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Australian Research Council

Report to the ARC

by the

Australian Protease Network

Special Research Initiative

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Seed Funding

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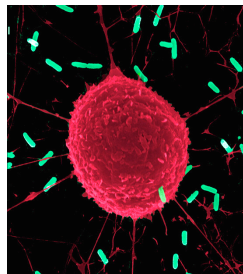
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1. NETWORK SUMMARY



This is a report for the ARC on the formation of the [Australian Protease Network](#). Proteases are enzymes that are essential for all forms of life. They account for 2% of the genomes of most organisms, including humans, and they control activation, synthesis and turnover of proteins in **all** organisms. Proteases are pivotal regulators of physiological processes during conception, birth, growth, maturation, ageing, diseases and death. Genetic and environmental factors can disturb the balance of protease-catalysed human physiology leading to abnormal development (left), poor health, disease and death. Proteases are also essential for replication

and transmission of viruses, parasites (below left) and bacteria (below centre) that cause infectious diseases in humans and animals; for the proliferation of insects and agricultural pests that damage plant crops and spread infection through animal stocks; and for growth and yields of all marine (below right) and terrestrial food sources. Because of their importance in health and disease, a few proteases have already been targeted by leading academic and multinational pharmaceutical companies, who have successfully developed exquisitely selective and non-toxic drugs for the treatment of HIV/AIDS, high blood pressure, and stroke/coronary infarction. Proteases are also used in domestic washing powders, cheese manufacture, meat tenderisation and processing, and baking. The field is clearly 'ripe for the picking', as evidenced by a growing number of protease inhibitors in clinical drug trials funded by leading multinational pharmaceutical companies.



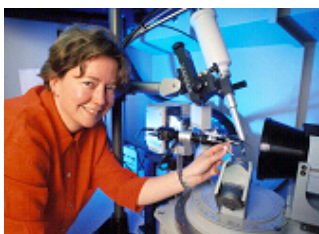
Despite these very compelling reasons to study proteases, our understanding of their detailed roles in many diverse processes remains limited and hence our ability to harness them for the benefit for humankind is compromised. It is, however, very clear that there are enormous, untapped, but tangible, benefits to be derived from increasing our research effort on these enzymes, particularly with regard to promoting and maintaining good health, and developing an environmentally sustainable Australia.



Australian scientists have made many major, innovative contributions to understanding the role and importance of proteases. However, these efforts have been uncoordinated and little networking has been undertaken. In this regard, the establishment of an Australian Protease Network has the potential (through national and international initiatives and incentives) to bring researchers interested in proteases, their inhibitors, and receptors together for the

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first time. Moreover, Network participants have over 100 research collaborators overseas, and these connections can also be more extensively utilised through a highly interactive Network. It will greatly enhance and extend current protease research activities, facilitate the recruitment of new researchers to the field, help cultivate and seed more intensive and extensive research collaborations than currently feasible, improve our understanding of protease biology, expand the capacity and horizons of Australian protease research, and ultimately facilitate translation of this knowledge into benefits for society.



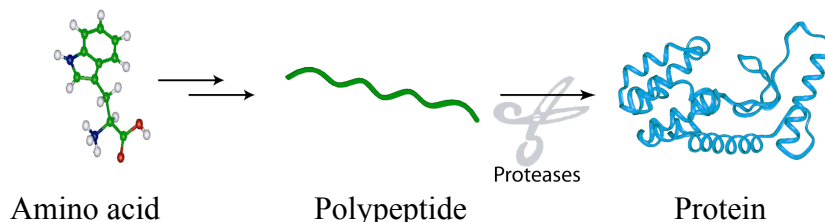
The Network aims to enhance research capacity by facilitating national and global research collaborations; seeding new research directions in Australia; enhancing communication between national and international researchers by coordinating specific conferences, meetings, workshops, and research/researcher exchanges; promoting more effective transfer of technology and skills; raising

awareness of proteases and their biology in the scientific and general community by developing and fostering educational programs; enabling sharing of equipment, educational materials and educators; and encouraging and facilitating the exploitation of proteases, inhibitors, and receptors for pharmaceutical and industrial applications. In these ways the Network will value add to Australia's contributions to protease biology and chemistry, while also creating new opportunities for, and more effective training and mentoring of, the next generation of Australia's research leaders and managers through an innovative succession plan.

2. PROTEASES AND THEIR IMPORTANCE TO ALL LIFE.

2.1 What Are Proteases?

Proteases are enzymes that are essential to all life. They are biology's version of Swiss army knives [\(1\)](#) that cut up biological polymers (called polypeptides) composed of *amino acids*, the common building blocks for all life. Humans, mammals and other organisms extract amino acids from their environment (diet) or synthesize them, link them together in long assemblies, following which proteases control their lengths and folded shapes through a variety of mechanisms leading to proteins. *Proteins* are responsible for all biological processes that characterise carbon-based life. Proteases [\(2\)](#) are essential for the synthesis of all proteins, controlling protein composition, size, shape, turnover, activation and ultimate destruction. Their actions are exquisitely selective, with each protease being responsible for splitting proteins at very specific sequences of amino acids under a preferred set of environmental conditions.



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2.2 Why Are Proteases Important?

There are over 500 human proteases [\(3\)](#), accounting for 2% of all human genes (DNA sequences that code for amino acids), and similar numbers of proteases occur in every mammal (vampire bat, right), plant, insect, marine organism and in every infectious organism that causes disease. Proteases (also called proteinases or peptidases) play pivotal roles in regulating conception, birth, digestion, growth, maturation, ageing, and death of **ALL** organisms. Proteases regulate most physiological processes by controlling the activation, synthesis and turnover of proteins. Different proteases are also essential in viruses, bacteria, parasites and insects for replication and disease transmission. As proteases are such potent biological regulators with high potential for tissue destruction, they are tightly regulated by a variety of naturally occurring inhibitors.



In **medicine**, proteases represent important targets for medical intervention because of their essential regulatory roles in human physiology. With regard to such regulatory proteases, it is now known that single amino acid mutations in at least 50 human proteases result in hereditary/genetic diseases [\(3\)](#), a few of which are listed in [Appendix 1](#). Also, other genetic or environmental conditions can result in an over- or under- abundance of a particularly crucial protease or of natural inhibitors/activators of proteases, leading to abnormal physiology and disease.



Based on understanding the roles of proteases in the replication of viruses, blockbuster **drugs** have been developed to block (inhibit) viral proteases required for replication of HIV and are currently the most effective treatments for HIV/AIDS. Other drugs block an important human protease (thrombin) involved in blood clotting and are now among the most effective treatments for *stroke* and *coronary infarction*; others block another human protease (ACE) that raises blood pressure and are among the best treatments for *hypertension*. Other protease inhibitors [\(4\)](#) are being developed to treat parasitic, fungal, and viral infections; inflammatory, immunological, and respiratory conditions; cardiovascular and neurodegenerative disorders including Alzheimer's disease, and cancers. Human proteases such as kallikreins have also been identified as important prognostic indicators of diseases. For example, *prostate specific antigen* is a kallikrein used in the **diagnosis** of prostate cancer. A number of other proteases are experimental **vaccines** in current development to fight infectious diseases.

