifically target and effectively deliver these drugs to tumour sites or into malignant cells. Drug delivery is a major research focus for universities using IN-PART who are developing innovative technologies to enable the effective delivery of therapies.

PROTECTING CARGOES

Researchers at King's College London have produced a novel system for delivering sensitive RNA cargoes into cells using a pH sensitive peptide (called ConFectin) that complexes and protects its RNAi cargo until taken up by cells in a process called endocytosis.

The ConFectin complex, once taken up into cellular endosomes, is subjected to a lower pH than within the extracellular milieu. The shift to a more acidic pH within endosomes frees the active molecules from the protective ConFectin peptide, enabling disruption of the endosomal membrane and subsequently – in the case of RNAi – interaction with target cellular mRNA in order to silence the production of target proteins. Importantly, the ConFectin complex protects nucleic acid cargoes from the action of nucleases, overcoming a major obstacle for clinical therapy.

Researchers at the University of Bristol have also developed a protective strategy for the delivery of therapies into target cells, and seek commercial partners to develop their technology which was recently described in a study published in Science Magazine[1].

Nano-cages of alpha-helical coiled coil peptides act as self-assembling building blocks forming hollow spheres *(see Figure 3 and 4)*. These structures mimic natural encapsulation architecture and are able to encase and protect therapeutic molecules for targeted drug delivery.

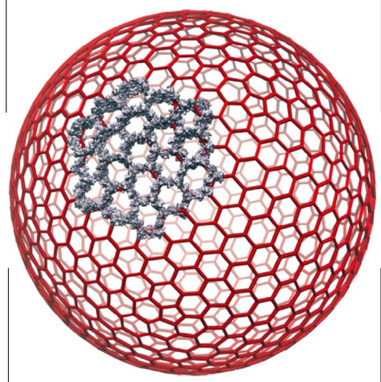


Figure 3. A computation model of a SAGE framework and molecular structure

A further innovative technology for encapsulating sensitive therapies, has been developed by the University of Tokyo. Utilising synthetic micelle structures called polyion complexes, Tokyo researchers are able to incorporate key cargoes for the successful delivery and treatment of several cancer types.

The basic composition of a polyion complex (PIC) is achieved by mixing block co-polymers and drugs. These components then self-assemble to form nanometer sized micelles[2].

Researchers at the University of Tokyo have used PICs for combination therapy, where two agents have been incorporated into a micelle, and early *in vitro* and *in vivo* data shows a high anti-tumour effect within various xenograft models of cancer.

Notably, anti-tumour effects using PICs for therapy have also been observed in cisplatin-resistant cancer, Epirubicin resistant cancer and metastatic cancer.

TARGETING CANCER

While the delivery of synthetic drugs into tumours is a successful avenue for developing an effective therapeutic strategy, academic groups are also investigating the repurposing of natural vehicles for the delivery of genetic cargoes, as well as their use in specifically destroying cancer cells.

In line with this approach, the University of Tokyo has genetically engineered measles virus (MV) as a therapy to specifically target cancer, and by virtue of its intrinsic mechanism of action as a lytic virus, destroy the cells.

Typically, MV enters cells using the signalling lymphocyte activation molecule (SLAM), which is expressed on cells of the immune system. Researchers at the University of Tokyo have generated a recombinant MV, selectively unable to use SLAM (rMVSLAMblind). Rather, the rMVSLAMblind virus uses PVRL4 as a receptor for entry into cells. PVRL4 expression has been reported as a tumour cell marker for breast, lung and ovarian cancers, and thus represents a suitable target for selectively infecting cancerous cells.

The genetically engineered MV, rMVSLAMblind, has been used to efficiently infect cancer cells, and has showed anti-tumour activity against tumour xenografts in immunodeficient mice. Data has also been recorded on safety *in vivo*, and the university has additional data that shows the successful administration of the therapy by intravenous injection[3].

The targeting of therapeutic genetic material like RNAi, specifically into hard-to-reach cancerous cells, is something many gene therapy techniques strive to achieve, and as such, has been a research focus at the University of Strathclyde, where researchers have developed a new technology.

From "seek-and-destroy" laboratory tests using their novel technology, there was an observed 90% disappearance of skin cancer tumours. More details about this promising discovery can be found by contacting the university, who are now seeking partners to develop or license this oncology product, designed with a high level of efficiency for intra-venous administration.

