Carolina Arancibia, Nuffield Department of Clinical Medicine (£9,990)

The role of the immune system and of host and bacterial metabolic functions in the pathogenesis of obesity and the response to bariatric surgery

One in four adults are obese in the UK and rising rates of childhood obesity are a national emergency. While obesity is one of the leading preventable causes of death, the long-term results of traditional weight loss therapies, including diet, exercise, and medications, are relatively poor. Bariatric surgery is the most effective treatment of morbidly obese patients to allow substantial, sustained weight loss and to improve or resolve obesity-associated comorbidities, thereby reducing mortality. These surgical procedures were initially thought to work mechanistically through stomach reduction and calorie absorption restriction through the shortened intestine. However, recent evidence has shown that bypass surgery improves glucose tolerance and insulin sensitivity independently of weight loss. The improvement of the metabolic disorder is likely secondary to immune changes that result in resolution of inflammation. Interestingly, the improved metabolism occurs with changes in the gut microflora. The gut flora is beneficial to the host in many ways, contributing to nutrient absorption and a healthy immune system. The aim of this project is to assess how altered host and microbial functions affect weight loss, metabolism and the immune system after bariatric surgery. Understanding more about the microbial flora and how this impacts the immune system will hopefully make way for new approaches in the treatment of obesity and metabolic disease.

Enric Domingo, Department of Oncology (£10,000)

Precision immunoprofiling by computational pathology for stratification of rectal cancer patients

Every year over 40,000 new cases of bowel cancer are diagnosed in the UK. The largest proportion of these cases arise in the rectum. Patients with rectal cancer most frequently require adjuvant chemoradiotherapy as part of their primary treatment. The development of personalized treatment regimens is of key importance to improve long term outcomes and to minimize treatment side effects for patient benefit. We have recently found an association between response to radiotherapy and infiltration of different types of immune cells in a cohort of rectal patients and now we need to refine and understand the interrelation between these different immune cell types. In the present study we aim to use novel technological platforms to quantify anti-tumoral immune cells in pre-therapeutic biopsies from a large cohort of over 200 rectal cancer patients with full clinicopathological and molecular information. By using state of the art cell visualization methods and computational image analysis, we will investigate the type, density and location of specific immune cells in very small tissue samples from rectal patients. We will then integrate this comprehensive morphological data characterizing a patient's immune response with the individual's molecular features, response to therapy and survival outcome. This data will allow us to develop new assays for improved risk stratification and will further promote the development of risk-adapted treatment strategies of rectal cancer patients in clinical practice.

Chantal Hargreaves, Nuffield Department of Medicine (£16,250)

Exploring T cell dysregulation as a cause of gut inflammation in CVID

Patients with Common Variable Immunodeficiency Disorders (CVID) are born with a genetic predisposition to developing an immune deficiency which makes them prone to repeat infection. The majority of patients are adults. A subset of patients develop an inflammatory immune response in their bowel, known as enteropathy, which significantly affects their quality of life. CVID enteropathy is often treated with steroids, however this can further increase their risk of infection and patients eventually stop responding. It is impossible to predict which patients will develop enteropathy. Methods to predict enteropathy and novel treatment options are needed for these patients. We propose to comprehensively profile the immune cells in the blood and bowel of CVID enteropathy patients, CVID patients without enteropathy and controls. In identifying which cells are present in the gut, we can potentially determine which cells to target with drugs. To further understand what is causing the inflammation, we will look at what molecules the immune cells in the gut are responding to, and whether they are derived from gut bacteria or from the body's own cells. Finally, we will sequence the unique receptors expressed by T cells. This will tell us if it is a particular cell that is multiplying to cause disease, or many different cells. By integrating the data, we can determine which cells are present in the gut, how diverse their receptors are, and what they respond to. This detailed analysis may reveal the underlying inflammatory causes of enteropathy in CVID patients, and identify potential therapeutic targets.

Maria Hawkins, Department of Oncology (£2,520)

Initial assessment of circulating immune cell populations in response to stereotactic body radiotherapy in patients with borderline resectable pancreatic cancer

Pancreatic cancer is a deadly malignancy and can be only cured by surgery. Unfortunately only a small number of patients can receive a curative operation as the cancer is found often to be close to important blood vessels making it impossible to remove or has spread to other organs. Research to improve outcomes in pancreatic cancer is a priority in UK. High dose radiation has been used to shrink the cancer away from the vessels and facilitate surgery in patients with non-metastatic pancreatic cancer part of a phase I clinical trial. Bloods were taken before, during and after radiotherapy. We plan to measure if the radiation has produced any changes in the immune response of the circulating blood as treatment that stimulate the immune response are available now and successfully used in other cancers. This would give us some indication on the best timing to administer the combination of radiation and immune combination, and provide direction for future testing on the bloods, more preclinical work and then testing the radiation immune drugs combination in clinical environment.

Joanna Hester, Nuffield Department of Surgical Sciences (£9,900)

Investigation into changes in regulatory T cells (Tregs) in renal transplant recipients receiving Treg cell therapy

Transplantation is the most effective treatment for terminal organ failure. However, organ rejection by the immune system remains a major risk. Organ acceptance is currently achieved with powerful immunosuppressive drugs, but use of these drugs may lead to serious side-effects such as cancer and kidney damage. Regulatory T cells (Treg) are part of the natural regulatory mechanisms able to control the immune response. These cells can be isolated from patients, grown in the laboratory and administered to transplant patients, therefore removing the need for immunosuppressive drugs. We are currently assessing the use of Treg therapy in a large clinical trial in Oxford. As this is a new therapy, there is a need to understand what is happening to these cells after we have given them and understand how they work in patients. To achieve this goal, we will analyse in detail the changes in Tregs in patients after they have been treated with the cell therapy. We hope that this information will help provide more information on how long cells survive, how they work, how safe they are and therefore how to design the next phases of clinical trials.

