SIR FRANK MACFARLANE BURNET
an extraordinary life
DIRECTOR’S REPORT

Welcome to the summer issue of IMPACT. We celebrate the 50th anniversary of one of Australia’s greatest virologists and immunologists, Sir Frank Macfarlane Burnet who received the Nobel Prize for Medicine in 1960.

Burnet’s discovery of acquired immunological tolerance, of how the body recognises the difference between self and non-self was enormously significant. His work here and more generally paved the way for numerous breakthroughs in our understanding of infectious diseases and the immune system and has led to the prevention and treatment of diseases in many different settings.

IN THIS ISSUE WE FOCUS ON A NUMBER OF ASPECTS OF BURNET AND LOOK AT HIS LIFE; HIS BROADER CONTRIBUTIONS TO THE COMMUNITY, HIS NOBEL PRIZE-WINNING DISCOVERY; AND THE IMPLICATIONS HIS RESEARCH HAS HAD ON SCIENCE AND MORE SPECIFICALLY IN THE AREA OF MEDICINE.

Burnet spent most of his working career as Director of the Walter and Eliza Hall Institute of Medical Research (1944 to 1965) and during his directorship led a change in direction to immunology, which at the time resulted in some controversy. This ultimately proved to be a major win for Burnet, with a huge contribution to the body of scientific knowledge, part of which was the development of the phenomenon of immunological tolerance. His theory was later validated by Sir Peter Medawar who shared the Nobel Prize with Burnet.

The advancement of the field of immunology during this time was led directly as a result of the discoveries of Macfarlane Burnet and this discipline has since gone from strength to strength. The areas of vaccine development, tissue transplantation, and the development of monoclonal antibody and associated therapies, have all developed through Burnet’s initial work.

We are very proud to have the Burnet Institute named after Sir Frank Macfarlane Burnet and our present day focus is remarkably compatible with his main areas of interests of virology, immunology and public health.

Burnet Institute’s mission, which we have recently reviewed, is ‘to achieve better health for poor and vulnerable communities in Australia and internationally through research, education and public health’. While resource-poor communities were not directly the primary focus of Macfarlane Burnet’s work, the impact of his ground-breaking discoveries have certainly opened the way for many of the global health issues that face these communities to be addressed. He, like the Institute that bears his name, tackled the big issues that impacted on humanity at the time. I believe Sir Frank would have been very proud of the work we undertake and, like us, very enthusiastic about the impact our work has had and will have in the future.

Professor Brendan Crabb, Director and CEO
HIV discovery brings new way to finding a cure

Scientists at the Burnet Institute, Monash University and The Alfred have made a major discovery in the fight against HIV leading to the possibility of an eventual cure.

They have identified the mechanism of how HIV enters resting cells – the main cell that persists in patients on anti-HIV treatment.

Co-head of the Burnet Institute’s Centre for Virology and Director of The Alfred’s Infectious Diseases Unit, Professor Sharon Lewin said one of the major barriers to curing HIV has been the mystery of how resting cells are infected and how the virus can lie hidden for years in these cells, despite prolonged treatment with anti-HIV drugs.

“Our team of researchers has now identified the path by which the virus can infect resting CD4-T cells and establish latency,” Professor Lewin said.

Understanding this mechanism will enable new treatment options to be developed which could block latent infection.

“The discovery heralds the beginning of a new chapter in the fight against HIV and AIDS.”

– PROFESSOR BRENDAN CRABB, BURNET’S DIRECTOR AND CEO

UNAIDS Executive Director, Mr Michel Sidibé visits Burnet

Executive Director of UNAIDS and Under Secretary-General of the United Nations, Mr Michel Sidibé met with Burnet staff and toured our laboratories during a recent visit to Melbourne.

Mr Sidibé discussed Burnet’s comprehensive and practical approach to HIV research with Co-head of Virology, Professor Suzanne Crowe; Associate Professor David Anderson; Associate Professor Gilda Tachedjian; Dr Mark Stoove; Bruce Parnell, Burnet Chairman Mr Alastair Lucas, and Julian Elliott from The Alfred.

Burnet Director and CEO, Professor Brendan Crabb said: “Mr Sidibé’s passion for advancing global health is greatly respected and he remains a tireless supporter of poorer communities gaining access to HIV prevention, treatment and care.”