As has been discussed in this section, a major issue within cancer therapy is drug delivery. One cancer type that particularly suffers from inefficient delivery is lung cancer.

The main drugs used in the treatment of lung cancer are platinum-based cytotoxic drugs such as cisplatin. However, cisplatin is poorly absorbed orally, and only 0.1% of the dose reaches the lungs after intravenous administration where it has a short residence time. Likewise, cisplatin has poor solubility and renal toxicity is a major problem in patients.

In order the meet the required need for a better therapy and delivery using cisplatin, the University of Strathclyde have developed candidates for an improved formulation that can be administered by inhalation. This has great potential to improve lung cancer treatment through improved efficacy along with reduced toxicity, compared with conventional intravenous cisplatin therapy.

Traditional cancer therapies such as radiotherapy and chemotherapies have always been restricted in their safety and efficacy because they induce collateral damage to healthy cells, which in extreme cases can lead to the growth of secondary tumours.

Reducing the exposure of healthy cells and tissues to toxic chemotherapies is difficult, especially when a drug is administered systemically via the blood stream. A very innovative solution to tackle this fundamental problem has been researched at the Okinawa Institute of Science and Technology (OIST), where researchers have developed a method of releasing liposome encapsulated drugs on a sub-second time scale by pulsed laser irradiation.

The variety of properties that can be controlled for laser irradiation enables far greater resolution in the area of drug delivery, enabling multiple factors to be accurately altered from patient to patient.

Data from the university shows that the characteristics of the laser pulse-train can determine the drug concentration, and temporal release profile of liposome encapsulated drug. The potential for this technology to enter the clinic as a routine clinical tool has exciting prospects for improving patient treatment. The university is interested in speaking with industry partners regarding the licensing of this technology.

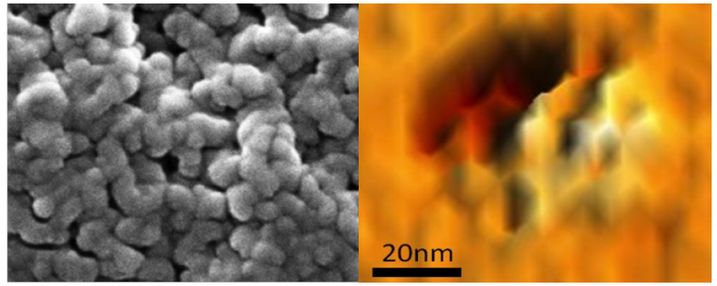


Figure 4. Left: electron micrograph of SAGE particles. Right: AFM of the SAGE surface | *OIST*

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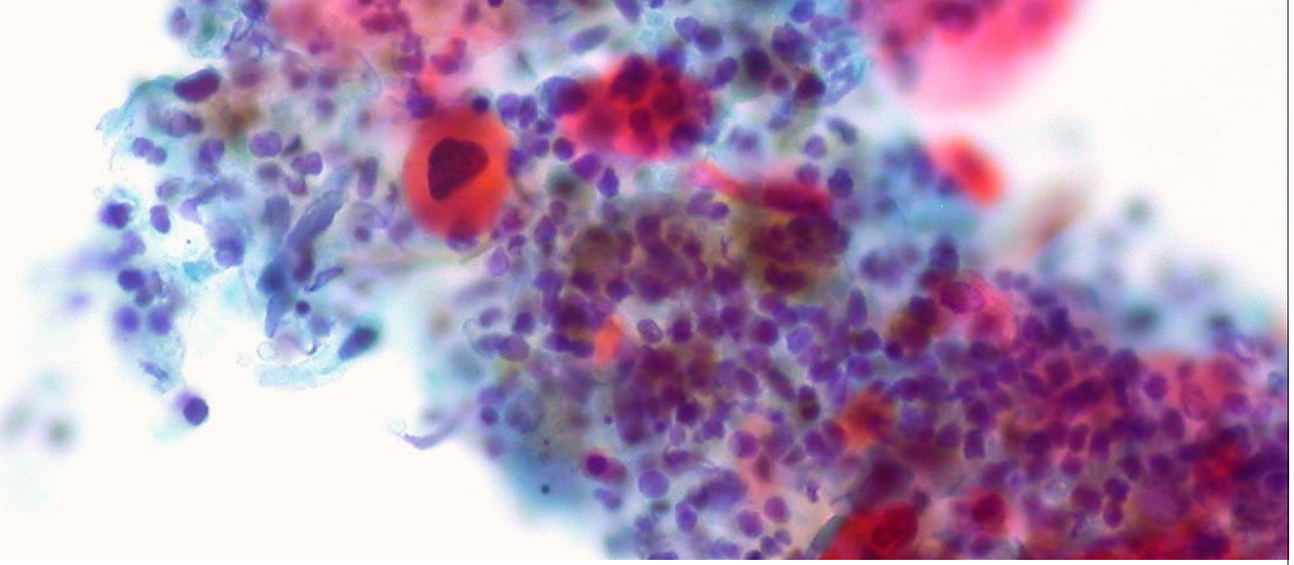

