Translation and treatment

Immunologist and oncologist Professor Michael Brown describes his varied work towards developing new clinical solutions that may aid in the successful treatment of cancer.

To begin, could you give an insight into your background and how you came to be Head of the Royal Adelaide Hospital Cancer Clinical Trials Unit in South Australia, as well as Head of the Translational Oncology Laboratory within the Centre for Cancer Biology?

I had originally trained as a clinical and laboratory immunologist. I have always been intrigued by the application of immunology to cancer treatment and was particularly fascinated by the early trials that Chief of Surgery Dr Steve Rosenberg at the National Cancer Institute ran on tumour-infiltrating lymphocyte therapy for metastatic melanoma. Monoclonal antibody technology has also always impressed me with its adaptable and versatile solutions that it offers for challenges confronting effective cancer treatment. In the last five years, I have run cancer clinical trials at the Royal Adelaide Hospital, which is the major teaching hospital in Adelaide, South Australia.

While we have a diverse range of approximately 40 clinical trials, my main interests have been in first-in-human studies as well as in trials for the tumour subtypes of melanoma and lung cancer. Since I returned to Australia from St Jude Children’s Research Hospital in Memphis, Tennessee, USA, 15 years ago, I have also run a laboratory. The laboratory’s focus has increasingly been on bringing innovative treatments from bench to bedside and in the last year this has led to my new role as Head of the Translational Oncology Laboratory in the Centre for Cancer Biology.

What breakthroughs in the cancer research field have you been most excited about in recent years?

It has been extraordinarily difficult to make progress in the treatment of both melanoma and lung cancer. However, in the last few years there have been breakthroughs that have changed the treatment landscape for these two cancers. Taking melanoma as an example, the BRAF inhibitors have shown rapid control of disease in most patients whose melanoma carries an activating mutation of the BRAF gene. But in most patients this tumour control does not last, and the emerging drug resistance results in regrowth of the tumour. At the same time, a completely different treatment approach has been applied successfully to advanced melanoma. In this approach, an antibody inhibits the immune checkpoint that limits the expansion of lymphocytes responding to stimulation. In the case of the ipilimumab (Yervoy) antibody, blocking the checkpoint in effect releases a brake on the immune system, allowing it to work against melanoma, but with sometimes life-threatening effects on normal body tissues such as skin, gut and liver. A new generation of immune checkpoint inhibitors like the anti-programmed cell death 1 (anti-PD1) antibodies offer great promise for durable control of melanoma either alone or with ipilimumab.

Which genomic technologies are you investigating as part of the Cancer Genomics Initiative?

Now that various small-molecule inhibitors are available for particular somatic genetic lesions in cancer, the task is to identify these treatable lesions as early as possible in the natural history of the patient’s cancer so as to maximise a patient’s opportunities for effective treatment.

The genomic technologies currently in use for making these molecular diagnoses are various polymerase chain reaction (PCR)-based assays, mass spectroscopy of PCR products and direct Sanger sequencing. However, in the near future next-generation sequencing is likely to supplement if not supplant some of these other genomic technologies in providing highly sensitive coverage of most of the therapeutically relevant genetic aberrations in a patient’s tumour.

We are particularly interested in applying these technologies at the time the pathologist makes the initial tissue diagnosis of cancer and then registering this information to allow study of its relationship to patient outcomes in the long term.

In your opinion, what can be done to speed the translation process for oncology therapeutics from bench to bedside?

More adaptive clinical trial designs, particularly of combinations, will speed up the translation process. What is needed most, however, is exploitation of the non-invasive, real-time information that is available through functional medical imaging of the patient. Functional medical imaging techniques such as positron emission tomography can be used either to trace metabolic changes in tumours in response to trial drugs or map the distribution and kinetics of trial drugs labelled with positron emitting radioisotopes. Together with image-guided, pre- and post-treatment tumour biopsies that yield genomic data, this information should be used to guide patient treatment choices and to aid go/no-go decision making in drug development, allowing early termination of infeasible drug candidates and thus enabling investment funds to be allocated efficiently.
Arresting cancer progression

The efficacy of chemotherapy for lung cancer has hit a plateau in recent years, but one team at the Royal Adelaide Hospital in Australia is attempting to move treatment forward with a new antibody-drug conjugate...