Thank you to the St Kilda Road Parkview Hotel for their support of our “21st Century Immunology” symposium on 2 December. Located close to the shopping precincts of St Kilda, Chapel Street and the CBD, the St Kilda Road Parkview Hotel is ideal for visitors to Melbourne.
Mac Burnet was one of four eminent scientists, all born in 1899, living in Melbourne who became lifelong friends. The others were Sir Ian Clunies Ross, veterinarian and the charismatic head of CSIRO, Dame Jean Macnamara who worked heroically treating polio victims in Melbourne and the bush in the epidemic of 1937-38 and crusaded for the introduction of myxomytosis to control rabbits, and Sir Ian Wark, metallurgist and educational administrator. Educated at Traralgon and

Above (left to right): Sir Frank with collaborator, Professor Sir Gustav Nossal AC, CBE; teaching young scientists; Burnet deep in thought whilst enjoying the outdoors.

We pay tribute to the legacy of Sir Frank in this 50th Anniversary year of his Nobel Prize for Medicine. Australia’s greatest virologist and immunologist, he made significant breakthroughs in our understanding of infectious diseases and the immune system (for which he won his Nobel prize) and for his contribution to disease prevention and treatment in many different settings.

BY PROFESSOR, THE HON. BARRY O JONES, AO
Terang State Schools, Geelong College and Melbourne University, Mac Burnet retained a deep memory of the influenza pandemic which swept the world in 1918-19 and worked on the virus for 25 years.

Based in London at the Lister Institute from 1925 to 1927, Burnet also worked at the National Institute of Medical Research from 1932 to 1933. As a young man he had been a Fabian and while studying in London greatly admired Bernard Shaw, H.G. Wells and – to a degree – Bertrand Russell. Appointed Assistant Director of the Walter and Eliza Hall Institute for Medical Research in Melbourne in 1928, he was its Director from 1944 to 65 and also held the chair of Experimental Medicine at Melbourne University. He irritated the medical faculty by advocating segregation of teaching and research. In 1944 he declined a glittering offer of a Harvard chair, determined to remain in Melbourne and was succeeded by his protégé Sir Gustav Nossal.

Burnet developed two international reputations, until 1957 as an authority on viruses, then as probably the world’s most distinguished theoretician of immunology. He developed ‘clonal selection theory’ which began a new era in immunology. He published 528 papers, more than 400 on his own research.

Essentially an old fashioned, solitary, intuitive researcher, Burnet had few collaborators other than Frank Fenner, Ian Mackay, Gordon Ada and Gus Nossal. He was rather suspicious of ‘big science’, heavy investment in equipment and setting up research teams and wary of clinical or applied research. That misused word ‘genius’ seems appropriate in his case. Burnet and Nossal were classic introvert and extrovert respectively, but Nossal was a consummate diplomat who made allowances for the older man.

Frank Fenner wrote: “A remarkable feature of Burnet’s career was that although he worked as a virologist until the age of 57, some 90 per cent of his experimental papers being on virology, the two contributions to science for which he became most renowned were in the field of immunology, on aspects in

“MANY OF US HAVE MOMENTS OF GENIUS BUT FEW ARE CONSISTENT. BURNET WAS EXTRAORDINARILY POWERFUL BECAUSE HE CARED ABOUT IDEAS SO MUCH.”
Nobel Laureate Peter Doherty AC
which he had done little or no experimental work. Such breadth and depth of understanding, and such self-assurance as to allow him to challenge established dogma in a field not his own, is rare in the present era of scientific specialization.”

He described himself as an ecologist and his capacity to integrate discoveries made in diverse fields of science was one of his great strengths. He was uncommonly broad in his interests and reading and had an excellent memory and he was a lateral thinker with an unparalleled capacity to link apparently unconnected observations.

Mac Burnet was a biologist of the old generalist school. He was incorrigibly curious about the mechanism of every natural phenomenon he encountered. His rare gift was to take apparently unconnected observations and fit them into whatever theoretical framework was his current obsession. A particular finding in the classical reductionist mode of normal scientific enquiry became a springboard for speculation on the nature of life processes. His experimental work on polio and influenza viruses, assisted by the use of electron microscopes after 1939, resulted in major discoveries about their nature and replication.

Burnet’s experiments had extraordinary reach, shaped by extensive reading and deep philosophical reflection. He liked to picture himself as a 20th century Erasmus, a prophet in his own land, the scholar and scientific humanist who could remain unattached.

His greatest scientific achievements were theoretical: the concept of ‘acquired immunological tolerance’ which underpins organ transplantation and skin grafts and the ‘clonal selection’ theory, a micro-evolutionary explanation of the adaptive nature of antibody production. Both proved to be cornerstones of our understanding of the immune process. Experiments by Gus Nossal and Joshua Lederberg provided formal proof of clonal selection.

Burnet worked with Frank Fenner on acquired immunological tolerance, the capacity of organisms to distinguish between ‘self’ and ‘not self’, which was confirmed experimentally in England by Medawar and Rupert Billingham.

Burnet and Medawar received the Nobel Prize for this work. Fenner and Billingham were very unlucky not to have shared the award because Nobel Prizes can be split into two or three awards, but not four.