Patient Treatment and Care

Following cancer diagnosis, effective patient care and accurate treatment is paramount to successful outcomes and patient health. Below are several opportunities from universities who have developed innovative technologies geared toward the enhancement of radiotherapy; both in its administration and to reduce its associated side-effects.

RADIOTHERAPY

Radiotherapy is a highly implemented low-cost treatment route for cancer, used on approximately 50% of all patients. The effect of radiotherapy is dependent on the absorbed dose delivered to the target area and surrounding critical organs[1]. As such, accurate administration of radiotherapy is crucial for the optimal treatment of tumours.

Researchers within the Radioisotope Physics team at the Institute of Cancer Research (ICR) and the Royal Marsden Hospital (RHM) have developed new methods and techniques for image quantification and dosimetry calculations. Over the last few years they have developed a software package called qDose, coded by professional software engineers, which uses image-based dosimetry to calculate 3D absorbed dose distributions of radiotherapy. This software package can provide personalised treatment planning for molecular radiotherapy, and can be modified for use with any radionuclide.

The ICR and RHM's technological approach to radiotherapy will significantly improve the effectiveness of radiotherapy treatments. The ICR is currently seeking a licensing partner to take their qDose product to market; the team are also interested in collaborating to further develop the software.

MANAGING SIDE-EFFECTS

Patients who require radiotherapy often suffer from highly debilitating side-effects. This is especially true for treatments carried out in the abdomen, pelvis, and/or rectum, which often results in nausea, vomiting, and diarrhoea.

When a wide area of the abdomen is irradiated during treatment, exposure and radiation damage of the intestine often occurs. The intestine is highly sensitive to radiation exposure, and is responsible for these adverse effects in patients following treatment[2].

The tumour suppressor gene p53, is considered to be a therapeutic target for Gastrointestinal Syndrome. Unfortunately, inhibition of p53 function impairs DNA repair[3]. Consequently no feasible prevention or treatment protocol for radiation-induced Gastrointestinal Syndrome currently exists.

Research currently being undertaken at the University of Tokyo seeks to develop a new treatment protocol to suppress radiation-induced Gastrointestinal Syndrome without affecting DNA repair.

Data has already been gathered that shows a reduction in adverse radiotherapy side-effects by inhibiting Toll-like receptor 3 (TLR3) activation. There is the potential for the TLR3 inhibitor used in these experiments to be developed as a drug that can be taken prior to radiotherapy treatment.

Moreover, observations have been made in mice that show alleviation of symptoms when administering the TLR3 inhibitor after the irradiation event. Translating this into a human setting may enable TLR3 inhibitors to be taken following radiation therapy for the treatment of Gastrointestinal Syndrome.

The adverse-effects experienced by patients who receive radiotherapy (such as those described above) vary between vary between individuals. Certain types of radiotherapy can even induce side-effects that are life-threatening in their severity. It is therefore a major concern amongst healthcare professionals that the treatment they provide is not only effective in targeting the tumour, but also in preventing radiotherapy-induced patient morbidity where possible.

Researchers at Brunel University London have developed a crucially needed patient-specific assay that can provide detailed information about which patients are susceptible to suffering severe side-effects from radiotherapy treatment regimes.

Their diagnostic test measures DNA damage and repair in blood lymphocytes from patients exposed to gamma radiation, and has the capacity to rapidly and reliably predict side-effects in patients.

Brunel University London's technology relies upon novel biomarkers, which can be used in conjunction with standard laboratory techniques to identify patients who will experience severe reactions to radiotherapy. Knowledge provided by this assay will enable other treatment routes to be utilised to minimise the risks to patients' health.

Brunel University London is currently seeking development partners to bring this technology to market.

