Basic Contact Information

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About

Our research focuses on the use of nanoparticles in cancer for therapy, imaging or drug delivery. The small size of nanoparticles means that they can passively accumulate in tumours due to the enhanced permeation and retention (EPR) effect. The EPR effect is the property by which certain sizes of molecules accumulate more in tumour tissues than in normal tissues. This occurs because newly formed tumour blood vessels are abnormal in form and architecture, and have poorly-aligned endothelial cells with wide fenestrations through which the molecules can pass. Furthermore, tumour tissues lack efficient lymphatic drainage.

Encapsulation of chemotherapy drugs within nanoparticles therefore enables them to be delivered directly to the site of the tumour, reducing systemic side effects, and enabling a higher dose to be reached in the cancerous tissue. Fluorophores and reporter molecules can be added to the nanoparticles for localization, and assessment of the efficacy of the treatment. Microparticle systems have also been developed for chemoembolization, in which the blood supply to the tumour is blocked causing the cancerous tissue to die. Other nanoparticles have also been developed which can be used to enhance the effect of conventional radiotherapy. Together with Isis Innovation we are working to commercialize this technology (http://www.isis-innovation.com/licensing/4465.html).

Ways in which nanoparticles can help in the fight against cancer are also discussed in a recent Guardian article http://www.theguardian.com/science/blog/2014/aug/13/nanotherapy-future-cancer-treatment#start-of-comments

In addition to cancer treatments, nanoparticles are useful for many other applications and we have collaborated with groups working, for example, on the use of nanoparticles to combat infertility (http://www.ox.ac.uk/media/news_stories/2013/131115_1.html), and for smart biocide delivery to specifically target harmful bacteria (http://www.isis-innovation.com/licensing/9992.html)
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Research group members, 2014

Left to Right: Rachel Morrison, Helen Townley, Malgorzata Rybak-Smith, Anna Hiraoka, Cindy Huang
Christmas Lunch 2013, Cherwell Boathouse; Thompson, Hankin & Townley groups

FINANCIAL SUPPORT FOR OUR RESEARCH

We are very grateful to the William’s Fund for supporting the research of our group. The Williams Fund was set up by Johanna and Peter Dodd, to raise money for research into childhood cancers.

http://www.williamsfund.co.uk/

Visit by Johanna and Peter Dodd, November 2013.

Johanna and Peter visited the John Radcliffe hospital to meet with the groups supported by the William’s Fund and to hear presentations on the research undertaken.

Left to Right: Michelle Potter, Peter Dodd, Cindy Huang, Helen Townley

Left to Right: Karl Morten, Michelle Potter, Cindy Huang, Helen Townley
Jeremy Burditt visited our labs in Begbroke in February to present a donation to the William’s Fund from the St James’s Place Charitable fund (http://www1.sjp.co.uk/about-st-james-place/our-responsibilities/st-james-place-foundation)

Left to Right: Helen Townley, Johanna Dodd, Jeremy Burditt
Combining chemotherapy drugs with embolic particles has been shown to have a synergistic effect on the reduction of tumour size. The aim of this project is to design and synthesize new embolic particles, combined with novel chemotherapeutics.