The Danish medical scientist Niels K. Jerne published a paper on natural selection in cell production. Burnet recognised a basic flaw and modified it radically in 1957 arguing, along Darwinian lines, the need for a receptor that selected a few cells from a very large library making use of pre-existing mutations favoured for multiplication and survival.

Jerne, who received a Nobel Prize in 1984, wrote: “I hit the nail, but Burnet hit the nail on its head.” Burnet regarded the clonal selection theory as his greatest achievement.

Burnet had some significant near-misses. He abandoned his work on poliomyelitis although it closely paralleled John Enders’ Nobel Prize-winning discovery. He failed to explore the phenomenon of haemagglutination (clumping of red blood cells) following attacks of influenza. He demonstrated interferon in action in 1951 but its significance was only recognised by his former co-worker Alick Isaacs in 1957. He had a notorious blind spot about molecular biology.

No other Australian medical scientist ever received so many awards for work carried out in Australia. Burnet received the Lasker Award in 1952, the Order of Merit in 1958, the Royal Society’s Copley Medal in 1959, and shared the Nobel Prize for Medicine in 1960 with Peter Medawar for their work on ‘acquired immunological tolerance’. Three times a knight (Knight Bachelor, KBE, AK) he

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**A MAN WHO THREW OFF IDEAS LIKE SPARKS WHICH CAUSED A BLAZE THAT LEAPT ACROSS TO THE MINDS OF OTHERS.”**

inscribed on Burnet’s tombstone in Tower Hill, near Port Fairy – quotes Plato’s words on Socrates
became the first recipient of the Australian of the Year award in 1961 and was President of the Australian Academy of Science from 1965-69.

Burnet, understandably proud of his honours, was the first Australian resident to be awarded the Order of Merit, a surprising distinction at that stage because among scientists it was generally awarded after a Nobel Prize, not before it. His first reaction to news of the OM was pleasure at “joining a select group, including my longtime literary hero G B Shaw,” a curious slip. (Shaw won a Nobel Prize but not the OM).

The OM and Nobel Prize helped enhance his credibility and authority as a scientist-philosopher. Although deeply shy and introspective, he became a leading public intellectual in the last 25 years of his life, welcoming invitations to speak, write and celebrate the achievements of Australian science, including his own. He involved himself in debate on many major issues. His contributions were invariably interesting, not invariably correct.

His industry was exceptional. In retirement, between the ages of 66 and 80, he wrote 16 books including ‘an atypical autobiography’, Changing Patterns (1968), delivered the Australian Broadcasting Commission’s Boyer Lectures for 1966 and wrote some important essays.

His books addressed a range of issues – global population pressure, the elimination of war, conservation, nuclear and solar energy, eugenics, the future of science, the progress (or, in some cases, the regress) of mankind. He supported programs for reducing human pain, misery and indignity.

When I interviewed Nobel Laureate Peter Doherty for The Age in 1999, he said:

“Burnet was a hero. Many of us have moments of genius but few are consistent. Burnet was extraordinarily powerful because he cared about ideas so much. Unlike Burnet, I was never a naturalist or a born observer. But I shared with Burnet an interest in ideas and generalisations. I am a deconstructionist. I take things apart…Burnet, I think, felt the same about himself.

“He published a book arguing that immunological surveillance of lymphocytes might assist in limiting cancer. It turned out that this was wrong. But the idea of surveillance was important. As was often the case, Burnet was partly right. He felt badly about the book. I wrote that it was an important book which generated a lot of controversy. When Rolf Zinkernagel and I discovered our phenomenon (on cellular immunity) we adopted the term ‘surveillance’ from him.”

In October 1968, Mac Burnet agreed to take part in discussion with Spike Milligan on the television program Encounter, which I hosted. I planned it in three parts – first Spike with me, then Mac with me, then the three of us together.

Each began from utterly different premises, knowledge and experience. Milligan was the man of instinct, a passionate tortured genius, on the edge of madness, with a wild self-lacerating humour and a brooding sense of chaos underlying human experience. Burnet saw the world as a self-contained rationalist and experimentalist, emotionally contained, sharply focussed, suspicious of the metaphysical. They were an odd couple. Despite his initial unease, after a few minutes the mixture started to work and I never heard Mac Burnet laugh so much.

Mac responded at once to Spike’s Blakean intensity and they found that, although starting from completely different premises, one rational and based on evidence, the other intuitive and based on instinct, they agreed on fundamentals. On a number of issues – nuclear disarmament, reducing third world poverty, children’s welfare, access to education and the arts, the campaign against smoking, preserving the environment – their views coincided. Each could understand how the other’s mind worked and could anticipate reactions. Both were unusually pleased with themselves.

