

Australian antivenom saving lives: Case Study

Snakebite causes suffering, disability and premature death around the world. Globally, almost 7,400 people are bitten by snakes every day, leading to about 2.7 million cases of envenoming (venom poisoning) and 81,000-138,000 deaths each year. Australia and its neighbours are home to a majority of the world's most venomous snake species and our region hosts many other venomous creatures. Consequently, Australian clinicians and scientists have been able to conduct world-leading research in the areas of envenomation first aid, antivenoms and associated public health measures. This case study focuses on the work of the NHMRC-funded Australian Venom Research Unit (AVRU) and the impacts of its work.



Origin

Due to its variety of venomous animals, Australia is an ideal place for research on toxins and has a long established research capability in this area.

The Commonwealth Serum Laboratories (now CSL, a private company) became involved in antivenom research in the 1920s and, in 1928, the first medical research grant provided by the Australian Government was used for the development of tiger snake antivenom, manufactured by CSL.

CSL released taipan, brown snake, death adder and Papuan black snake antivenoms during the 1950s and, in 1976, a team at CSL led by Dr Struan Sutherland successfully identified the major toxin in the venom of the funnel-web spider, leading to the development of an antivenom.

In 1994, Sutherland left CSL to establish AVRU within the Department of Pharmacology at the University of Melbourne.



CTCC Laboratory Manager, Mr Owen Paiva, milking the venom from a Papuan taipan. Image: Dr David Williams

For more than 100 years, the primary treatment for snakebite has been the administration of antivenoms. Good-quality antivenoms can literally make the difference between life and death. However, due to variability among snake venoms (both within and between species), there is currently no universal snake antivenom.

Grants and Investment

AVRU was established with seed funding from CSL and The University of Melbourne. The unit was also supported by grants from the Victorian State Government and from contract consultancy work.

Department of Health / NHMRC funding

From 2001 to 2011, AVRU received annual funding from the Australian Government Department of Health. Since 2011 NHMRC has administered this funding. NHMRC has also supported AVRU staff through the following grants:

Dr Ken Winkel
Project Grant: 2012

Dr David Williams
Peter Doherty Biomedical Fellowship: 2017

Other government funding

- Department of Foreign Affairs and Trade (DFAT): 2016, 2018
- Department of Health and Ageing (DoHA): 2007
- Victorian Government: 2002, 2011

Associate Professor Bryan Fry
Australian Research Council (ARC): 2004

Other funding

- Australia-Pacific Science Foundation (APSF): 2001, 2004, 2007
- CASS Foundation: 2006
- CSL: 2001, 2002, 2018
- ExxonMobil (PNG): 2017
- Hermon Slade Foundation (HSF): 2001
- Lillian Lincoln Foundation (LLF): 2018
- National Geographic (NG): 2017
- Papua New Guinea (PNG) Research, Science and Technology (PNGRST): 2015
- Sutherland Trust: 2002-2010
- The University of Melbourne: 2015, 2016

Collaborations

Antivenom research and envenomation treatment is a global effort, and AVRU contributes through collaborations with both domestic and international organisations. Collaborations include work with:

National

- The Australian Institute of Health and Welfare, the Australian Bureau of Statistics and the National Coronial Information System: to enable the analysis of venomous injuries and deaths across Australia through data linkages
- Seqirus (a part of CSL): to co-develop Australian antivenoms and the *Australian Bites & Stings* app.

Regional

- The PNG Snakebite Partnership, which includes PNG National Department of Health, the Australian Government, the University of PNG (UPNG) and Seqirus: to distribute life-saving Australian antivenoms across PNG.
- Instituto Clodomiro Picado (ICP), University of Costa Rica, UPNG and Port Moresby General Hospital: to develop a novel taipan antivenom.

International

- Bio-Ken Snake Farm (Kenya), Consejo Superior de Investigaciones Científicas (CSIC), Spain, and University of Oxford, United Kingdom: to audit venom quality and antivenom efficacy.
- Evolutionary Venomics Laboratory, Indian Institute of Science: to investigate convergent venom evolution and its consequences for antivenom manufacture.

World Health Organization

- Expert consultation on the development of both a snakebite envenoming roadmap and antivenom guidelines.

Trials and Results

New antivenom to treat taipan bites in PNG

AVRU, in collaboration with ICP, developed the first new snake antivenom for human use in over 50 years. The novel taipan antivenom was developed at a fraction of the cost of the existing antivenom. In 2012-2014, an NHMRC-funded Phase II clinical trial in PNG found that the new antivenoms safely and effectively neutralised the toxic effects of taipan venom in snakebite patients.

Adjunct therapy for taipan bites

In 2017-2019 AVRU collaborated with Ophirex Inc. to preclinically assess the efficacy of the snake venom inhibitor *varespladib* as an adjunct treatment for taipan envenoming. This preclinical study established that delayed oral doses of *varespladib* increased survival and antivenom effectiveness following lethal doses of taipan venom.

Assessing the efficacy of Australian antivenoms

Polyvalent antivenoms contain antibodies raised against multiple snake species. Overlap in venom profiles across species may result in polyvalent antivenoms offering protection against bites from snakes whose venoms were not used in the original immunising mixture. Work by Dr Williams and Associate Professor Christine Wright discovered that Seqirus' Polyvalent Snake Antivenom neutralised the venom lethality of PNG's small-eyed snake (2014) and the Papuan black snake (2017).