Embolic particles can be introduced into the bloodstream close to the target, and by lodging in the small vessels which feed the tumour restrict the nutrient and oxygen supply to shrink the tumour. Incorporation of chemotherapeutic drugs into an embolization particle (chemoembolization) also allows a drug to be delivered directly to the cancerous cells, and whereas systemic chemotherapy delivers the drug into the bloodstream and exposes the whole body to the toxic effects of the compound, chemoembolization hones in on the site of the cancerous cells. The embolic particles in this study were designed to have a high surface area for maximal drug loading. Spherical microparticles were coated with mesoporous silica nanoparticles which have a nanoporous structure for a high loading capacity. Silica is known to have good biocompatibility, and could be further functionalized if desired with, for example, peptides or siRNA. The pores are also tuneable to the size of the particular drug to be delivered for maximum loading and unloading.
Mesoporous silica nanoparticles (MSNPs) are receiving increasing interest from the scientific community for their potential as drug delivery systems both \textit{in vitro} and \textit{in vivo}. MSNPs typically have particle diameters in the 50-300 nm range and narrow pore size distributions of the order 2-6 nm. The structure and morphology are controllable at both the nanometre and micrometre scale, yielding high surface area and pore volumes of the MSNPs and enabling a high cargo carrying capacity. The silica surface has a high density of silanol groups which can be modified with a wide range of organic functional groups, allowing for modification with targeting agents such as peptides, antibodies or folic acid, or biocompatible polymers such as polyethylene glycol (PEG) to minimize opsonisation which would lead to a rapid clearance of nanoparticles. In addition, the ability of silica to decompose into relatively harmless silicic acid by-products presents fewer challenges for long-term use than, for example, carbon nanotubes or gold nanoparticles which are not metabolized.

In terms of drug delivery, the external diameter of nanoparticles for drug delivery is of particular importance. The circulation of nanoparticles and their uptake by different tissues varies widely, and uptake by diseased tissue differs to healthy tissue. The tight junctions of the blood-brain-barrier only permits passage of particles below 1 nm whereas continuous capillaries such as those found in the muscle, skin and lungs are permeable up to approximately 6 nm. Larger particles of up to 50-60 nm are able to exit the fenestrated capillaries of the kidney, intestine, and some endocrine/exocrine glands. The largest particles of up to 600 nm will be able to accumulate in the liver, spleen and bone marrow.
However, it has been shown that the bio-distribution of nanoparticles is altered in animal models bearing tumours compared to control animals. The microvasculature surrounding tumours is highly permeable and leaky, and tumours have less efficient efflux mechanisms (the EPR effect) which will influence the overall bio-distribution. This means that nanoparticles of the right size will likely passively accumulate at the tumour site.

This project assesses the suitability of engineered mesoporous silica nanostructures in terms of potential drug delivery vehicles, and evaluates the nanoparticles in terms of their physical and nanostructural attributes, interaction with model-drug molecules, and time-dependent behaviour in conditions that mimic those of the human body.

**Building the supply chain; ‘Flame spray pyrolysis for doped titania synthesis’**

Malgorzata Rybak-Smith, PDRA

The aim of the current study is to improve the efficacy of the nanoparticles and to scale-up the synthesis to produce a commercially viable product with a clear supply chain. The particles will be synthesized using flame spray pyrolysis; a technique developed by Johnson Matthey. The nanoparticles made at lab-bench scale are polycrystalline and approximately 65nm. Attempts will be made to produce single crystal nanoparticles which are less likely to suffer losses of energy within the particle and therefore produce ROS with greater efficiency. The distribution of rare earth ions will also be assessed and methods developed to produce a highly uniform distribution of ions. Furthermore, the combination of rare earth dopants will be investigated and the nanoparticulate diameter modified since the production of smaller particles may allow access in to the nucleus with resulting increases in efficacy.

**Rare Earth doped titania nanoparticles for Augmented Radiotherapy**

Rates of cancer mortality have remained virtually unchanged since the 1950's while death rates from heart disease and stroke have dropped significantly. Surgical treatments are often limited by physical access to the tumour, and are usually augmented by other therapies due to the large risk associated with remaining malignant cells after removal of the main tumour. Chemotherapeutic approaches have extremely unpleasant side effects and cancerous cells often become resistant...
to the drugs and at present the efficacy of radiation therapy is limited by damage to healthy tissue and associated side effects. Nanoparticulates provide a better penetration of therapeutic and diagnostic substances within the body, at a reduced risk in comparison to conventional therapies.