Frank Macfarlane Burnet died at his son’s home in Port Fairy on 31 August 1985, aged almost 86. On his tombstone in Tower Hill, near Port Fairy is a quote from Plato about Socrates: “A man who threw off ideas like sparks which caused a blaze that leapt across to the minds of others”.

Burnet teaching young scientists.
**Burnet’s Nobel Prize:**

**TACKLING THE BIG ISSUES OF HIS TIME**

On 20 October, 1960 Sir Frank Macfarlane Burnet was announced as the winner of the Nobel Prize for Medicine ‘For Discovery of Immunological Tolerance.’ Prime Minister Menzies declared in The Sun News Pictorial: “An honor conferred on Sir Macfarlane Burnet is an honor which every good Australian will enjoy.”

*BY LAUREATE PROFESSOR PETER DOHERTY AC AND ASSOCIATE PROFESSOR ROSEMARY FFRENCH*

Sir Frank Macfarlane Burnet shared the 1960 Nobel Prize for Physiology or Medicine with Brazilian-born, English zoologist, Peter B. Medawar. The Nobel citation reads: ‘For Discovery of Immunological Tolerance.’ Burnet’s contribution was essentially conceptual while Medawar’s was experimental.

Medawar demonstrated, for example, that skin could be transplanted into the brain across a species barrier (xenotransplant) providing that there was no direct exposure of the immune system to the foreign proteins on the graft. That is, the graft was ‘tolerated’ so long as it did not provoke a host response. That work was done in the context of an interest in tissue grafting, Medawar’s focus during World War II. At that time, Burnet was developing an influenza vaccine and thinking a lot about immunity.

Science was much smaller then than it is today and the lines of specialisation between different disciplines were less tightly drawn. Most medical virologists were also interested in the nature of the host response, and virology was yet to move (from the 1960s) into the obsession with tissue culture. In thinking about tolerance, Burnet drew intellectually on Medawar’s experiments, on Ray Owen’s analysis of cattle blood chimeras and on Erich Traub’s studies of lymphocytic chorimeningitis virus (LCMV) which causes a persistent, inapparent infection in mice infected in utero. The experiments that Rolf Zinkernagel and Peter Doherty did with LCMV injected into adult mice led to the 1973 discovery of MHC-restriction for CD8+ “killer” T cells which, with the consequent conceptual framework they developed, led to the 1996 Nobel Prize. In more than one sense, this work was in the Burnet lineage.

Back in the 1950s when Burnet was turning more of his interest towards immunity, Jim Gowans was showing that lymphocytes recirculate from blood, to tissue and to lymph, and Jacques Miller was about to discover (1961) the role of the thymus. That was soon followed by the realisation that there are separate categories of T and B lymphocytes. Though Paul Ehrlich, who is regarded by many as the ‘father of immunology’ had raised the problem of ‘horror autotoxicus’ early in the 20th century, it was Burnet who proposed the central idea of acquired immunological tolerance formulated around the perceived necessity to ensure discrimination between self and non-self. That statement is central to our view of how immunity operates. However, with advances in understanding and technology, the lines defining self versus non-self may be somewhat less rigidly interpreted than was the case in Burnet’s thinking.

The world was a very different place in 1960. The use of cable rather than telephone to get a
Burnet pioneered the use of chick embryos to grow and count viruses.

message to someone living in the far antipodes led to a short period of confusion. Burnet heard rumors but he was, for a time, uncertain. Much worse was the considerable embarrassment suffered by ANU neurophysiologist Sir John (Jack) Eccles. When Canberra scientists heard the news of an Australian Nobel Prize winner, they broke out the champagne. Then they learned that it was Burnet. Along with English researchers Andrew Huxley and Alan Hodgkin, Jack Eccles was to have his day in 1963. Andrew Huxley, the only survivor of the 1960 and 1963 Nobel Prizes, is the grandson of T.H. Huxley (Darwin’s bulldog) and the younger brother of the novelist Aldous Huxley (Brave New World, Eyeless in Gaza).

Burnet and Eccles shared the experience of being University of Melbourne medical graduates in the 1920s and for a time, the two of them dominated the somewhat small Australian biomedical research scene. They were, however, very different. Burnet’s embrace of evolution was absolute and he rejected any theistic view of the world early in life. A devout Catholic, Eccles argued the idea of the ‘ghost within the machine’: in the process, he lost the respect of many of his neuroscience colleagues, including Andrew Huxley.