THE WORD ‘CHEMOTHERAPY’ has ultimately come to be associated more closely with the disease it aims to treat than the healthy state it is intended to return a patient to – as is the case with many forms of therapy. Yet although it may be unfair to make this association, chemotherapy is often seen by patients as part of the problem as well as the solution. Chemotherapies work because they are cytotoxic, killing cells that divide rapidly – including not just cancer cells, but also cells of the gut, bone marrow and hair follicles. Patients undergoing chemotherapy can expect a range of side-effects that vary depending on the chemotherapeutic agent or agents used, with immunosuppression, anaemia and hair loss being common problems. Unfortunately, the adverse effects of chemotherapy will sometimes be felt more keenly than the symptoms of the cancer itself.

The problem is that chemotherapies are only targeted in the loosest sense of the word – ultimately, these drugs end up attacking the whole body rather than just the part that is a tumour. In recent years, one route to overcoming this problem has arisen, as scientists have found ways to use monoclonal antibodies coupled with cytotoxins against cancer. The purpose of an antibody is to bind with a specific antigen, tagging it for the immune system; its structure allows it to bind with only that antigen, fitting like a key fits a lock. Antibodies therefore present an attractive way of ensuring that drugs can find and focus on their targets. If scientists could identify antigens specific to the cancer cells which needed to be eradicated, cytotoxins could be coupled with the matching antibodies in a powerful new cancer treatment.

A LUNG JOURNEY

Globally, lung cancer is the most common cancer and the commonest cause of cancer death. In the US alone, it is estimated that 224,000 people will be diagnosed with lung cancer over the next year, with 159,000 dying from the disease – accounting for 27 per cent of all cancer deaths. Non-small cell lung cancer accounts for as many as 90 per cent of lung cancer cases, and it is the most prevalent form of cancer in which the majority of patients initially present with advanced disease. Hence, this is among the most pressing health issues that humanity faces, and the efficacy of front-line treatment using platinum-based doublet chemotherapy has hit a plateau. The addition of Avastin – the one monoclonal antibody licensed for use in non-small cell lung cancer – to chemotherapy has produced modest improvements in survival. Continuing treatment beyond platinum-based chemotherapy with maintenance pemetrexed chemotherapy or erlotinib kinase inhibitor therapy has also extended survival.

Now, one research group in Adelaide may have found another monoclonal antibody that can improve treatment further. Using a novel antibody-drug conjugate (ADC), Principal Investigator Professor Michael Brown and his team at the Royal Adelaide Hospital in South Australia hope to develop a novel solution for eradicating tumours in lung cancer cases, and break the stalemate...
INTELLIGENCE

A THERANOSTIC APPROACH TO TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER

OBJECTIVES

To bring innovative antibody-drug conjugate (ADC) treatments, such as APOMAB® technology, from bench to bedside for the treatment of metastatic non-small cell lung cancer.

KEY COLLABORATORS

Dr Alexander Staudacher, Centre for Cancer Biology
Dr Fares Al-Ejeh, QIMR Berghofer Medical Research Institute
Dr Doug Smyth, Nuclear Medicine Department, Royal Adelaide Hospital (RAH)

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CONTACT

Professor Michael P Brown
Director, Cancer Clinical Trials Unit
MDP11, Level 4, East Wing
Royal Adelaide Hospital
North Terrace, Adelaide
South Australia 5000
Australia
T +61 8 8222 4157
E michael.brown@health.sa.gov.au
www.centreforcancerbiology.org.au/m_brown.htm

PROFESSOR MICHAEL BROWN graduated with First Class Honours in Medicine from the University of Sydney before achieving specialist qualifications in clinical and laboratory immunology. He undertook postgraduate research in the genetics department at the University of Melbourne before becoming a research associate under the supervision of Professor Malcolm Brenner at St Jude Children’s Research Hospital, USA. Brown subsequently retrained as a medical oncologist with Professor Ian Olver at the Royal Adelaide Hospital and also obtained a PhD in Gene Therapy and Cancer Immunotherapy at the University of Adelaide.

between research and disease. Rather than eclipsing chemotherapy, the new treatment will work alongside it to maximise the assault on the tumour, but it will do so in a rather unusual way. In non-small cell lung cancer, researchers have struggled to find target antigens within cancer cells for antibody treatments for some time. The innovation of the Adelaide group has been to search not in living cancer cells, but in dead ones.