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A note from IN-PART

We would like to thank all of the universities who provided their latest research to IN-PART. These universities represent those with the foresight and vision to enhance their presence amongst the commercial R&D community, and as such, the potential impact of their academics' research on the world.

IN-FOCUS is now scheduled for publication every quarter. Each issue will cover university opportunities for collaboration within Natural Sciences, as well as Engineering and high-tech R&D sectors. Our next issue within the Life Sciences stream will focus on Medical Technologies. If you would like to secure a copy of this issue, email info@in-part.co.uk, with the subject: "IN-FOCUS subscription".

If you are from a university and would like your academics research to be featured, or your laboratories and expertise highlighted, in IN-FOCUS, email info@in-part.co.uk with subject: "IN-FOCUS feature".

IN-FOCUS:

Translating oncology research at the University of Strathclyde

Translational oncology research at the University of Strathclyde is extremely diverse. It includes pre-clinical drug discovery programmes, a novel inhalable formulation of cisplatin and other drugs, laser plasma-driven very high energy electrons (VHEE) for cancer therapy, and gold-nanoprobes for early cancer diagnosis.

Together with University of Glasgow and the NHS, Strathclyde have established unique and robust patient-derived prostate cancer cell lines for the production of xenografts, for use in the validation of predictive biomarkers.

FIRST-IN-CLASS IKK-ALPHA SELECTIVE COMPOUNDS

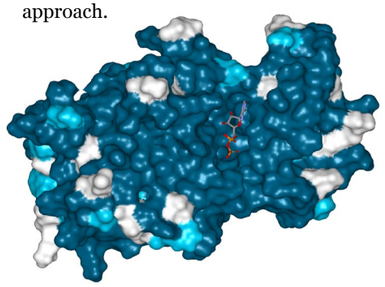
With support from Cancer Research UK, Prostate Cancer UK and the Medical Research Council, scientists at Strathclyde have developed a first-in-class, selective lead series of IKKα inhibitors with nanomolar potency which can arrest the growth of cancer.

IKK-a Lead Series:

- Potent, selective, chemically tractable
- Broad selectivity (>100 fold) against panel of 40 representative kinases
- Low Mwt. (250 - 350) and good ligand efficiency
- Orally bioavailable
- Appropriate ADME properties (permeability, plasma stability, plasma protein binding, cyp450/HERG inhibition)

The pharmaceutical industry has devoted considerable effort to generating NF-κB pathway inhibitors but reported inhibitors have either been pan-IKK or IKKβ selective. To date there have been no reports of IKKα selective compounds.

Despite being proposed as a target for treating inflammation, inhibition of IKKβ has been associated with various side effects including development of inflammatory skin disease, gastrointestinal side effects[1] and severe liver toxicity[2]. By contrast, knock-in mice for catalytically inactive IKKα do not display any adverse effects. Development of selective IKKα inhibitors is therefore an attractive approach.



IKK-α overlaid with IKK-ß, ADP in the active site. Dark blue are identical residues, light blue not-identical but similar, and white - non-identical and dissimilar.

A THERAPEUTIC RATIONALE

The rationale for achieving clinical benefit in castrate resistant prostate cancer (CRPC) by selective inhibition of IKKα comes from recent clinical data and over 15 years of increasingly compelling target validation work

Michael Karin, a collaborator of Strathclyde's from the University of California San Diego, has shown that siRNA rundown of IKKalpha in transgenic adenocarcinoma mouse prostate with emerging CRPC results in a significant and reproducible 3-4 week delay in CRPC re-emergence. An extrapolation to human CRPC suggests a 2-3 year delay in progression to CRPC for patients undergoing androgen ablation therapy (AAT) if combined with IKKα inhibitor treatment.

The study also demonstrated that the nuclear translocation of IKKα is a component of the inflammatory response elicited by the death of the primary tumour and contributes directly to the failure of AAT.

Whilst compelling clinical data for IKKα as a target has been generated for CRPC, evidence for its role in pancreatic cancer,[3-7] chronic lymphocytic leukaemia (CLL),[8] multiple myeloma,[9] sub-types of breast cancer,[10,11] and colorectal cancer is becoming increasingly persuasive.[12,13]

Responding to this situation, the University of Strathclyde have developed a first-in-class, lead series selective for IKKα with nanomolar potency for optimisation. Ongoing collaborations investigating the effectiveness of these compounds in CPRC, pancreatic cancer, CLL and multiple myeloma and are on track to produce an advanced lead compound for full preclinical development and future clinical trial testing.