Thinking way beyond the narrow confines of their science, Burnet and Eccles also wrote elegant and thoughtful books that addressed broader issues. Eccles collaborated on a volume with Karl Popper and was generally influenced by the more formal elements of philosophy and theology, while Burnet’s thinking was always based in biology and, particularly, in teleological Darwinism. Each of those approaches has the potential for heading down dangerous paths and the arguments they pursued would not all be regarded as felicitous today. Social Darwinism is a hideous perversion, and religiosity and science are best kept apart. But they lived with different realities in an intellectual and scientific world that is increasingly remote. We should not fall into the trap of historicism and judge them by current prejudices.

Burnet and Eccles were ‘great men’ in a time when ‘great men’ were still tolerated! Eccles was outgoing and athletic while Burnet was neither, though he did have a very substantial ego. There’s a story, perhaps apocryphal, that they were being awarded honorary degrees together, but the academic ‘floppy hat’ didn’t fit Burnet, who went off with someone to see if they could find one more suitable. Eccles is said to have remarked: “They’ll never find a hat big enough for that bastard!”

Both left strong research ‘schools’ behind them. When Burnet switched the focus of the Walter and Eliza Hall Institute to immunology in 1957, the Australian virology mantle transferred to his former student Frank Fenner and the Microbiology Department at the John Curtin School of Medical Research.

Immunology has gone from strength to strength from the time of Burnet, with foci of excellence being widely disseminated throughout the Australian academic scene. For some years the rise of molecular science, particularly transfection techniques, eroded virology’s position as a central intellectual discipline, both here and globally. That changed though, with the emergence of HIV/AIDS and the realisation that viruses, bacteria and parasites continue to cause major loss of life in, particularly, the developing world. Now, when anyone thinks of research on infectious disease in Australia, the name of the Burnet Institute immediately comes to mind, especially if the context happens to be the problems faced by the disadvantaged. Though the third world was not Burnet’s primary focus he did, like the Institute that bears his name, tackle the big issues of his time.
21st century immunology: BURNET’S MEDICAL RESEARCH AND PRACTICAL ACTION

Sir Frank Macfarlane Burnet was a theoretician and also a pragmatist. He understood, even in the late 1950s, the practical value of immunology as having ‘greater practical use in medicine’ than the research fields it superseded. In this 50th Anniversary year of Burnet’s Nobel Prize, five of the top 10 drugs used in the treatment of human disease are based on monoclonal antibodies. Burnet’s theoretical centrepiece of his prize-winning research was ‘clonal selection’ – a watershed in medical research.

**THE NATURE OF BURNET’S DISCOVERY:** Burnet shared the 1960 Nobel Prize with Peter Medawar. They revealed the way the immune system can distinguish between foreign things (bacteria and viruses, organ transplant or transfusion) and the normal parts of the body (normal cells, tissues and organs).

The centrepiece of this research was Burnet’s theory of ‘clonal selection’ for which Medawar provided supportive experimental evidence. Burnet’s pithy, visionary and far-reaching theory is central to modern immunology. The work was a watershed in medical research because it underpinned so much that was to come.

Burnet predicted how immune cells were selected to distinguish normal tissues or ‘self tissues’ from foreign or ‘non self’ agents. Burnet’s theory predicted that one immune cell - a clone - was selected to respond to a foreign antigen (a small part of a foreign molecule) or if it recognised ‘self antigen’ it was selectively eliminated. By this selection process the immune system generated millions of clones, each specific for one distinct antigen. Collectively, the immune system is then able to respond to millions of different foreign antigens and importantly, those with the potential to do self-harm have been eliminated.

**THE INDUSTRIAL REVOLUTION IN IMMUNOLOGY:** The clonal selection theory laid the foundation for one of the greatest applications of technology to come to modern medicine. This is the discovery of methods to immortalise Burnet’s theoretical clones, generating monoclonal antibodies.

Burnet’s idea that one immune cell - a clone - harbours one specific protein available to attack a foreign entity is the essence of the monoclonal antibody technology. Where Burnet had predicted the existence of clones that recognised a single antigen, the Danish immunologist Nils Jerne
proved this to be so for the white blood cells that make proteins called antibodies. Antibodies are the immune system’s main weapon in the blood and they are very effective at killing foreign invaders. Drs Kohler and Milstein in Cambridge were also studying how white blood cells made antibodies and discovered a method that could immortalise a single cell clone, making antibody of a single specificity; a so-called monoclonal antibody. Thus, for the first time it was possible to produce unlimited quantities of some of the most potent and specific therapeutic drugs known.

Jerne shared a Nobel Prize with Kohler and Milstein in 1984 and a decade later the first therapeutic monoclonal antibody was released onto the market. The immune-based industrial revolution: It is difficult to overstate the importance of monoclonal antibodies to diagnostic medicine and the treatment of previously incurable diseases, and their importance to pharmaceutical industries for the ‘blockbuster’ revenues they generate. These biological drugs have completely changed the treatment landscape, especially in cancer and inflammation. For example, Herceptin improved treatment in breast cancer; Rituxan effectively cures non-Hodgkin’s lymphoma in over 50 per cent of patients; and Humira, Infliximab or Tocilizumab offer transformative treatment for 50 per cent of rheumatoid arthritis patients. Collectively these antibodies earn in excess of $13 billion annually.