In our **environment**, proteases are key regulators of the life of insects and other agricultural pests, key regulators of growth and health of farm animals, and principal regulators of plants and marine food sources. Research into these relatively under-studied proteases has the potential to contribute spectacularly to our **economy** by improving plant and animal health through enhanced



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growth and treatment/prevention of parasite infections, crop protection through new herbicides and pesticides, and increased or faster production of food resources.

3. NETWORK BACKGROUND

3.1 Network Scope

The Australian Protease Network was formed in 2004 by over 80 research groups ([Appendix 6](#)) from 28 universities/institutions/hospitals/companies in 6 states of Australia (Queensland, New South Wales, ACT, Victoria, South Australia, Western Australia). Each of these groups represents multiple researchers including postgraduate and undergraduate students working in the area of proteases, protease inhibitors and protease receptors, supported by the Australian Research Council, National Health and Medical Research Council, host institutions, industry, and local and national charitable organizations. The participants have individual links to collaborators in 20 countries (Belgium, Brazil, Canada, China, Denmark, France, Germany, Hong Kong, Ireland, Italy, Japan, Korea, New Zealand, Poland, South Africa, Sweden, Switzerland, Thailand, UK, USA). One of our first initiatives has been to fill an unmet need, to build both National (www.protease.net.au) and International (www.protease.net) protease network registers, with the blessings of the International Proteolysis Society (www.protease.org). This reveals the scope of our vision, to draw not only on Australians but also on researchers around the globe to catalyse research collaborations, make new connections, enhance the capabilities, and expand the horizons of Australian as well as international researchers.



The Network capitalises on an area (protease research) of national research strength, and will coordinate it (for the first time) through high profile National and International collaborations to target fundamentally important processes in life, ageing, health, and death that are associated with National Research Priorities [\(5\)](#). Network participants have formulated a wide ranging spectrum of initiatives and strategies specifically designed to promote, extend, and link both current and anticipated research and educational activities both nationally and globally. All participants share common interests in the nature, properties and importance of protease enzymes or their receptors or their inhibitors in biology. However their collective interests and expertise are also [interdisciplinary](#), extending beyond proteases and transcending the traditional boundaries defined by the disciplines involved in their research portfolios, namely genomics, genetics, transcriptomics, proteomics, bioinformatics, immunology, molecular/cellular/developmental/structural biology, physiology, inflammation, microbiology, cancer biology, neurobiology, enzymology, glycobiology, pharmacology, cardiovascular research, chemistry, computing, and the design and development of drugs, vaccines, and diagnostic agents.

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3.2 Network Aims

Australians have made innovative contributions to understanding and regulating proteases. However this initiative aims to network their efforts by value-adding to current protease research through promoting national and international collaborations to improve our understanding of biology, seed new innovative research efforts at the cutting edge of the field, and encourage ultimate exploitation of proteases/inhibitors/receptors for pharmaceutical and industrial applications.

The principal objectives are to build a highly interactive research and educational protease network within Australia; to catalyse the exploration of new frontiers and opportunities for developing important new protease-related research programs relevant to life, ageing, disease and death; and to coordinate and target a significant proportion of protease research effort at problems of national or international significance. Ultimate health and environmental outcomes will have long lasting potential to create exciting and lucrative new opportunities for the Australian economy.



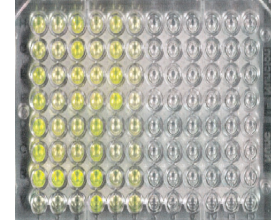
Specifically the Network Aims :

- To value-add to current protease research by promoting more effective/extensive national and international collaborations to improve our understanding of biology.
- To unite, for the first time, the efforts of those Australians currently researching the biology and chemistry of proteases (including structures, functions and control), while also increasing awareness of the importance of proteases among other Australian scientists who could be potential recruits into the Network.
- To increase the capacity, and expand the horizons, of Australian protease research through developing more intensive links with current international collaborators, while sourcing potential new collaborations via more effective international networking.
- To facilitate global networking by building, maintaining, and communicating through, national and international website registers of protease researchers; using them to catalyse more extensive collaborations, communications, and information/researcher exchange through specialist meetings, workshops, and electronic contact.
- To create new networking, management and leadership opportunities for established and younger scientists, fostering student and postdoctoral exchange of Australian and overseas researchers;
- To provide financial, vocational, mentoring and grant writing support to current or prospective protease researchers, especially younger investigators.
- To promote interdisciplinary research approaches and education programmes by also connecting Australian and global researchers through the rapidly growing disciplines of genomics, proteomics, transcriptomics, bioinformatics, as well as more traditional disciplines of genetics, structural/molecular/cell/developmental biology, enzymology, physiology, immunology, microbiology, pharmacology, chemistry & drug discovery.

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- To create opportunities for sharing equipment, techniques and new technologies, infrastructure, and knowledge through lab visits and web-based document accessibility.
- To connect research groups, individual students and researchers with potential end users including each other, and to engage the community through Network activities.
- To generate new opportunities for, and facilitate commercial exploitation of, proteases/inhibitors/receptors through future recruitment of pharmaceutical, biotech and industrial participants.

These networking initiatives have been designed to promote research collaborations, encourage lateral thinking, train and educate participants in new activities and diversify their interests, all towards improving our capacity to understand biology. Separate initiatives will be described to facilitate the ultimate exploitation of information accrued on proteases/inhibitors/receptors for pharmaceutical and industrial applications.



3.3 Network Structure

The Australian Protease Network has an interim management committee comprising 10 people :

Network Administrator :

[To Be Appointed, protease.network@imb.uq.edu.au](mailto:protease.network@imb.uq.edu.au)

National Convenor :

[Professor David Fairlie,](#)

University of Queensland,

Brisbane

(07 3346 2989, d.fairlie@imb.uq.edu.au)

[Deputy : Dr. John Hooper,](#)

Queensland University of Technology,

Brisbane (jd.hooper@qut.edu.au)

[Deputy : Dr. Joel Tyndall,](#)

University of Queensland,

Brisbane (j.tyndall@imb.uq.edu.au)

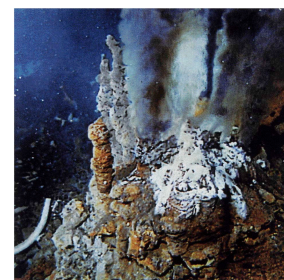
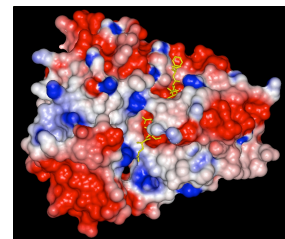
ACT Node Coordinator :