AN UNMET NEED

There are 36,000 new cases of prostate cancer reported every year and this figure is predicted to double over the next 20 years. Of 1 in 8 men diagnosed with prostate cancer, 25% die of metastatic disease.

Current treatment for prostate cancer includes surgery, radiotherapy, AAT and chemotherapy. In advanced disease treated with AAT, CRPC, which causes 10,000 deaths annually, arises in 80% of patients and is linked to poor prognosis with only palliative treatments available. Newly approved CRPC treatments have only extended survival by 3-9 months.

For pancreatic cancer, around 9,000 new cases per annum arise in the UK. Early diagnosis is limited and only 4-6% survive for 5 years – making it a disease with some of the highest unmet need in oncology. Preclinical evidence for the IKKα-regulated non-canonical NFkB pathway being constitutively amplified in pancreatic cancer suggests that selective IKKα inhibition could offer a new therapeutic approach.

CLL is the most common leukaemia in the Western world, accounting for a third of all leukaemia cases. Current treatments, which are not molecularly targeted, are associated with significant toxicity and are especially hard on elderly patients. Multiple myeloma is the second most common blood cancer. The disease remains incurable and most patients with multiple myeloma will eventually relapse.

Targeting IKKα with small molecules will for the first time attack an underlying cause of these cancers and will be of particular benefit to patients identified in our clinical analysis that lack further treatment options.

Recently, down-regulation of IKKα in mice with collagen-induced arthritis[14] suggests that it could offer an effective, novel therapy for the treatment of chronic inflammatory disease.

SPHINGOSINE KINASE INHIBITORS

One of the major problems in terms of successful cancer treatment is the development of chemotherapeutic resistance resulting in unopposed metastasis of the cancer. The mechanisms responsible for the induction of chemotherapeutic resistance need to be identified to allow the development of therapeutics that can prevent resistance, thereby providing an effective means of killing cancer cells.

Researchers at Strathclyde have found that sphingosine kinase-1 (SK1) is present in high levels in the tumours of breast cancer patients. It has also been found to induce resistance in breast and androgen-independent prostate cancer cells. Both indicate that the enzyme may have a role in the generic development of resistance. Furthermore, cancer cells are dependent on these enzymes for their survival, making them excellent targets for cancer therapeutics.

The IKKα research team at a morning briefing, led by project lead, Professor Simon Mackay, right.

Scientists at Strathclyde are developing inhibitors of SK1 for solid tumours. These have a unique mechanism of action as they promote degradation of the enzyme itself. This offers a means of increasing efficacy over what simple reversible inhibitors of activity can achieve. SK1 inhibitors also induce apoptosis of cancer cells, thereby providing an effective means to killing these cells. Sphingosine kinase 2 (SK2) inhibitors targeted at haematological cancers are also being developed.

AUTOTAXIN INHIBITORS FOR FIBROSIS & CANCER TREATMENTS

The autotaxin (ATX) enzyme controls levels of lysophosphatidic acid (LPA), an important phospholipid involved in cell signalling which has been strongly linked to disease pathology characterised by abnormal cell migration. Modulation of ATX is likely to have a profound effect on lung disease progression including cancer growth and metastases and idiopathic pulmonary fibrosis (IPF).

Scientists at Strathclyde have developed novel chemical entities as potential inhibitors of ATX. We are developing cell-based assays to confirm the effect of these potential inhibitors before conducting in vivo testing.

A HISTORY OF RESEARCH

The University of Strathclyde has a history of success in oncology drug research. Along with the late Professor Hamish Wood, Professor Suckling pioneered 6S-Leucovorin in the early 1980s. Leucovorin was an established drug made from folic acid, but it contained unnecessary molecules which were not biologically active and could be harmful. Concern peaked when it emerged that such molecules were the cause of the birth defects seen in the babies of mothers taking Thalidomide. As regulators called for purer drugs, Professor Suckling recognised the scientific challenge and began to develop a pure form of Leucovorin. Leucovorin is now used across Europe in the treatment of colorectal cancers and the technology has earned around £6 million in royalties for the University.

