Researchers at The University of Auckland, in collaboration with the Peter MacCallum Cancer Centre in Australia, are developing first in class small molecule inhibitors of perforin, to develop novel therapeutics for a range of autoimmune and infectious diseases.

Why Inhibit Perforin?
Perforin is a pore-forming protein secreted by cytotoxic lymphocytes (CTL) or natural killer (NK) cells – immune cells which are critical for killing virus-infected, malignant and foreign cells. Perforin kills target cells by assembling into barrel-shaped pores in the cell membrane, allowing the delivery of toxic components and/or leakage of cellular contents, which promotes apoptosis.

While stimulation of CTL and NK cells is essential in the innate immune system, these cells are also implicated in auto-immune disorders and infectious diseases.

Current therapies to suppress activity of the CTL and NK cells have a wide range of side-effects due to multiple molecular targets being affected simultaneously. By inhibiting perforin specifically, there is the potential to find a potent and more selective immunosuppressive therapy with greatly reduced side-effects.

Applications
A small molecule inhibitor of perforin has great potential as a potent and highly selective immunosuppression agent for autoimmune diseases such as transplant rejection and graft-versus-host disease and infectious disease, such as malaria. Small molecule perforin inhibitors provide a way to selectively and accurately modulate immune function in a controllable manner.

Because pore-forming toxins such as perforin are widely distributed in nature, inhibitors of perforin may also have broader applications in anti-bacterial settings.

IP Position
PCT/AU2005/000291”Recombinant perforin, expression and uses thereof” filed by Peter Mac in 2005 relating to methods of expressing perforin and screening assays as well as compounds identified by the screening assays and uses thereof. National phase applications filed in several countries including USA, Europe, China, Canada, Australia, Japan, India and New Zealand with benefit of a priority date of March 3rd, 2004.

Two new US provisional patent applications have been filed by Peter Mac and UniServices claiming composition of matter of the small molecule and their use as perforin inhibitors. UniServices and Peter Mac have joint intellectual property pending on further small-molecule drug candidates.
**Drug discovery at The University of Auckland**

Combining creativity, innovation and outstanding science.

**Auckland Cancer Society Research Centre (ACSRC)**

Within the last decade the ACSRC has taken eight compounds into the clinic, with one registered and four in late stage clinical trials.

Professor Bill Denny is co-Director of the ACSRC and leads the medicinal chemistry division, which has an impressive track record and cutting edge expertise in the design and synthesis of small molecular kinase inhibitors, vascular-targeting agents, pro-drug therapies, hypoxia-activated cytotoxins and DNA-targeting agents.

Professor Denny received his PhD (organic synthesis) and DSc (drug design) degrees from The University of Auckland, and his research interests include all aspects of the design and evaluation of small-molecule chemotherapeutic agents. He is past-President of the New Zealand Institute of Chemistry and the New Zealand Society for Oncology, and was appointed an Officer of the New Zealand Order of Merit in 2003. His awards include the Rutherford Medal of the Royal Society of New Zealand (1995), the Adrien Albert Medal of the UK Royal Society of Chemistry (2005), the Albert Award of the Royal Australian Institute of Chemistry (2006) and Biotechnologist of the Year (NZBio co-award 2007).

He has been closely involved in design and development of twelve new cancer drugs brought to clinical trials in New Zealand, the United States and Europe, and is an author on around 600 scientific papers and 120 patents and applications.

**Peter MacCallum Cancer Institute (Peter Mac)**

Dr Joe Trapani is the lead biology investigator at the Peter MacCallum Cancer Institute. Upon completion of his medical degree, PhD and physician training in rheumatology, Prof. Trapani became interested in the biology of cytotoxic lymphocytes (CTLs) as a post-doctoral fellow. He cloned granzymes B and H and cloned and characterized the mouse perforin gene. More recently, he has elucidated the molecular and cellular pathways to granzyme B-mediated apoptosis and the mechanisms of perforin/granzyme synergy.

Prof. Trapani is currently Deputy Director of the Research Division at Peter Mac, and his current research interests include the immunopathology of viral diseases, apoptosis induction by CTLs and cancer immunotherapy. He is the author of over 150 primary research papers, review and book chapters covering histocompatibility, apoptosis and cancer immunotherapy.

**The University of Auckland**

The University of Auckland is New Zealand’s world-ranked university. It is ranked in the top 100 in the QS World University Rankings, and the only New Zealand university ranked among the world’s top 200 universities by the Times Higher Education World Rankings of Universities. The University of Auckland is also the highest ranked New Zealand university in the Shanghai Jiao Tong Academic Ranking of World Universities.

The University of Auckland is an international centre of learning and academic excellence. It is New Zealand’s pre-eminent research-led institution and has key linkages with many of the world’s top research intensive universities. The University actively seeks to work with government, other universities, research organisations, businesses and commercial consultancies in research, development and education.

Established in 1883, it is an international centre of learning and academic excellence. It is New Zealand’s largest University with over 5,000 staff and 40,000 students, including over 5,500 international students.

**Auckland UniServices Limited**

Auckland UniServices Limited is the commercial research, knowledge transfer and custom education company for the University of Auckland - dedicated to connecting the University’s capabilities to business and investors, Government and the community. UniServices is a wholly-owned company of the University of Auckland.

In just 25 years UniServices has grown to produce an income of over NZ$135 million per annum, far surpassing any similar organisation in New Zealand and Australia. Our income derives from contract research and consulting, customised education programmes for 25,000 students around the world and from transferring intellectual property developed by staff and students at the University to the public and private sectors.

We are a substantial organisation with over 700 employees, working in 45 countries, and with access to many more academic staff from the University of Auckland. The work of UniServices supports the leadership position of the University of Auckland, and allows the University to expand and enhance its capabilities in commercial and basic research.

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