[Dr. Rohan Baker,](#)

Australian national University,

Canberra

(02 6125 3824, Rohan.Baker@anu.edu.au)



February 6, 2004**NSW Node Coordinator :**[Professor Phil Hogg](#),

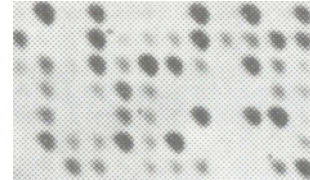
University of New South Wales,

Sydney

(02 93851004, p.hogg@unsw.edu.au)**VIC Node Coordinator :**[Associate Professor Rob Pike](#),

Monash University,

Melbourne

(03 99053923, Rob.Pike@med.monash.edu.au)**Qld Node Coordinator :**[Professor Paul Alewood](#),

University of Queensland,

Brisbane

(07 33462982, p.alewood@imb.uq.edu.au)**SA Node Coordinator :**[Professor Sharad Kumar](#),

Institute for Medical and Veterinary Science,

Hanson Institute & University of Adelaide,

Adelaide

(08 82223738, sharad.kumar@imvs.sa.gov.au)**WA Node Coordinator :**

Professor Geoff Stewart,

University of Western Australia,

Perth

(08 9346-3915, geoffrey@cyllene.uwa.edu.au)

Professor Fairlie will coordinate the overall program, supported by two Early Career Researchers namely Drs. Hooper and Tyndall and a full time Network Administrator. Associate Professor Pike (Victoria), Professor Alewood (Queensland), Professor Hogg (New South Wales), Dr. Baker (ACT), Professor Kumar (South Australia), and Professor Stewart (Western Australia) will act as local coordinators for each of the State nodes.

An International Protease Network website register (www.protease.net) is also being created to facilitate global communications and collaborations between protease researchers and end users. A core group of eminent international protease researchers have been enlisted by the Australian Protease Network as scientific advisers and conduits to the international community. Expatriate Professor Chris Overall will chair this advisory group which currently comprises :

February 6, 2004**CANADA:**

Professor Chris Overall
North American Degradomics Group,
University of British Columbia, Vancouver
chris.overall@ubc.ca

USA :

Professor Guy Salveson
North American Degradomics Group,
The Burnham Institute, San Diego
gsalvesen@burnham.org

Professor Ben Dunn
President of the International Proteolysis Society
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UK :

Professor John Mayer
Council Member UK Biochemical Society
University of Nottingham Medical School
Nottingham
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GERMANY :

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The network will endeavour to recruit International protease researchers, as opportunities arise, for relocation to Australia. Network recruits who relocated to Australia between Oct 2003 – May 2004 are [Professor John Dalton](#) (Dublin City University to University of Technology, Sydney), [Dr. John Deadman](#) (Thrombosis Research Institute, London to AMRAD, Melbourne), [Dr David Dougan](#) (Heidelberg University) and [Dr. Kaye Truscott](#) (Freiberg University) to La Trobe University, Melbourne. Among international participants who are expatriate Australians are Prof. Chris Overall (UBC, Canada), Prof. Terry Spithill (McGill, Canada), Prof. Toni Antalis (George Washington, USA), Prof.

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Paul Brindley (Tullane, USA), Drs Donmienne Leung and Michael Kelso (SCRIPPS, USA), Dr. Matt Glenn (Yale, USA), Assoc. Professor Andrew Abell (Canterbury, NZ), Dr Catherine Gilchrist (Auckland, NZ).

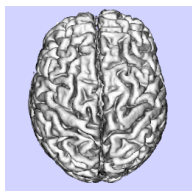
3.4 Network Participants

Australian Participants : Over 80 Australian research groups have so far joined the Network and supplied 1 page entries to www.protease.net.au on their specific protease research activities and interests. Their names, research (Appendices [3](#), [4](#), [5](#)), and web links ([Appendix 6](#)) are shown below.

International Collaborators : Over 100 international researchers from 20 countries are listed collaborators in the individual entries to www.protease.net.au by Australian Network participants. These and many other protease researchers will be recruited to the international network www.protease.net.

The international participants complement/augment the skill base of the Australian team to enhance discovery and broaden investigative capabilities in protease research. Among expected outcomes that unifying collaborations between Australian and International protease researchers could produce are the discovery of new serine, metallo, cysteine, aspartic and threonine proteases, identification of new mutations in proteases that lead to hereditary diseases, classification of new clans or families of proteases, unravelling of new protease cascades, finding of new cellular receptors and pathways influenced either directly or indirectly by proteases, characterisation of new protease functions and new three dimensional structures, newly revealed enzymatic properties, establishment of new roles for proteases in physiology and disease, validation of proteases as new drug targets, creation of new inhibitors as new drug leads, development of proteases as prognostic aids for diagnosing diseases, and as new vaccines. This initiative also forms a development pipeline for identification of new knowledge on the biology of proteases, their structures, and their functions *in vitro* and *in vivo*.

4. SUMMARY: STATUS OF INTERNATIONAL PROTEASE RESEARCH



Historically, the importance of proteases in humans has been under-rated, dismissed in the past as enzymes used mainly to degrade proteins such as digestion of ingested food. We now know that proteases ([2](#)) are pervasive mediators of most biological processes, present in the GI tract, blood, cells, the brain, heart and all other organs, and even in the airways. In fact every organism uses proteases in a sophisticated network of endogenous regulators of cellular function. The challenge is to unravel the highly specific roles carried out by each protease in every living organism and to determine their respective importance to life, health, ageing, disease, death and ultimately their value to man in medical, industrial and other applications. The following areas of international activity are considered by us to represent some of the most important issues in the field, yet are currently under-explored and would benefit significantly from intensified and coordinated new research effort in Australia.

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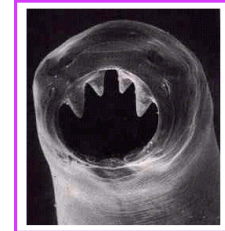
4.1 Genetic variants of proteases, inhibitors and receptors.

An increasing number of **hereditary diseases** are becoming associated with mutations in protease enzymes ([Appendix 1](#)), suggesting a need for more genetics/bioinformatics studies of cDNA sequences in diseased individuals, for directed efforts at identifying the properties of protease knockout animals, and for evaluating the properties of proteases with specific types of mutations.