We have designed a system based on the semiconductor, titanium dioxide (titania), which exhibits a high photoactivity which generates Reactive Oxygen Species (ROS) upon excitation of valence band electrons to the conduction band by absorption of photons. Titania nanoparticles, especially those of the anatase crystallographic phase may be used for ultraviolet light stimulated ROS production for photodynamic therapy (PDT). The penetration depth of light limits this technique to tumours on, or just under, the skin. We have generated nanoparticles which have been designed to optimize the interaction of the titania with X-rays, a more deeply penetrating energy source. The nanoparticles have been doped with elements which have been selected to absorb the maximum energy from a typical medical X-ray with a broad emission spectrum centred around 60keV. This allows the nanoparticle ROS treatment to be extended to deep tissue and large tumours which could not be treated by photodynamic therapy.

The doped TiO2 nanoparticles have been coated with silica to improve biocompatibility and have been shown to passively enter cells in monolayer culture. In the absence of irradiation there is no significant decrease in cell viability illustrating the bio-compatibility of the particles. Excitation of the nanoparticles by X-rays has been demonstrated in vitro to generate ROS and exposure of the cells containing nanoparticles to X-ray results in generation of cell-damaging ROS from the titania.

Preclinical trials have tested the efficacy of the particles against xenografts of lung non-small cell carcinoma. Tumours which were injected with the nanoparticles prior to irradiation were shown to be half the size of those treated with radiotherapy alone. The scale-up of the nanoparticles will ensure the reproducible production of a homogeneously doped nanoparticle with a uniform biocompatible coating and particulate size control. This will enable translation of the technology to Pharma and reduce the time taken to reach the clinic.
UNIVERSITY SPIN-OUT: XERION HEALTHCARE

The technology underpinning the augmented radiotherapy will be commercialized by the University spin-out company Xerion Healthcare.

To date, work on this project in the University has attracted funding from:

**UCSF Investment (March 2014)**

*Nanoparticle enhanced radiotherapy; Economic Health Assessment, and regulatory pathway*

**TSB Nanoscale technology enabled healthcare: building the supply chain (Aug 2012-Aug 2014)**

*Flame spray pyrolysis for doped titania synthesis*  
Collaborative application with Johnson Matthey.

**UCSF IUIF Investment**

*Nanoparticle enhanced radiotherapy*
Allowed for collaboration with Stanford University to perform preclinical tests.

**EPSRC Pathways to Impact Award**

*Nanoparticle augmented radiotherapy: market assessment as part of an IP commercialization plan*.

**EPSRC Pathways to Impact Award**

*Nanoparticle augmented radiotherapy: production of a scientific animation to increase accessibility of the research to the general public, third sector and next stage investors*.

**Development fund, Oxford Cancer Research Centre**
Equipment grant

**Radiation Oncology Specialists PC, Michigan, USA**

*Preclinical trials for doped titania nanoparticles for augmented radiotherapy*
RECENT PUBLICATIONS


Helen E Townley. Applications of Rare Earth elements in cancer imaging and therapy. Current Nanoscience 2013, 9, 686-691

Recent conference presentations

1st International Symposium on Nanoparticles/Nanomaterials and Applications. Caparica, Portugal, 20th-22nd January 2014

Presentations
Rachel Morrison, Peter Dobson, Alison Noble, Helen Townley. Multimodal embolic core-shell particles for cancer therapy.

Posters
Cindy Huang, Neil Young, Helen Townley. Development of a Novel Mesoporous Silica Nanoparticle System for drugs.

EMC2012 (The 15th European Microscopy Congress)
Cindy Huang, Neil Young, Helen Townley Synthesis and characterization of mesoporous silica nanoparticles towards delivery of chemotherapeutics
Malgorzata Rybak-Smith, Benedicte Thiebaut, Simon Johnson, Helen Townley. Flame Spray Pyrolysis as a high-throughput method to generate Gadolinium Doped Titania Nanoparticles for augmented radiotherapy.

**Patents**


(Highlighted in ‘ISIS Insights’ no.60 ‘X radiotherapy’ Project 4465)

Townley HE, Barkalina N, Kashir J, Jones C, Coward K. ‘Use of mesoporous silica nanoparticles as a delivery system for reproductive or embryonic cells’ Filed

Chan A, Townley HE, Thompson IP. ‘A nanoparticle delivery system for controlled biocide release’ Filed