Acquired immunological tolerance, challenges and intractable diseases: The power of the immune system to deal with diseases is evident from the spectacular success of vaccines – polio, smallpox, measles, tetanus and the like – however many diseases still require better treatment. Despite the great optimism of the 1980s, there is still no effective vaccine for HIV. The human immunodeficiency virus (HIV) infects over 30 million people worldwide and despite two decades of prodigious effort a vaccine still eludes us. Similarly, cancer is of particular interest because it has a dual personality as far as the immune system is concerned. A cancer arises within the body and so is ‘self’ and should not be recognised, however cancer cells are by their nature different to normal cells and perhaps should be immunologically foreign. Hope is on the horizon. New immunotherapies that re-educate the immune system and get otherwise controlled selected clones to attack cancer cells are in development. Our breast/ovarian cancer vaccine at the Burnet Institute is advancing through clinical trials in the US.

Fifty years on, over 200 monoclonal antibodies are on the market or in clinical testing, and by 2014 seven of the top 10 drugs will be monoclonal antibodies. Several immunotherapy ‘vaccines’ will be registered for the treatment of cancer and we will be closer to the effective vaccination of challenging diseases like malaria and AIDS. Burnet’s view of his role in ‘the discovery of acquired immunological tolerance’ was, in his words, simply “the formulation of an hypothesis that called for experiment.” Australian songwriter Paul Kelly encapsulates the achievements in his song From Little Things, Big Things Grow.
Novel analgesic improves pain and quality of life in patients with severe, HIV-neuropathy pain

Neuropathy (nerve damage in the feet) is common among people with HIV, affecting ~40% of Melbourne HIV patients. Neuropathy frequently causes chronic pain and treatment is often ineffective. No available analgesic has been shown to work better than placebo to relieve HIV-neuropathy pain. In collaboration with Relevare Pharma Inc and The Alfred hospital Clinical Research Unit, the Cherry Laboratory recently conducted two trials that showed flupirtine (a novel, oral analgesic) effectively relieves HIV-neuropathy pain in patients with severe (≥5 out of 10) pain despite the use of regular opioid (morphine related) analgesics.

Eleven patients took part in a 13 week, randomised, controlled trial where they received six treatment weeks (four different doses of flupirtine and two weeks of placebo added to their regular medications) alternating with seven ‘wash out’ weeks. Daily pain scores showed dose-related improvements during flupirtine treatments compared with placebo. At the highest flupirtine dose studied (400mg per day), patients’ average pain scores were 12 per cent lower than during placebo treatments (p<0.01). These results make flupirtine (with opioids) the first drug other than smoked cannabis to be shown to improve HIV-neuropathy pain in a randomised, controlled trial.

Eight patients subsequently entered a 12-month open-label study. Two patients left the study: one developed a drug rash and one moved overseas. The remaining six patients added 400-600mg flupirtine to their daily analgesic regimen. They all enjoyed a clinically meaningful reduction in average pain scores (mean 31%) and improved quality of life (mean 26%) that continued at 12 months. Based on these findings, The Alfred hospital pharmacy has agreed to provide ongoing access to flupirtine to the patients involved in the study until this drug becomes available under the Australian Pharmaceutical Benefits Scheme. All patients remain on flupirtine today and all patients continue to benefit substantially from this medication (Figure).

Figure: Patients with severe pain due to HIV-neuropathy have enjoyed a sustained improvement in their pain (left panel) and their pain has interfered less with their daily activities (right panel) with adding flupirtine to their daily analgesic regimen.

FINDING NEW TARGETS FOR HIV ANTIVIRALS

In the absence of an effective vaccine, antivirals are essential to treat the ever-increasing number of people living with HIV. However, drug resistant viruses can emerge, highlighting the need to find new targets for antivirals. Chan-Sien Lay and Ashraf Khasawneh are studying the membrane fusion process, which is an early step of the viral replication cycle and an obvious target for antiviral development.

Fatty layers or ‘membranes’ enclose both HIV and the immune cells that it infects. These membranes act as barriers to infection which are overcome by the gp41 protein on the surface of HIV. gp41 causes the membranes to fuse and to form channels, linking the virus and immune cell interiors. The viral genetic material then penetrates into the cell via these channels. A major goal of The Virus Fusion Laboratory is to understand how gp41 enables membrane fusion.