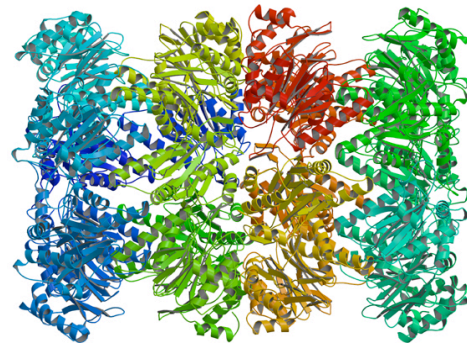
4.2 Proteases and Infectious Diseases

In relation to **infectious diseases**, the success of inhibitors of HIV proteases ([6](#)) in the treatment of HIV/AIDS has spurred on efforts (albeit limited) to target proteases important in the replication of other viruses (e.g. Hepatitis C ([7](#)), Cytomegalovirus ([8](#)), Rhinovirus 3C ([9](#)), SARS ([10](#)), Dengue ([11](#))). There is also a significant research effort to block parasite proteases that mediate the major parasite-induced diseases like malaria (plasmepsins) ([12](#)), schistosomiasis (cathepsins) ([13](#)), and hookworm (right) infections (cathepsins) ([14](#)).

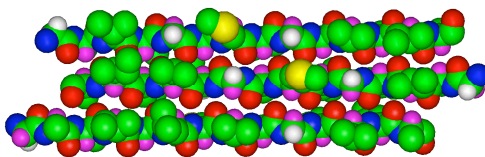


4.3 Proteasomes

An exciting development in recent years was the discovery of the **proteasomes** (right) ([15](#)), a cylindrical multidomain protease enzyme that functions much like a sausage machine in destroying proteins. Cells use such proteases to selectively turnover and remove oxidised or otherwise damaged proteins, in addition to destroying regulatory proteins for which a short half-life is critical for their function. While it is known that ubiquitin marks such proteins for destruction, the precise mechanisms by which proteins are selected for ubiquitylation and selectively recognized by proteasomes remains largely unknown. The interplay between proteases and molecular chaperones appears to be a particularly important new field of protease research, and recent studies show that inhibitors of proteasomes induce apoptosis has sparked interest in therapeutic possibilities for this class of protease too.



4.4 Proteases and Protein Folding

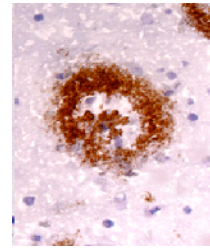


One category of **damaged proteins** are the so called 'mis-folded' proteins ([16](#)) now associated with over 20 amyloidogenic diseases, including Alzheimer's disease and other neurodegenerative diseases. These are thought to involve mis-folded proteins that aggregate into neurotoxic species of as yet unknown composition. Proteases responsible for formation of these aggregating 'mis-folded' proteins are thus assuming prominence as prospective drug targets, most notable progress being made for Alzheimer's disease.

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4.5 Proteases and Aging

In the early 21st century we live in an ageing community, with mounting pressure to find new and effective treatments for **diseases of the aging**, like Alzheimer's disease, arthritis, osteoporosis, inflammatory syndromes, cancers, diabetes, high blood pressure and heart diseases. All of these conditions are associated with proteases, the inhibition of which can potentially lead to effective treatments ([Appendix 2](#)). Inhibitors of BACE (beta secretase) show considerable promise for reducing amyloid formation (right) associated with Alzheimer's disease and are in early clinical trials. Inhibitors of tumour necrosis factor alpha convertase (TACE) and interleukin converting enzyme (ICE/caspase-1) are being trialed for arthritis, where TNF α and IL-1 β are known to be key pro-inflammatory agents. A great deal of effort has been devoted to developing neutrophil elastase inhibitors for controlling irreversible lung destruction in diseases such as chronic obstructive pulmonary disease and cystic fibrosis, though many drug trials have been discontinued. Cathepsin K inhibitors have progressed to Phase III clinical trials for osteoporosis, while inhibitors of complement proteins and MMPs are in development for varied inflammatory conditions. Inhibitors of matrix metalloproteases and caspase-1 have shown some promise for treating cancers, though the former have stalled in Phase III clinical trials. Inhibitors of dipeptidyl peptidase IV (left) ([17](#)) are in clinical development of diabetes. Thrombin inhibitors are now prescribed in man for treating stroke and coronary infarction, while inhibitors of other proteases involved in blood coagulation (e.g. factor Xa, VIIa) are in clinical trials. Inhibitors of angiotensin converting enzyme (ACE) are currently used to treat hypertension, while renin inhibitors are in trials for the same purpose. All of this work ([Appendix 2](#)) speaks to the promise of protease inhibitors for medical applications, including those related to National Research Priorities in Australia.



4.6 Proteases and Development

At the other end of the age spectrum, proteases play vital roles in **conception, birth and developmental biology**. Problems of infertility, endometriosis, healthy foetus development, and healthy births have assumed paramount importance in modern Australian society. Endometrial proteases and the roles of deubiquinating enzymes are being studied in Australia and globally in relation to contraception, infertility, and developmental biology.



4.7 Proteases and Inflammatory Diseases



Major problems in young Australian children are **asthma and allergies**. Mast cell tryptase ([18](#)) is a protease that has attracted a lot of attention for the treatment of asthma with encouraging clinical responses to inhibitors. Exciting developments in more recent times were the discoveries of proteases in dust mites (left), scabies and other allergens and the identification of protease

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activated receptors (PARs) [\(19\)](#) which are sensors that are activated by proteases in the airways and many other tissues. There has been a significant increase in research on PARs in recent years with their detection in a wide range of cells & tissues of the central nervous system, vasculature, intestine, airway epithelium, pancreas, skin, joints, etc and predicted roles for PAR ligands in asthma, inflammatory diseases, and cancers. Australians are at the forefront of this research.

4.8 Proteases, Diagnostics and Vaccines

In recent times proteases have been considered as potential **diagnostics** and **vaccines**. The overexpression of proteases such as matrix metalloproteases in cancers and inflammatory disorders, and kallikreins and cathepsins in cancers, has raised the prospect of using them as prognostic markers of disease. One kallikrein is now referred to as prostate specific antigen [\(20\)](#), and others look to be promising markers for ovarian and colon cancers. Proteases are also being examined as potential vaccines in parasite and viral infections, and could lead to vaccination programmes in less developed countries where diseases like malaria, schistosomiasis, and Dengue fever are rife. With regard to toxins, protease such as those produced by *Clostridium tetani* (tetanus toxin) represent important vaccine target antigens and similar toxin-associated proteases may also represent suitable candidate vaccine antigens, for example, *Bacillus anthracis* (anthrax toxin). Similarly, proteases produced by other infectious agents that play important somatic roles within the organism per se may also prove to be important vaccine targets.



4.9 Proteases and Cell Death

Finally, **cell death** [\(21\)](#) is mediated by proteases. A great deal of international research, as well as research by Australians, is currently focussed on understanding the mechanisms of protease-mediated cell death in development and disease. Cysteine proteases such as caspases 2, 3, 7, 8, 9 and 10, as well as serine proteases like granzyme B are used to kill harmful cells, including damaged cells, cancer (right), autoreactive immune cells and virus-infected cells. A better understanding of proteases in cell death may lead to new generations of drugs for the treatment of degenerative disorders, heart disease, autoimmune diseases, stroke, cancer and ageing.