1. Pubmed ID: *19855404*
2. Pubmed ID: *10195897*
3. Pubmed ID: *15093710*
4. Pubmed ID: *19502791*
5. Pubmed ID: *19646419*
6. Pubmed ID: *23301098*
7. Pubmed ID: *23617340*
8. Pubmed ID: *24219331*
9. Pubmed ID: *20053756*
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12. Pubmed ID: *19513071*
13. Pubmed ID: *23041317*
14. Pubmed ID: *24498990*

INDUSTRY INSIGHT:
ONCOLOGY INTELLECTUAL PROPERTY

John Dean, Life Sciences and Chemistry Patent Attorney at **Withers and Rogers LLP**, provides an exclusive insight into the intellectual property landscape of European and US oncology inventions

Effective intellectual property protection, which is principally obtained through patents, underlies the significant investment needed for the commercial development of new diagnosis and treatments for cancer.

Patenting activity in the cancer area is very high. A quick look at Patentscope showed up over 700,000 patent publications from around the world mentioning cancer". More specifically, looking at European Patent Office Register for cases with "cancer" in the title throws up 13,000 European patent applications, many of these relating to novel cancer biomarkers.

Interestingly, the majority of these European patent applications come from Universities and state-funded research agencies in Europe, USA and Japan. Perhaps reflecting the raison d'etre for IN-PART's technology partnering service, relatively few early stage cancer-related technologies are coming from "big pharma" at present.

Whilst patenting is the usual approach to protecting inventions in this area, other approaches include the use of trade secrets. For example, some antibody-based anti-cancer treatments offered on IN-PART are reliant on keeping antibody sequences confidential for as long as possible. Strategies for protection of new technologies should consider all options, but in practice, patent protection is usually going to be the most useful route.

INSIGHTS FROM THE US: THE MYRIAD GENETICS CASE

Patent protection for different technologies in oncology are generally well-established and non-controversial. Investors and researchers should not be put off by the recent US Supreme Court decision relating to Myriad Genetics' BRCA gene-related cancer tests, which were developed in collaboration with university partners, because, in reality, little has changed from a research and commercial perspective.

The US decision was rather disappointing as it went against the established position on the patentability of isolated nucleotides taken some years before by the three major patent offices of the world (US, Japan and Europe) after significant public discussion. Despite it no longer being possible to obtain patent protection in the US for human gene sequences, even when they have been isolated, it is still possible to achieve commercially-valuable patent protection for genetic tests and other diagnostic and therapeutic inventions.

John Dean
Withers & Rogers LLP
Life Science & Chemistry Patent Attorney

In a 30 year career working with industrial and academic biotech clients across Europe, John has gained wide experience and works often with clients on IP strategy. He specialises in recombinant DNA technology, nuclear receptors, vaccines, antibodies and derivatives, drug discovery methods, microbiology and biomedical products as well as medical devices. He has significant IP due diligence experience and prepares reports for investors, and for Stock Market listings.

World Summit on the Information Society Forum 2013 - Brazil | *ITU Pictures / Flickr / CC BY 2.0*

In the immediate aftermath of the ruling there was, in some areas, confusion about what it would mean for biotech businesses. Now the dust has settled it is clear that the judges made an important distinction in determining that human gene sequences were not eligible for patent protection in the US, whereas complementary DNA or cDNA could still be patented. This means that the ruling is far less obstructive to protecting outputs of cancer research than some may have initially thought.

Other elements required for performing genetic tests also remain patentable in the US and elsewhere. The fact is that such screening tests can still achieve commercially-valuable patent protection in the US, and therefore it makes sense for the academic and industry sectors to continue to development with the expectation of gaining useful protection so they can continue to play their part in disease prevention and intervention in the future.

It is important to remember that the decision which attracted lots of press attention is relevant for the United States only, and does not affect the position for the protection of biomarkers, and other nucleotide-related inventions in Europe.

KEEPING ABREAST OF PATENT PUBLICATIONS IN ONCOLOGY

Patent publications represent a very important source of technical information. Often, details of commercially developed technology only become publicly available for the first time when a patent application is published.

The summaries of technologies featured on IN-PART have details of representative IP protection. Finding out more about the representative IP protection and patent publications in the cancer sphere is very straightforward these days through resources like Espacenet and Patentscope. An important tip is to make sure you know if you're looking at a published application or granted patent and where the patent family extends i.e. where corresponding applications have been filed.