Two features define the membrane fusing properties of gp4. First, hairpin-like structures at its extremities (transmembrane and fusion domains) that insert into the virus and cell membranes, respectively; second, its ability to form a hairpin-like structure that brings the captured membranes together. Our recent work has revealed that membrane fusion is also dependant on two short sequences that are adjacent to the transmembrane and fusion domains, forming a clasp at the end of the hairpin-like structure. The clasp sequence change very little during the evolution of HIV, making them favourable targets for antivirals that block fusion.

PROJECT NAME: Defining the membrane fusion properties of gp4. LENGTH OF PROJECT: Ongoing.
Understanding Myeloma

The Centre for Immunology has a number of groups attempting to develop new approaches to the treatment and elimination of blood cancers including leukaemias, lymphomas and myelomas.

Dr George Grigoriadis from the Department of Clinical Haematology, Monash University is a haematologist undertaking postdoctoral studies in the laboratory of Professor Steve Gerondakis and is developing a research program in a particularly difficult cancer called myeloma. Multiple myeloma is a type of cancer that develops from cells in the bone marrow called plasma cells which normally produce antibodies in the blood. In Australia more than 700 patients died from myeloma in 2006, representing a significant burden of disease to the community. In addition, myeloma is the most common cancer to involve bone, with up to 90 per cent of patients developing bone lesions. Up to 60 per cent of patients develop fractures. Thus, bone disease is a major cause of morbidity in myeloma. Despite extended disease-free intervals, the majority of patients with myeloma continue to suffer recurrent disease relapse and increasing resistance to the currently available drugs. Moreover, why some patients respond to certain therapies and not others is not clear and highlights a need for new therapeutic strategies.

Little is understood about how gene changes re-program the biochemical pathways that determine myeloma growth and survival. This lack of knowledge about how biochemical pathways might vary amongst myelomas with different genetic lesions has limited the application of such information to treatment, with the current approach to therapy essentially adopting an ‘all sizes fits one’ policy.

As our research in myeloma evolves it is essential to accurately predict prognosis and tailor treatment regimens for individual patients. We are establishing a novel and innovative research program that is aimed at understanding the contribution key biochemical pathways make to the pathogenesis of myeloma. Our aim is to develop a combined clinical-scientific approach to change myeloma from a disease with a median survival of 3-4 years associated with significant morbidity to a chronic medical condition that has little impact on the patients quality of life.

PROJECT NAME: Establishing more effective therapeutic strategies for the treatment of myeloma. COLLABORATORS: Professor Andrew Spencer, Alfred Health and Monash University, Department of Clinical Haematology; Professor Steve Gerondakis, Burnet Institute; Associate Professor Ricky Johnstone, Peter MacCallum Cancer Centre.

RELOCATION OF THE STRUCTURAL BIOLOGY GROUP TO PRAHRAN

The restructure of Burnet is now complete with the protein structural unit, headed by Dr Paul Ramsland, relocating from the Austin campus. The structural unit has been very active in establishing collaborations across all Centres at Burnet, which has ensured integration across the Institute’s key research themes in infectious diseases. Techniques employed by this group are protein crystallization, X-ray crystallography, computational protein modelling and in solution protein particle/aggregation analysis.

Protein crystals are generated by the empirical screening of a broad range of crystallization conditions. Once grown, X-ray crystallography using our microfocus ‘in house’ and Synchrotron sources will determine the arrangement of the atoms within the protein by passing an X-ray beam through the crystal and collecting the diffraction pattern (similar to the picture one gets of bones when analyzing an X-ray). Typically a crystal is rotated through 180 degrees and diffraction patterns taken at every degree. The interpretation of the angles and intensities of these diffracted beams allow for a detailed three-dimensional image of the protein to be reconstructed.

The group also employs computer modelling to predict the structures of proteins and key interactions of central importance to biology, such as those between proteins and carbohydrates (Structural Glycobiology). Complementing both X-ray crystallography and protein modelling is the technique of dynamic light scattering (DLS). DLS allows the same proteins to be examined in solution and uses wide-angle scattering of a laser to probe the distribution of sizes and the uniformity of a protein sample.

The structural group is also actively engaged in training students and staff in any facet of Structural Biology. Their goal is to work with all Burnet’s Centres and foster collaborations across the Alfred Medical Research and Education Precinct (AMREP). In addition, they will maintain active research in Structural Glycobiology, collaborating with researchers at Austin Health (Ludwig Institute and University of Melbourne) and Monash University, Parkville.
As such, transition programs provide opportunities to address the health, social, substance use and criminogenic needs of people who inject drugs. However, our ability to intervene at these crucial points is limited by a poor understanding of the trajectories of this group as they move back into the community. Understanding these trajectories will help to inform transition programs and limit the continued cycling of this population through the criminal justice system.