Sarosh Irani, Nuffield Department of Clinical Neuroscience (£9,890)

The single cell transcriptome of B cells in cerebrospinal fluid: towards therapeutic markers for the treatment of CNS autoimmunity

The immune system normally protects humans from foreign infections. However, on occasion, it can mistake one's own body as foreign, leading to autoimmunity. In the last decade, in addition to multiple sclerosis, an emerging number of autoimmune diseases of the brain have been recognised in which an immune system component, known as the B cell, wrongly recognises the brain as foreign. However, despite this clear clinical need, few drugs specifically target these B cells. Also, one which non-specifically prevents their access to the brain causes severe side-effects. Further, overall, very little is known about B cells that surround the brain. Therefore, firstly, we aim to identify molecules on B cells within the fluid surrounding the brain which could be specific therapeutic targets. In addition, some of these B cells have an immune signature which implicates them as causative. Hence, secondly, we aim to use this signature to identify these autoreactive cells and discover whether they carry markers which may be even more specific targets of future drugs. Such drugs would aim to exclusively target the causative cells, preventing potential side effects. Further, isolation of these autoreactive cells will also allow us to clone some of their markers. These markers will act as critical reagents to model these diseases *in vitro*, and hence better understand disease causation. Taken together, these experiments aim to better define targets on brain-resident autoreactive B cells which can be drug targets to help alleviate the increasingly recognised set of autoimmune diseases of the brain.

Shivan Sivakumar, Department of Oncology (£10,000)

Characterising the immune landscape of pancreatic cancer

Pancreatic cancer is the most deadly human cancer. Our own work has suggested that an individual's defense system, known as the immune system, may be important in influencing pancreatic cancer survival after surgery. We have seen that if patients have higher levels in their cancer of a particular component of their immune system called T cells, they will live at least 2-3 years after an operation for pancreatic cancer. In contrast, we see that patients who have higher levels of the immune system component called neutrophil cells in their cancer, they will live for a shorter duration of months. We know there are many other different components of the immune system that may also be important in influencing cancer risk and progression. We therefore plan to use a technique called flow cytometry to study the immune cells of numerous pancreatic cancer patients, in order to understand the variety in the different immune system cells they have. Using this information, we hope to understand the landscape of pancreatic cancer. This give us an idea to generate hypothesis on how we can drug the immune system in pancreatic cancer.

Sarah Snelling, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Science (£10,000)

Exploring the influence of polymer chemistry and nanoarchitecture on leukocyte mediated foreign body reactions

Rotator cuff tendon tears are painful and disabling. They are the most common cause of shoulder pain and require surgical repair. Unfortunately, current surgeries, which focus on improving the strength of repairs, fail in almost half of patients. We are developing novel manmade materials (electrospun scaffolds), that can be made into patches that are placed over tendon tears to help them heal. The patches are strong and can support the growth of tendon cells (tenocytes) that make new tendon tissue. These electrospun patches could therefore encourage biological healing of the tendon as well as making the repair stronger. However, another key population of cell present in tendon disease are inflammatory cells. They are found in torn tendons but are also found in blood. When a patch is surgically placed on a torn tendon, it is the inflammatory cells from the blood that first see and attach to the patch. These "first on the scene" inflammatory cells then direct the behaviour of other cells in the tendon and nearby. Understanding how inflammatory cells react to scaffolds is therefore critical to repair success. Furthermore, early patches that were not electrospun, negatively triggered inflammatory cells and were associated with an adverse reaction necessitating removal. We believe that we can modulate the shape and composition of ES scaffolds to provide cues that cause helpful, rather than harmful responses from inflammatory cells. This would allow us to produce safe materials resulting in stronger and more effective rotator cuff repairs.

Paresh Vyas, Radcliffe Department of Medicine (£24,633.40)

Pilot Project: Mechanisms Regulating Immunological Control Of Acute Myeloid Leukaemia (AML) Following Allogeneic Stem Cell Transplantation (Allo-SCT)

The most common curative cancer cellular immune therapy is allogeneic stem cell transplantation (allo-SCT) (24,000 patients worldwide/year), where patients receive blood-forming stem/progenitor cells from another person. Acute Myeloid Leukaemia (AML) is the most common indication for allo-SCT. Patients with more aggressive AML are initially treated with chemotherapy, to reduce disease burden, but this fails to eliminate all AML cells. Patients then receive an allo-SCT to eradicate AML to give the best chance of cure. Donor stem/progenitor cells generate T cells that recognize the patient's residual AML cells as foreign and destroy them. This is known as graft versus leukaemia (GvL). However, if GvL fails, residual AML cells proliferate causing fatal AML relapse in 40% of patients. How donor T cells recognize AML cells as foreign and how GvL overcomes AML is not understood. Our multi-disciplinary team will test the feasibility of deploying multiple methods, never previously used to study GvL. We will study 20 patients to identify how donor T cells recognize AML cells. We will test how an incipient donor anti-AML T cell response gradually eliminates AML in cured patients, or fails to develop sustainably in relapsed patients. If successful, this data will support a future funding application studying a large AML patient cohort asking:

a. Can we define the ideal donor(s) to provide a protective GvL response for any individual AML patient. Currently, we do not know how to do this.
b. Can we understand the mechanisms why GvL responses fail, so we can prevent this.