Withers & Rogers has an active Life Sciences & Chemistry patent practice headed by Adrian Tombling which works for universities and innovative companies in Europe, USA and Japan to protect early-stage and later technologies in the cancer field. The team represents several organisations with technologies featured on IN-PART. More details of the team can be found at *the Withers and Rogers website.*

RECOGNISING EUROPEAN ONCOLOGY INVENTORS

Over the last 10 years, the European Inventor awards have been organised by the **European Patent Office** to honour inventors in all areas of technology. It is noteworthy that every year researchers looking at very different aspects of cancer diagnosis and treatment have been honoured:

- **Patrick Couvreur:** Nanocapsules for cancer medicines containing significantly higher dosages of anti-cancer drugs.
- **Yves Jongen:** Proton radiation therapy for cancer treatments
- **Leigh Canham:** Silicon nano-structures that can be injected with anti-cancer drugs.
- **Blanka Říhová:** Synthetic polymeric drugs combining highly effective drugs with human antibodies to combat cancer
- **Albert Gelet *et al.*:** Therapeutic prostate cancer treatment using a highly focused ultrasound probe
- **Napoleone Ferrara *et al.*:** Anti-VEGF antibodies marketed under the name Avastin
- **J. Zimmermann and B. Druker:** Novel treatment against chronic myelogenous leukaemia - the main active ingredient in the drug marketed as Glivec

Finalists for the 2015 European Inventor Awards will be announced in April 2015, with a strong possibility of further oncology researchers receiving recognition. Inventors are encouraged to apply for 2016.

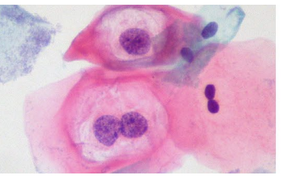
Europaisches Patentamt
European Patent Office
Office européen des brevets

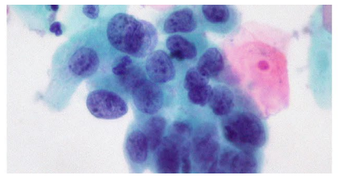
IN-FOCUS:

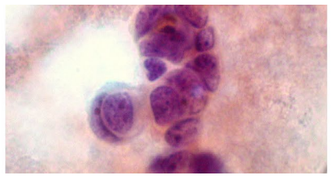
The University of York,

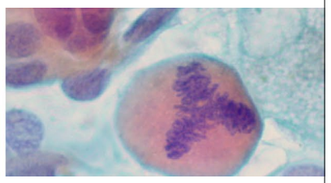
Professor Norman J. Maitland,

Near-patient xenografts for prostate cancer









CELL HISTOLOGIES : ED UTHMAN / FLICKR

IN 1990, Professor Maitland was appointed to the newly-established Chair of Molecular Biology and as the Director of the Yorkshire Cancer Research (YCR) Cancer Research Unit, bringing molecular sciences expertise to the study of cancer at the University of York. Funding for the Cancer Research Unit has been provided by a programme grant from Yorkshire Cancer Research, providing core running expenses and essential personnel.

Professor Maitland's research is focused on the development and aetiology of human prostate cancer. His approach has been to separate the tumour (and the corresponding normal tissue) into its cellular components, then to study the role played by different cell types. Of particular interest are the roles played by epithelial stem cells and the hormone-sensitive stromal cells within the tumour and normal prostate

LEADING THE WAY

Professor Maitland's laboratory has compiled gene expression profiles for the various cell types, using the Affymetrix platform, and has mined these data for genes and signalling pathways that affect cell fate. Much of the ongoing research is concerned with hypothesis testing, based on the genes identified in the array studies, using complex multicellular in vitro models and developing xenograft models of the tumour.

Professor Maitland has shown that heterogeneity within human prostate cancers is due to both carcinogenic changes and aberrant differentiation - these are two independent phenomena. Current therapies are directed against the majority of cells in the tumour (the most differentiated cells) but tend not to affect the minority population, which are the tumour initiating cells, or cancer stem cells. It is the cancer stem cells that form the basis of post-therapy recurrence of the disease.

NEAR-PATIENT XENOGRAPHS

Professor Maitland's patient-derived primary cell cultures and xenograft (PDX) models of prostate cancer represent a remarkable and powerful resource for investigating the origins and progression of malignancy and notably, for testing the effectiveness of candidate drugs. Samples of tissue are routinely collected from patients that exhibit a range of disease progression states, then, following a patented process, serially transplantable tumours are established in an *in vivo* system.

The serially transplantable tumours closely resemble the diseased tissue of origin and reflecting this, they are referred to as *"near patient"* xenografts.