5. AUDIT OF AUSTRALIAN PROTEASE RESEARCH

5.1 Audit Summary.

An audit of Australian protease research was conducted in January 2004 and Researcher profiles are collected in a database ([Appendix 6](#)) that is searchable by key word. A summary of some of the important information in the data base is shown in [Appendices 3-6](#). Some of the strengths and opportunities created by the establishment of an Australian Protease Network are described below.

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5.2 Strengths

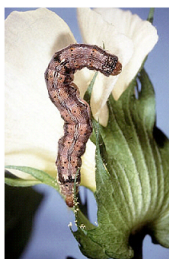
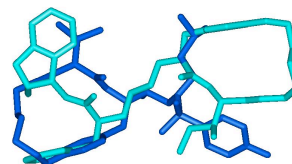
It was clear from the audit of current Australian activity that Protease research is an area of National Research Strength, but that it is largely in individual researcher laboratories and may therefore suffer a lack of researcher communication, stimulation of ideas, and availability of valuable reagents and expertise. However, the survey also revealed that substantial complementarity would be gained through highly interactive national networking.



There are around 100 research groups in Australia which have protease research as a significant component of their research portfolios. About 65% of these groups are in Victoria and Queensland. The Victorian research effort is primarily driven by biology, particularly molecular and cellular biology, genomics, genetics, bioinformatics, enzymology and immunology, with a particular strength in proteinaceous inhibitors highlighted by an NHMRC Program grant team working on systems biology of serpins (left). Other features of Victorian-based research include a number of independent efforts on the biology of

serine, cysteine, and metallo proteases, and two new ARC QEII fellows working on relationships between chaperones and proteases in cellular removal of damaged/toxic proteins.

Research in Queensland is driven more by interests in gaining molecular insights to protease structures and functions through structural biology, chemistry, drug design, molecular pharmacology, microbiology, proteomics, genomics and developmental biology. Three ARC Professorial Fellows are working on synthesis, structures, and design of small molecule protease inhibitors. Kallikreins, caspases, ADAMTS and toxin-generating proteases are also prominent features of Qld research.



Research on microbial, viral and parasite proteases also represents a national strength and is studied by multiple researchers in Qld, NSW, WA and Vic. Insect proteases are being studied in Victoria, Qld and ACT including at CSIRO.

Research in NSW focuses on bioinformatics and data mining, particularly of the serine protease family, and the biochemistry and cell biology of proteases that play important roles in asthma and cancer.

Researchers are working with industry to develop inhibitors of mast cell proteases for the treatment of asthma and the use of protease fragments to inhibit tumour growth.

South Australian research features caspases in mammals and insects, ubiquitination, reversible ubiquitin marking of proteins for destruction by proteases, and roles of

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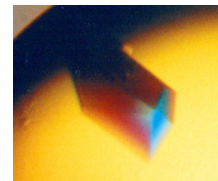
dipeptidylpeptidases in disease, areas that are also studied in ACT, NSW and Victoria, making these strengths as well.

Western Australian research has a major strength in protease activated receptors. These are proteins (G protein-coupled receptors) found on surfaces of a wide range of cells including inflammatory, cancer and airway cells. They are activated by trace levels of extracellular proteases and are particularly important in allergies, asthma and cancers. Pockets of researchers in Victoria and Queensland also work on PARs, but there is little current interaction between the states in this area of national strength.

Overall, Australian research groups characteristically use wide ranging interdisciplinary approaches to protease research with most investigators working in more than three disciplines ([Appendix 5](#)) from genomics, genetics, bioinformatics, transcriptomics, proteomics, structural/developmental/molecular/cellular biology, immunology, enzymology, physiology, immunology, microbiology, pharmacology, chemistry & drug discovery. There is considerable scope for harnessing these knowledge bases and interdisciplinary skills, supplemental to protease expertise, for educational purposes as well as research cross-fertilization.

A significant strength of Network participants is that many have been very successful in publishing (> 1500 papers since 1998), attracting funding including research grants (>300 ARC, NHMRC & other grants), and commercialising their research through patents, consultancies, contracts, and startup companies. This augers well for a network environment that promotes a free flow of information exchange and sharing of research capability, grantsmanship skills, and commercialisation experience and knowhow.

There are many opportunities for Australian researchers to band together and tackle important problems in a concerted manner. More collaborative research can be expected to address roles and specific classes of proteins in regulating life processes in humans and other organisms, resulting in new knowledge that is important for understanding life, ageing and death.



New protease inhibitors, diagnostics and vaccines can also be expected to result down the track from more effective networking both in Australia and overseas. Based on protease inhibitors that are already in clinical trials ([Appendix 2](#)), we can expect that a more extensive and collaborative Australian-led effort on protease research will result in new drug leads for clinical trials for the treatment of important diseases in Australia, such as stroke and heart disease, diabetes, cancers, arthritis, and Alzheimer's disease.

6. PROPOSED RESEARCH DIRECTIONS, CONFIGURATIONS, INFRASTRUCTURE & FACILITIES

(a) Proposed Research Directions

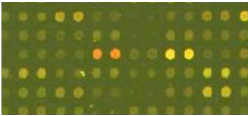

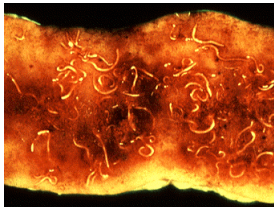
Most of the protease research that will be undertaken by network participants will be that for which funding is already awarded through individual research grants from

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organizations like ARC, NHMRC, NIH, companies, local institutions, charitable organizations, etc. A substantial component of the network budget will therefore be used to value add to that research effort through specific networking initiatives such as conferencing, workshops, research/researcher exchange, young investigator promotion, and educational activities.

The remainder of the budget will be used to expand Australia's research capacity, particularly focussing on stretching the horizons of Australian protease research, catalysing and supporting high-risk new research activities that have the potential to change the landscape of Australian protease research.

