

Examples of current Brunel projects:

Investigating therapies for Friedreich ataxia

Brunel is using an established mouse model of the lethal inherited neurological disorder called Friedreich ataxia (FRDA) to gain further understanding of the disease mechanisms and to identify novel therapies. The symptoms and signs of FRDA first occur in children who present with uncontrolled movement as toddlers. FRDA patients then get progressively worse, becoming wheel-chair bound in their teens and most commonly living only until their twenties or thirties. There is currently no known effective therapy for this disorder. However, this project aims to undertake essential preclinical investigations that will ultimately lead to effective therapies. Specifically, the project will investigate potential treatments aimed at reducing, halting or reversing FRDA disease pathology. This form of pre-clinical study in mice will be of great benefit before proceeding to clinical trials in human individuals. The experimental protocols of this project that assess motor coordination ability of the mice are completely non-invasive and are unlikely to cause any pain, distress or harm. This project has chosen to use the mouse because this is the lowest vertebrate species that manifests a representational genetically modified model of FRDA. The data obtained from protocols in this project can be directly translated into pertinent data for FRDA disease patients to achieve successful medical advances. To date, preclinical studies that have been performed as part of this project have contributed to the development of three potential new therapies, HDAC inhibitors, nicotinamide and interferon gamma, which have now all progressed to Phase II or Phase III safety and efficacy clinical trials in FRDA patients. Brunel currently has a gene therapy programme to offer permanent treatment of this disease using safely engineered viruses that carry the essential gene needed to correct FRDA.

Research in Autoimmunity and Arthritis

Investigators at Brunel are keen to understand the mechanisms of immune responses that have fundamental importance to the processes of ageing, cancer and the role of the host immune system in vaccine development to improve quality of life. Key mechanisms used by the host to identify cancer and trigger immune responses against tumours are being explored. Key to this work is the use of mouse models that have similar immune function to humans. A range of *in vitro* studies are being developed from this work to replace these models. Laboratory techniques such as immunofluorescence, Western blotting, electrophoretic mobility shift assays, and semi-quantitative real-time RT-PCR are being compared in vivo and vitro for this purpose. Ultimately, we aim to determine the efficacy of novel vaccines to destroy tumour cells.

Understanding liver cancer to discover new ways to prevent or treat this disease

Liver disease or hepatocellular carcinoma (HCC) is one of the most common human cancers worldwide, with 70-85% of liver cancer deaths caused by this disease in 2008. It is the 14th most common cancer in Europe. Unexpectedly, whilst using gene therapy to treat model mice with haemophilia B we discovered that non-primate derived gene therapy lentivirus vectors caused HCC in virtually all the mice that were treated. Importantly, because these virus vectors insert themselves into the host chromosomes we were able to discover cancer genes that had been disrupted by the gene therapy vector. This process, called insertional mutagenesis, is now being used at Brunel in a programme to discover genes that, when mutated, are involved in HCC. Because HCC is a complex solid tumour

type, it is hoped that this new technology will help us discover what goes wrong in the liver to cause this disease; and that it will provide new targets for HCC drug therapy.

Several patients suffering from severe combined immunodeficiency have been successfully treated with gene therapy. Unexpectedly however, a small number of these patients also developed leukaemia. This led to intense research in order to understand what went wrong, and it was soon discovered that insertional mutagenesis played an important part. As a result of this, our mouse model will be used to understand how gene therapy vectors can identify liver cancer genes and to screen these vectors for any other potential side effects.

Understanding the role of the MYB gene in Adenoid Cystic Carcinoma.

Adenoid Cystic Carcinoma, also known as ACC, is a rare tumour of the salivary glands that can also originate in the breast, sinonasal tract, bronchoalveolar tree and other exocrine glands. Although ACC is a slow growing tumour, it is relentless and most patients with metastatic disease do not survive after 10 years. This is also due to the fact that ACC responds very poorly to chemotherapy, radiotherapy and other treatments. A major breakthrough in ACC research has been the identification of a molecular aberration in tumours in which two genes encoding the transcription factors MYB and NFIB are fused, forming a chimeric product. This new product, called MYB-NFIB, is thought to be the primary cause of the disease. Finding drugs specifically inhibiting this molecule could thus hold the promise for a more effective and personalised therapeutic approach for this cancer. However, the creation of a faithful cellular and animal model of the fusion is an essential prerequisite for the development of specific drugs targeting the oncogene. Using a new technology called DNA editing we have been able to demonstrate that it is possible to modify the genome of mouse cells to induce the formation of a MYB-NFIB fusion gene identical to the corresponding human lesion observed in ACCs. We will induce the formation of the MYB-NFIB fusion gene in cells and tissues relevant to ACC to assess whether this causes tumourigenesis in vivo. Given the great similarity of the mouse and human systems, the in vitro and in vivo models developed in this study will be invaluable for the understanding of the molecular causes of the disease and the validation of new drugs.

Queen's Anniversary Prize

Brunel's Institute for the Environment has been awarded the Queen's Anniversary Prize for Further and Higher Education in recognition of ground-breaking research into the link between exposure to water pollution and sex change in male fish in UK rivers. In 2016, one of Brunel's researchers was awarded an OBE for services to the science of ecotoxicology in the aquatic environment. Drawing on research with animals, this research also provided the impetus for human health research linking chemical exposure with increasing rates of infertility and testicular, breast and prostate cancer in human populations.