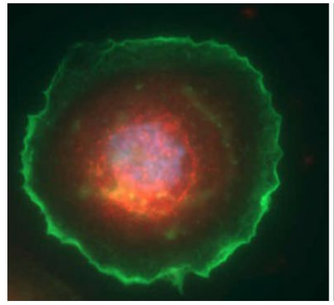
By contrast, established cancer cell lines that are commonly used for commercial prostate cancer drug testing in vitro, or in vivo (as xenografts) have undergone huge expansion in culture. This long-term expansion drives adaptation of the cells to their culture environment, establishing genetic and epigenetic changes that are of questionable relevance to the natural history of prostate cancer initiation, progression and response to treatment, in humans.

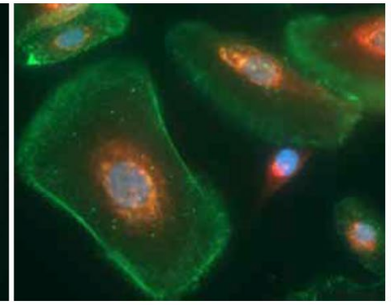
Near patient xenografts, on the other hand, offer far greater opportunities to evaluate candidate drugs in a system that more accurately represents the disease biology of prostate cancer. Indeed, Professor Maitland has undertaken research projects with major pharmaceutical companies to examine the effects of their compounds on prostate cancer, with a particular focus on the resistance to treatment of the stem cell component of the disease that causes post-treatment relapse.

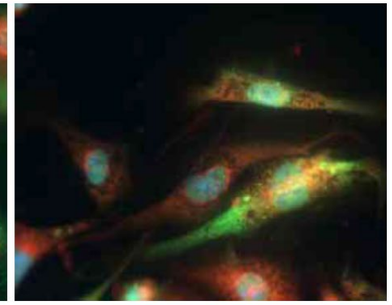
AN OPPORTUNITY TO COLLABORATE

Approaches from industry to evaluate the performance of licensed and experimental drugs are welcomed, being both scientifically interesting and perhaps contributing to life-saving outcomes as well as the avoidance of futile trials.

STEM CELLS : UNIVERSITY OF YORK







INDUSTRY INSIGHT:

The University of York,

Dr James Walsh

Business Development Manager

Could you start by describing your role as a Business Development Manager at the University of York and your involvement with Professor Maitland's research?

I liaise principally with academics, University management, industry and funding bodies to develop commercially-focussed research opportunities and to promote exploitation of research discoveries.

Collaborative projects using Professor Maitland's patient derived models of prostate cancer have already been undertaken. Can you tell us anything about these? What has emerged from these so far?

Professor Maitland's prostate cancer models have served to highlight the limitations of industry-standard approaches to testing the efficacy of anti-cancer drugs. Collaborative projects with industry have generated significant interest in exploring new molecular targets and in developing drugs capable of killing prostate cancer stem cells, or nullifying their malignancy.

Is it possible that Professor Maitland's 'near-patient' xenografts could become an industry standard for testing new prostate cancer therapeutics? If so, what will it require for this to happen?

It is indeed possible that the prostate cancer xenografts developed at York could become an industry standard for drug testing. Pharma companies frequently outsource this type of testing to CROs; these service providers are typically better-placed than universities to deal with high-volume work of a routine nature. In order to provide a CRO licensee with the technical expertise needed to work with the York xenografts, a technology transfer process would need to be implemented.

What potential will realising the role of the drug-resistant, stem cell components of tumours have on the development of prostate cancer treatments?

Even when prostate cancer responds well to treatment, unless the cancer stem cells can be reliably eradicated, or rendered harmless, the scene is set for the disease to return. Greater understanding of the biology of the stem cell component of prostate cancer paves the way toward interventions that will more commonly provide cure, rather than respite.

What do you think the future holds for university-industry collaborations in general?

Public and charity funding for university research seems likely to remain under pressure for the foreseeable future. The prospects for producing near-term, tangible benefits, outside of academia, will very probably continue to be a major consideration in research funding decisions.

University-industry collaboration is an effective approach for designing and undertaking research projects that are academically prestigious and whose outputs are commercially valuable. Such collaborations, especially those involving smaller companies, will continue to arise on an *ad hoc* basis.

Notably, though, larger scale, strategic collaborations between universities and companies are becoming ever more prevalent. Research-intensive universities will continue to be highly receptive to the needs of industry and especially amenable to jointly-conceived projects that benefit from industrial sponsorship.

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