Network participants have so far identified 12 new research directions that could result from establishment of the Network and help to push Australian protease research further to the forefront of international protease research. They are now foreshadowed as areas currently worthy of increased research collaboration and greater focus in Australia over the next 5 years :

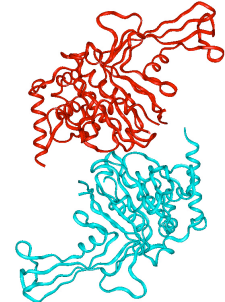
- (1) **Protease Genetics.** It is only relatively recently that associations have been made between mutations in protease enzymes and hereditary diseases. Further systematic examinations of the effects of protease knock out mice and effects of protease mutations on developmental biology and disease development in animals would be valuable adjuncts to clinical studies of genetic defects in disease. We also propose to team up with the Network on Genes and Environment in Development (www.nged.adelaide.edu.au).
- (2) **Viral Proteases.** New studies towards identifying and inhibiting new proteases required for viral replication/infection would be important. Current awareness is high in Australia and overseas of HIV/AIDS, and 'new' infections by viruses like SARS, bird influenza, and flaviviruses like Dengue and West Nile. Comparatively small efforts by Australian protease researchers are ongoing, but would benefit from more collaborations and recruitment of new Australian protease researchers into these areas, with the promise of new information about viral infection (the scourge of the 21st Century) and potential development of new antiviral leads, vaccines, or diagnostic kits.
- (3) **Proteases in the Tropics.** Discovery of new proteases in tropical parasites and in venomous creatures, together with the validation of those proteases as drug targets, is a worthwhile objective already being pursued to limited extent by Australian protease researchers who are at the forefront of these areas. Australia is the closest developed nation to substantial South East Asian populations infected by tropical diseases like

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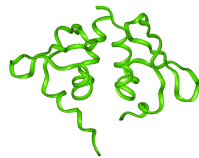
malaria, hookworm infections (above), schistosomiasis, etc. It is also home to some of the world's most venomous animals, from snakes and spiders to marine animals, and toxins isolated from these creatures are providing valuable clues to new medicines.

(4) **Proteases in Protein Turnover and Destruction.**

Mechanisms by which intrinsically short-lived regulatory proteins, or misfolded, oxidised or otherwise damaged proteins, are marked and recognized for proteolytic destruction and removal from an organism deserve more intense research focus due to their importance. Researchers in Canberra, Adelaide and Melbourne are currently investigating these areas but could benefit significantly from initiatives designed to exchange researchers and research information through enhanced networking within Australia and overseas.

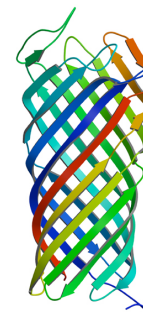


(5) **Proteases in the Cell Nucleus.** The nucleus is the site of central functions such as gene transcription, which are vital to maintenance of normal healthy cells. A number of proteases and their inhibitors have recently been found in the nucleus, their important functions being turnover of transcription factors and chromatin remodelling. The identity of proteases and their inhibitors in the nucleus is being investigated mainly



by researchers in Melbourne, but this work would be considerably enhanced by interaction with researchers in other states, allowing Australian research to take a leading role in this important new area of research.

(6) **Intramembrane Proteolysis.** There is a growing number of proteases that have been identified to process intramembrane substrates. Whether such processes actually occur in the membrane is not yet certain. However this a very important class of under-studied enzymes that promise to tell us something new about membrane proteins and their biology. Membrane biology is a frontier science and the important role of proteases in generating and regulating membrane proteins (right) deserves Australian research effort. A workshop on Membrane Protein Structure is being held in Melbourne on 6 February (www.wehi.edu.au/news/events/workshop_mps.html).



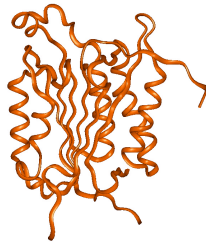
(7) **Identification of Protease Substrates In Vivo.** Despite a great deal of research having been carried out to assess the function of individual proteases, the functional profiles of many proteases, particularly those inside cells, remains incomplete. This is in part because the complete range of *in vivo* substrates is not known. At a national level, a computer (Linux computer cluster, below)-assisted bioinformatic approach is being used to build models that allow scanning of the proteome for cleavage sites for a particular

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protease, based on knowledge of its cleavage preferences. Putative substrates can then be verified both *in vitro* and *in vivo* to provide a better understanding of protease function. Such computer programs are intended to become national and international resources which could considerably aid the identification of *in vivo* substrates for proteases.



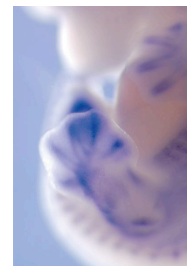
- (8) **Proteases in Apoptosis and Tumours.** Australians have been at the forefront of unravelling the mechanisms leading to cell death, and there is continuing research on proteases that mediate cell death and on tumour resistance to



apoptosis mediated by proteases. The development of orally active and highly selective inhibitors of each of the proteases identified as important in these mechanisms would provide valuable *in vivo* tools for this research (caspase-8, left). Increased international connections, information flow, and researcher exchange programs in this fast moving field would also significantly help Australian protease researchers to advance their efforts towards understanding and

interfering with cell death.

- (9) **Proteases in Developmental Biology.** Proteases are crucial in conception, birth, and developmental biology. Australians are currently examining endometrial proteases, caspases and the roles of deubiquitinating enzymes in relation to contraception, infertility, endometriosis, healthy foetus development, developmental biology, and birth. However these efforts barely scratch the surface of what is needed to understand the important roles of protease enzymes in developmental biology. This network will make significant new links between Australian and international protease- and non-protease researchers to identify these roles, including fostering links with researchers in the Network on Genes and Environment in Development (www.nged.adelaide.edu.au).



- (10) **Protease Activated Receptors.** Protease activated receptors (PARs) are being increasingly found on different types of human cells, and seem likely to be only the first of many groups of extra- and intra- cellular receptors for proteases. PARs are already implicated in the airways as sentinels for sensing trace quantities of proteases, and have been implicated in a variety of inflammatory disorders, cancers and proliferative diseases. Australian researchers are at the forefront of studies on PARs relevant to asthma, allergy, inflammation and cancer, with asthma and allergies being particularly problematic for young Australian children. A present difficulty



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in this field is the lack of truly selective and potent small molecule agonists and antagonists that can be used as tools to properly validate the roles of these receptors in biology. The network will encourage collaborative interactions within Australia and with overseas researchers to advance Australian capacity in this field.

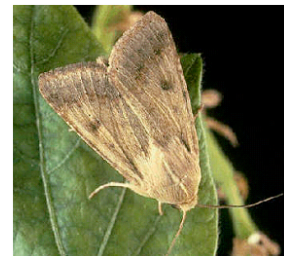
(11) **Proteases As Diagnostics and Vaccines.** Australians have already made



important contributions to proteases like kallikreins and metalloproteases that are used as diagnostic markers of cancer. Further efforts to associate protease overexpression with diseases could find application in the development of new diagnostics.

Similarly, Australian researchers are in the process of developing experimental vaccines based on proteases associated with parasites (hookworms, malaria, schistosomiasis) and viruses (Dengue, RSV, West Nile). What is needed, that the network could potentially provide, is some coordination and collaboration (through networking) of these efforts towards the development of new diagnostics and new vaccines.