THE ARRIVAL OF APOMAB

APOMAB® is a patented monoclonal antibody technology in which the antibody matches up with the lupus-associated antigen (La). The Adelaide team, as well as others, has shown that La is overexpressed in tumours, and accounts for a poorer prognosis in lung cancer. This knowledge is useful because it means that APOMAB can track down and bind with tumours, carrying any conjugated drugs with it. But APOMAB is even more specific in its targeting, for a number of reasons. Firstly, because apoptosis causes the breakdown of the cancer cell's plasma membrane and the migration of La from the nucleus to the cytoplasm, the antibody binds within apoptotic cells. Secondly, it is more likely to bind with apoptotic cells when the apoptosis is caused by DNA-damaging therapies such as chemotherapy. And finally, it does not bind significantly with cells that are non-apoptotic, or non-cancerous. Unlike in normal body tissues damaged by chemotherapy, the dead cells linger in cancerous tissue and are available for binding with APOMAB. Because of these characteristics, Brown's group hopes that APOMAB will be useful in ADC therapy – a treatment which involves transporting a highly potent cytotoxic drug to dead cells in the tumour and releasing it at the tumour site to give surrounding living cells a lethal dose of the drug.

In earlier studies of APOMAB labelled with radioactive material, the group showed proof of concept of this approach. They found that the radioactivity would gather inside the dead cells of a tumour, killing the surrounding or 'bystander' cells with radiation, and thereby making more dead cells available to take on more APOMAB. In conjunction with chemotherapy, the researchers have demonstrated the approach to be even more effective, and the heterogeneity of tumour cells, which is retrograde to most forms of treatment, presents no problem for APOMAB-conjugate therapy. In fact, any therapy that kills cancer cells could make a suitable companion for APOMAB.

ENSURING EFFECTIVENESS

Having developed the APOMAB-conjugate approach for bystander killing of tumour cells, the Australian researchers’ work has since focused on fine-tuning the method for safety and efficacy. Their studies showed both of these aspects were best served if mice were given APOMAB radioimmunoconjugates 24 hours after chemotherapy, when any normal cells killed by the drugs will have been cleared by the body, and tumour cell death peaks. They also tested a number of beta-emitting partners for the antibody, but ultimately found that the radioimmunoconjugates were equally effective regardless of whether ‘hard’ emitters such as yttrium-90 or ‘soft’ emitters like lutetium-177 were used. This was because of the fact that chemotherapy shrinks the tumour before the radioimmunoconjugate treatment begins, so although yttrium emits more damaging radiation, it also risks damaging healthy tissues, and so the dose of yttrium-90 that can be used is less than that of lutetium-177.

IMMUNO-IMAGING

To help the Adelaide scientists understand more about the appropriate dose of ADC therapy for lung cancer patients after chemotherapy, an imaging form of APOMAB will be produced. Intact monoclonal antibodies have the longest circulating time in the body, and are therefore best suited for capturing the process of tumour cell death over a long period. The team is therefore in the process of developing a chimeric APOMAB antibody labelled with zirconium-89, a long-lived positron-emitting radioisotope, with the intention that the resulting APOMAB imaging agent might be useful in positron emission tomography (PET). A number of major pharmaceutical companies are very interested in the possibilities of PET because of its high sensitivity and resolution, and the APOMAB imaging agent may give an insight into tumour cell death after chemotherapy, as well as indicating the pharmacokinetics of the APOMAB-ADC.