

Research progress of projects supported by William's fund

December 2010

1) Molecular characterisation of metastatic genes associated with Rhabdomyosarcoma (RMS)

Researchers: Dr Elizabeth Rapa, Dr Sophie Hill & Dr Karl Morten

Over the last four years using a variety of genetic and cell biological techniques we have identified significant differences between aggressive (difficult to treat) and less-aggressive forms (treatable) forms of rhabdomyosarcoma. Genes associated with the aggressive form of RMS include genes which increase cell motility. Our hypothesis was that these genes would increase cell invasion and hence the chance of developing metastatic disease. This was tested in the laboratory by increasing the levels of cell motility genes in non-aggressive and normal muscle cells. In both cases the ability of the cells to migrate through an artificial matrix was increased. In addition, reducing the levels of these genes in the aggressive RMS cancer cells reduced their ability to migrate through the matrix.

Manuscript submission: We are currently in the process of completing a paper on this work which we aim to submit to *Oncogene* in the New Year.

2) Targeting cancer cell invasion genes as a therapeutic strategy in RMS.

Researchers: Ms Cindy Huang (D Phil student), Dr Helen Townley & Dr Karl Morten.

This is a new project starting in January 2011 and will look to build on a collaboration between Dr Helen Townley (Engineering Science) and Dr Karl Morten (Medical Sciences). The project aims are to specifically deliver molecules (siRNA gene knockout systems) to cancer cells to reduce their ability to develop metastatic disease. The project utilises a new branch of science termed nanomedicine in which small molecules less than 10^{-8} of a metre are developed for use as therapeutic agents. Drugs or in our case siRNA are encapsulated into 100-200 nano meter particles and modified to specifically interact with cancer cells. In our study we are looking to use the folding properties of aptamer molecules to recognise specific binding sites on the surface of the cancer cells. Aptamers recognise and bind to cells in a similar way to antibodies. In summary the nanoparticles will protect the siRNA molecules as they move through the blood stream, the aptamer molecules increase the chances of the payload siRNA getting to the cancer cells where it can inactivate cell motility genes reducing the ability of the cancer cells to invade. This project is very much the follow on study from (1) where we already know knocking down cancer cell invasion genes reduces their cell invasion properties in the laboratory.

Support from the Williams Fund: The Williams fund support will help towards the laboratory consumables of this project. Projected costs in the region of £18,000 over 3 years.

3) Energy metabolism as a novel therapeutic target in glioblastoma and rhabdomyosarcoma.

Researchers: Ms Michelle Potter (D Phil Student), Dr Karl Morten & Dr Heiko Schiffter (Biomedical Engineering).

This project started in October 2010 and is entirely support by the Williams fund. Solid tumours have a very different method for generating energy compared to normal tissue. The low oxygen (hypoxia) levels found in the middle of tumours triggers a series of events that allow cancer cells to survive in this hostile environment. These changes also render the cancer cells resistant to both chemo and radiotherapy, turning on genes that allow their spread. Recent studies in the laboratory and more recently in a small clinical trial have shown that allowing cancer energy metabolism to follow the normal pathway using a compound called Dichloroacetate (DCA) slowed the growth of brain tumours and provided clinical benefit to the patients.

In our study we aim to investigate this phenomenon further adding additional pharmacological agents to DCA to enhance the effect of switching metabolism and increase the burden of toxic radicals on cancer cells. Drugs we intend to investigate include vitamin C and vitamin K3 which have already shown efficacy in prostate cancer when used in the formulation Apatone. In addition vitamin C and K3 have shown promise as radiosensitising compounds for radiotherapy. This will be studied further in a collaboration with the Radiobiology unit.

As the above drugs show minimal toxic effects on normal cells our hope is that we will kill the cancer cells but leave normal tissue relatively unaffected. In the later stages of this project we will look to integrate the compounds into nanodelivery vectors as in (2) to increase cancer cell targeting and improve efficacy.

Support from the Williams Fund: A student stipend for the student, University & college fees and laboratory running costs £80,000 over 3 years.

4) Nanomedicine and microfluidic separation of nanoparticles

Researchers: A variety of groups from Biomedical Engineering and Medicine are involved in this research effort.

Aim: To develop nanoparticles and targeting strategies capable of delivering therapeutics to cancer cells.

Support from the Williams fund: In 2010 Dr Karl Mortens lab received £6,000 support for the running costs of a sandwich student and MSc student investigating Aptamer molecules as delivery systems for nanotherapeutics. This work is ongoing and will require a similar level of support in 2011.