(12) **Proteases In Insects And Plants.** Many plants are now known to produce high concentrations of proteins that inhibit proteases, and these proteinaceous inhibitors provide the plants with significant protection against pests and pathogens. For example, certain serine protease inhibitors from tobacco (*Nicotiana glauca*) either expressed in transgenic plants or supplied in artificial diets affect growth and mortality of *Helicoverpa armigera* and *H. punctigera* larvae, the major insect pests for cotton in Australia. One research effort between Melbourne and Brisbane is seeking to use these protease inhibitors to enhance insect resistance in transgenic cotton. Researchers in Canberra and Melbourne are characterising insect proteases, which potentially represent very important targets for new inhibitor-based insecticides. Overall the field of plant and insect protease research is very much under-studied in Australia and has the potential to generate lucrative new opportunities for Australia in herbicides, insecticides and pesticides.



(b) Configurations

In addition to enlisting recruits to, and enhancing more intensive collaborations among, current research teams through currently funded projects, the Network will use some of its funding to initiate or enhance the above twelve proposed research directions through creation of extensive team-based research programs. The Network will, once funded, call for interested participants to fall into purpose-built teams to collaborate on the research

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frontiers described briefly above or modified versions that may result from future Network meetings between February-July. The National Network meeting in Brisbane (Jan 22, 2004) clearly identified key players in each of the above initiatives, but the Network wishes to expand those groups into much larger teams and to provide the cohesive links necessary to make important and significant inroads to these frontiers.

(c) Infrastructure and Facilities

Network Participants' Institutes, Universities, Centres and Hospitals are listed in [section 8.5](#) of this report. Access to Facilities and Infrastructure at those 32 institutions is through individual researchers listed in our audit, most of which have contributed protease-specific summaries of research activities and interests in links under [Appendix 6](#). In addition, the Network participants have collaborators in 20 countries and our preliminary efforts to build an international protease network (www.protease.net) will help facilitate global exchange of research and researchers, as well as access to infrastructure and facilities around the world.

7. NATIONAL BENEFITS

7.1. National Benefits

National benefits resulting from the establishment of an Australian Protease Network will include:

- (1) Many internationally important discoveries on key biological roles of proteases, suggested by the diverse range of physiological and biological functions already known for proteases in humans and organisms. This new information will be essential in understanding details of fundamental biological processes that are a matter of life and death.
- (2) New diagnostic kits, which can be expected to be developed based on Australian research, since proteases are already recognized as prognostic indicators of diseases (e.g. cancer, asthma, chronic inflammation, etc).
- (3) New inhibitors for proteases validated as important in disease, which could fuel the creation of new Australian startup companies, with economic benefits for the country. Proteases are already well recognized by the pharmaceutical industry as viable drug targets, blockbuster drugs currently being used in man to treat HIV/AIDS (HIV protease inhibitors), stroke and coronary infarct (thrombin inhibitors), hypertension (ACE inhibitors). The industry needs both validation of other proteases as drug targets and new selective inhibitors of those proteases for future commercial success.
- (4) International access to a highly skilled research network for collaborating pharmaceutical/biotech companies and academic research groups.

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(5) New opportunities for student exchange, student and postdoctoral employment, sabbaticals, value-added joint grant applications, opportunities for industry support, product marketing and commercialisation, and global information and researcher exchange.

(6) Increased Australian visibility in this very important field of basic and applied research, enrichment of Australia's capabilities in interdisciplinary biological-chemical research, increased commercial involvement in what is becoming a very lucrative industry, and many discoveries important to the biology of life, ageing and death, and maintenance of good health.

(7) End-user engagement, including other network participants working on proteases in different areas, pharmaceutical and other companies, hospitals, educators, and the general community.

(8) A Young Investigator Program with initiatives to fast track the next generation of researchers for management and leadership roles in Australian science. Components of this program will include student travel bursaries for workshops, conferences, lab exchanges, participation in and representation at network activities, fellowship/grant assistance through organized mentoring, formal employment/vocational guidance.

(9) Marketing and advertising of protease research, researchers, publicity for selected network activities and reporting of clinical or other international successes to the community.

(10) Educational materials and programmes which will emerge as a result of the networking activities with outreach especially to university and hospital teaching.

7.2. Capturing the National Benefits

In addition to generating the significant and synergistic benefits described above, the Australian Protease Network will endeavour to ensure that these benefits are retained within Australia. In this regard, the perceived benefits may be essentially grouped into (a) scientific advances, b) commercialisation, and (c) education.

With regard to scientific advances, significant national benefit will be captured in the form of increased numbers and quality of publications as well as higher citation rates of members of the Network, both of which will further enhance the international reputation of Australian researchers. An annual conference will provide a major opportunity for organized and wide-ranging scientific exchange and targeted research recruitment. The national and international websites will provide a convenient forum for reporting and publicising Network activities, advances, and benefits. Scientific advances and these activities will, in turn, facilitate increased postgraduate education opportunities within

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Australia, enhance further scientific exchanges between states and countries, encourage the return of expatriates, and relocation of other highly regarded scientists to Australia.

With regard to commercialisation, increased communication between Network members as well as increased scientific productivity will result in increased capture and exploitation of intellectual property, with concomitant effects on the national economy. Sharing of commercialisation knowhow and experience can facilitate the mentoring of a new generation of entrepreneurial scientists.

Finally, one of the main mechanisms for capturing the benefits derived from the establishment of the Australian Protease Network will be in the area of education at both undergraduate and postgraduate levels, where new knowledge generated will enhance Network members' ability to teach at the cutting edge of protease research. The network will also be producing web-based reports on conferences, workshops and training programs, listings of material and equipment resources, highlighting scientific papers, and soliciting expert comments on topical issues of public interest. These reports will be valuable end-user targeted resources of interdisciplinary information and public relations materials for use by educators, students, researchers and the general community.

8. ANNOTATED HYPERLINKS TO RELEVANT WEBSITES

8.1 Aligned Web Sites

International Protease Network register of researchers
www.protease.net

International Proteolysis Society official web page
www.protease.org

Network on Genes and Environment in Development
www.nged.adelaide.edu.au

8.2 Conferences

January 22

Australian Protease Network : 1st National Meeting

Institute for Molecular Bioscience
University of Queensland,
Brisbane, Queensland, Australia

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Workshop on Membrane Protein Structure

Lecture Theatre, 7th floor
Walter & Eliza Hall Institute of Medical Research
1G Royal Parade, Parkville, Victoria, Australia
http://www.wehi.edu.au/news/events/workshop_mps.html

February 6, 2004**February 6-8****Australasian Proteomics Society : 9th Lorne Proteomics Society**

Lorne, Victoria

<http://www.ludwig.edu.au/jpsl/news/lps2004/>**February 8-12****29th Lorne Conference on Protein Structure and Function**

[Protease Session on February 9]

Lorne, Victoria

<http://www.lorneproteins.org/>**March 21-25****XVIIth International Congress on Fibrinolysis and Proteolysis**

Melbourne, Australia

<http://www.icms.com.au/isfp2004>**March 2004****IBC's ScreenTech(R) World Summit 2004**<http://www.lifesciencesinfo.com/screentech/section.asp?page=event&view=3>

A discovery and development conference featuring four in-depth scientific programs:
Protein Kinases and Phosphatases, Protease Inhibitors, Neurodegenerative Diseases,
Advances in HTS & Assay Technologies.