The Centre for Population Health at the Burnet Institute recently completed a study of the post-prison release experiences of people with a history of injecting drug use. 141 participants were interviewed within one month of their release and again at three and six-months post-release. 106 participants completed at least one follow-up interview.

The study findings showed that the immediate post-release period for people with history of injecting drug use contains many challenges, such as finding stable and secure accommodation, financial security, drug treatment, and mental health and emotional support. These challenges overlap and combine to make ongoing drug use and criminal behavior almost inevitable.

An overwhelming majority (85%) of participants returned to injecting drug use within one month of release, with almost one-third reporting daily injecting. Finding stable, long-term accommodation was a problem for most participants, with those relying on short-term boarding house accommodation suggesting that this actually facilitated their return to injecting drug use – “They put you in accommodation with other drug users and criminals ... it’s hard not to use when other tenants do ... the place isn’t secure ... I have contacted many housing services but they keep putting me in these hostels.”

Mental health morbidity among participants was substantial, with 42 per cent reporting taking at least one medication for mental health. Of concern was that two-thirds of these participants were not in contact with specialist mental health services. While this was due to traumatic past experiences for some participants, many were frustrated by the lack of pre and post-release support to access such services. This necessity to self-navigate a fragmented and uncoordinated post-release service sector was a common theme across many service domains, including accommodation, social support and drug and alcohol treatment.

Findings from this study indicate that the current pre- and post-release service system, and the lack of inter-service coordination, impede effective support for this population. This finding is most clearly demonstrated by the high rates of drug use, extreme psycho-social stress, the rapid return to crime and limited access to services following release from prison.

The report to the Victorian Government from this study has outlined many recommendations for improving policy and practice. This study has also provided pilot data to support and much larger study currently being considered by the National Health and Medical Research Council.
at-risk people are covered by comprehensive HIV/AIDS services by 2015. Burnet is working with the SUM II lead organisation, Training Resources Group (TRG) from the US, and the other consortium members, RTI International (US) and AIDS Projects Management Group (Australia).

The SUM Program (SUM I and SUM II) is funded by the United States Agency for International Development and will be guided by the Indonesian National AIDS Commission and Ministry of Health. SUM I, implemented by Family Health International, will focus on technical capacity building and strategic information while SUM II will focus on building the capacity of CSOs and implement a small grants program in eight targeted provinces where most-at-risk populations (MARPs) are concentrated. It will engage representatives from MARPs and HIV-positive groups to assist in designing and implementing HIV prevention, treatment, care and support activities. All partners will be involved in tackling the issues of stigma and discrimination around HIV/AIDS.

Every province in the country now has an AIDS Committee and many have been active in developing a ‘condom culture’ in parts of the country where the virus has spread the fastest. “While our neighbour faces many other health challenges such as high maternal and child mortality rates, there is cause to congratulate PNG on this latest good news,” he said.

Burnet supporting SUM II project in Indonesia

The Burnet Institute will contribute its expertise to a US$20 million project to expand HIV prevention, treatment and support activities throughout Indonesia over the next five years. The project, Scaling Up for Most-At-Risk Populations: Organizational Performance (SUM II) will focus on improving the performance of Indonesian civil society organisations (CSOs) to scale up effective, integrated HIV and AIDS interventions to ensure that at least 80 per cent of most-at-risk people are covered by comprehensive HIV/AIDS services by 2015.

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Burnet began working in Indonesia in 1987 and has been the technical partner on all three AusAID HIV bilaterals since 1995, including the current HIV Cooperation Program. Our country office, established in 2002, has expertise in HIV prevention and care, women’s and children’s health, and sexual and reproductive health.

‘Good news’ about declining HIV rates in PNG

Australia has played a key role in supporting the fight against HIV and AIDS in PNG, having invested close to $100 million in the national response,” Mr Toole said.

“The actual estimate of the percentage of the adult population infected by the virus in 2009 is 0.9 per cent, a figure endorsed by the world’s peak body, the United Nations Joint Program on HIV and AIDS.”

Between 2008 and 2009, there was a decrease in the number of newly diagnosed HIV infections of 37 per cent even though around 120,000 people were tested in each of those years. At the peak of the epidemic in 2005, 15 per 1000 pregnant women tested positive; in 2009, just seven per 1000 were positive. The decline has been even more pronounced in rural areas.

An important milestone in PNG’s response to the epidemic was the passing by Parliament in 2003 of a law that outlawed discrimination on the basis of HIV status. This enabled more and more people to get tested with less fear of stigma and for prevention efforts to be scaled up despite widespread anti-condom rhetoric.

While our neighbour faces many other health challenges such as high maternal and child mortality rates, there is cause to congratulate PNG on this latest good news,” he said.

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