Venom Evolution

Associate Professor Bryan Fry's work identified the common ancestor of reptile venom delivery systems (Nature, 2006). Dr Timothy Jackson's work has highlighted the influence of ecology on venom composition and activity (2019).

Health Outcomes

The AVRU team has leveraged its knowledge of Australia's venomous creatures to benefit snakebite victims around the world.

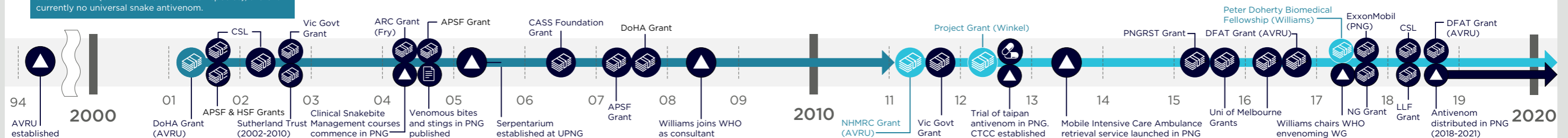
Saving lives in Papua New Guinea

Many venomous snakebites in PNG are caused by snakes also found in Australia. The work conducted in PNG helps to inform snakebite management in Australia.

- Establishment of the Charles Campbell Toxinology Centre (CTCC) Snakebite Clinic at Port Moresby General Hospital. The clinic treated 300-350 snakebite cases per year and introduced treatment protocols that lowered fatality rates from 14.9% to just 2.2%.
- Development of a Clinical Snakebite Management course (2004-present) to upskill health workers in snakebite patient management. A guidebook, *Venomous bites and stings PNG* (2005), was published to guide patient management.
- The PNG Snakebite Partnership. More than 800 vials of lifesaving antivenom (donated by Seqirus) have been distributed to 54 health centres across PNG since 2018. This project is led by Dr Watt and has saved more than 300 lives using Australian antivenoms.

Putting snakebite on the world stage

In 2017, Dr Williams chaired the WHO Snakebite Envenoming working group. The AVRU team were instrumental in advocating for snakebite to become a top category Neglected Tropical Disease (2017) and for snakebite issues to be addressed globally (2018). In 2019, Dr Williams led the development of the WHO's strategic roadmap for the prevention and control of snakebite envenoming.



Australian Venom Research Unit

AVRU undertakes research on Australia's venomous creatures and their toxins, and on care of the envenomed patient. Key themes of the Unit's work are education, mapping and investigation.

Education and advisory service

Dr Winkel, in partnership with Maningrida College and the Djelk Rangers (Bawinanga Aboriginal Corporation, Maningrida, Northern Territory), developed award winning educational programs and pocketbooks incorporating local knowledge with venom first aid. In addition, AVRU has partnered with Seqirus to develop the *Australian Bites & Stings* app, a free smart-phone app that provides users with a first aid guide to Australian venomous creatures; publishes *The Venom Patrol*, a children's book about venom first aid that was distributed to all Australian schools (2008); and runs a weekly online blog on all things venom.

Mapping Australia's venomous injuries

Dr Ronelle Welton led work revealing that contact with venomous animals and insects resulted in more than 41,000 hospital admissions between 2000 and 2013. Bees and other insects accounted for 76% of these cases, snakes accounted for 15%, and marine creatures 9%. Sixty-four of these encounters were fatal. The major causes of death were snakebites (42%) and wasp and bee stings (42%). Men aged 30-35 were particularly prone to venomous injury and more than half of the fatal encounters occurred at home.

Investigating Australia's venomous creatures

AVRU's work involves a focus beyond venomous snakes. The Unit's research into the cardiovascular actions of Irukandji (*Carukia barnesi*) jellyfish venom, for example, has been translated into real-life emergency interventions for sting victims.

Prof Struan Sutherland AO

Professor Struan Sutherland (1936-2002) was a clinician researcher and founding Director of AVRU (1994-1999). He studied medicine at The University of Melbourne (1960) and served in the Royal Australian Navy (1962-65) before joining CSL in 1966, where he served as the Head of Immunology Research (1966-1994). In 2002, he was appointed an Officer of the Order of Australia for his work in clinical toxicology.

Dr David Williams

David Williams was an NHMRC Doherty Research Fellow and former Director of AVRU (2015-2019). He was the Chair of the WHO Working Group on Snakebite Envenoming (2017-2019). He is the CEO of the Global Snakebite Initiative and a consultant for the WHO on snakebite envenoming.

Dr Ken Winkel

Ken Winkel is a clinician researcher and former AVRU Director (1999-2015). He is a Senior Research Fellow at The University of Melbourne.

Associate Professor Christine Wright

Christine Wright is Head of the Cardiovascular Therapeutics Unit at the University of Melbourne. She was Co-Director of AVRU (2013-2015) and remains a senior collaborator.

Associate Professor Bryan Fry

Bryan Fry leads the Venom Evolution Laboratory at The University of Queensland and was deputy Director of AVRU (2003-2006).

Dr Andrew Watt

Andrew Watt is a medical researcher with a background in neuroscience. He has led the PNG Snakebite Partnership since 2018 and has been co-Head of AVRU since 2019.

Dr Timothy Jackson

Timothy Jackson established AVRU's "Venomics Laboratory" and has led the team's basic research agenda since joining the group in 2017. Since 2019, he has been co-Head of AVRU.

Dr Ronelle Welton

Ronelle Welton is a Research Fellow with AVRU (2014-2017; 2020-). She is co-lead of the Australian Venomous Injury Project.