June 26 - July 1, 2004**FASEB Summer Research Conference**

Ubiquitin and Protein Degradation

Saxtons River, Vermont, USA

http://src.faseb.org/2004_sch.htm**6 - 10 September 2004****Joint 59th Harden/EMBO Conference**

The Ubiquitin Proteasome System in Health and Disease

Cirencester (Cotswolds), England

http://www.biochemistry.org/meetings/programme.cfm?Meeting_No=H59**June 5-9, 2005****4th International Symposium on Serpin Structure, Function and Biology**<http://www.serpins2005.org/>

8.3 Individuals, Societies, Organizations

The American Society for Cell Biologywww.ascb.org

Website devoted to the exchange of scientific knowledge related to areas of cell biology.

The Cell Death Society

www.celldeath-apoptosis.org

This site is primarily concerned with mechanisms cell death and apoptosis.

CellDeath.de

www.celldeath.de/mainfram.htm

This apoptosis and cell death related website is a non-profit initiative, maintained by PhD students.

Cells Alive

<http://www.cellsalive.com/>

Interactive cell biology resource.

European Cell Death Organization

www.ecdo.dote.hu/

This society aims to facilitate the exchange of scientific information, developments and links between researchers and research into cell death.

The Protease Consortium

<http://www.vicc.org/protease/>

A website devoted to proteolytic enzymes as therapeutic targets for cancer.

American Society for Biochemistry and Molecular Biology

<http://www.asbmb.org/ASBMB/site.nsf>

Scientific and educational organisation for the advancement of the sciences of biochemistry and molecular biology

Australian Proteome Analysis Facility

www.proteome.org.au

Proteome centre working with the aim of using new technologies to aid in the discovery of therapeutic, diagnostic and quality markers for biotechnology, agricultural and academic industries.

The Proteome Society

www.proteome.org

Society for scientific information exchange, scientific discussion and a general information resource concerning proteomic sciences.

Prolysis

<http://prolysis.phys.univ-tours.fr/Prolysis/>

A protease and protease inhibitor web server.

8.4 Sequence & Structure Data Bases

MEROPS: The Protease Database

merops.sanger.ac.uk

Information resource and database for peptidases, (also known as proteases, proteinases and proteolytic enzymes) and their protein inhibitors.

SCOP: Structural Classification of Proteins

scop.berkeley.edu/index.html

Database containing structural classification of proteins, proteases, peptidases etc.

HIV Protease Database

mc11.ncifcrf.gov/hivdb/

Database of three-dimensional structures of HIV proteases and complexes.

The Calpain Family

ag.arizona.edu/calpains.index.html

Website devoted to the calpain family of proteases.

ProLysED: The Bacterial Proteases Database

cgat.ukm.my/prolysed/

Database of annotated SWISSPROT and PDB primary datasets containing additional information such as predicted structures, known inhibitors, biochemical pathways etc.

Peptidases

<http://delphi.phys.univ-tours.fr/Prolysis/peptidas.htm>

Classification of peptidases into families, clans, and catalytic type based on structural similarities.

A Protein Degradation Resource

<http://www.biochem.emory.edu/labs/genekdw/protdeg2000/home.html>

Information resource on protein degradation.

Ubiquitin and the Biology of The Cell

finley.med.harvard.edu/ubiquitin/

Free web-based copy of the book Ubiquitin and Biology of The Cell, with additional structural information and other resources.

8.5 Network Participants' Institutions, Universities, Centres, Hospitals

Australian National University

<http://www.anu.edu.au/>

Baker Heart Research Institute

<http://www1.baker.edu.au/index2.php>

Box Hill Hospital

<http://www.easternhealth.org.au/boxhill/bhh.html>

Flinders University

<http://www.flinders.edu.au/>

Griffith University

<http://www.gu.edu.au/>

Hanson Institute

<http://www.hansoninstitute.sa.gov.au/>

Heart Research Institute

<http://www.hri.org.au/>

Institute for Molecular Bioscience

<http://www.imb.uq.edu.au/>

Institute for Medical and Veterinary Science

<http://www.imvs.sa.gov.au/>

La Trobe University

<http://www.latrobe.edu.au/>

Murdoch Children's Research Institute

<http://murdoch.rch.unimelb.edu.au/default.asp>

Monash University

<http://www.monash.edu.au/>

Peter MacCallum Cancer Center

<http://www.petermac.unimelb.edu.au/>

Queensland Institute of Medical Research (QIMR)

<http://www.qimr.edu.au/>

Queensland University of Technology (QUT)

<http://www.qut.edu.au/>

Royal Melbourne Institute of Technology (RMIT)

<http://www.rmit.edu.au/>

Royal Children's Hospital

www.rch.org.au/index.cfm

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Royal Prince Alfred Hospital

<http://www.cs.nsw.gov.au/rpa/>

Royal North Shore Hospital

<http://www.nsh.nsw.gov.au/rnsh/>

St George Hospital

<http://www.sesahs.nsw.gov.au/sgh/>

St Vincent's Hospital

<http://www.svhm.org.au/infoabout/svh/svhm.htm>

University of Adelaide

<http://www.adelaide.edu.au/>

University of Canberra

<http://www.canberra.edu.au/>

University of Melbourne

<http://www.unimelb.edu.au/>

University of Queensland (UQ)

<http://www.uq.edu.au/>

University of New South Wales

<http://www.unsw.edu.au/>

University of South Australia

<http://www.unisa.edu.au/>

University of Sydney

<http://www.usyd.edu.au/>

University of Technology, Sydney

<http://www.uts.edu.au/>

University of Western Australia

<http://www.uwa.edu.au/>

Victor Chang Cardiac Research Institute

<http://www.victorchang.com.au/index.asp>

Walter and Eliza Hall Institute of Medical Research

<http://www.wehi.edu.au/>

APPENDIX 1.¹

DISEASES CAUSED BY MUTATION IN PROTEASE GENES

Protease	Gene	Disease
ADAMTS-13	ADAMTS13	THROMBOTIC THROMBOCYTOPENIC PUR PURA
CALPAIN 3	CAPN	MUSCULAR DYSTROPHY TYPE 2A
CATHEPSIN C	CTSC	PAPILLON-LEFEVRE/HAIM-MUNK SYNDROMES
CATHEPSIN K	CTSK	PYCNODYSTOSIS
CARBOXYPEPTIDASE E	CPE	HYPERPROINSULINEMIA
CASPASE-8	CASP8	AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME I
CASPASE-10	CASP10	AUTOIMMUNE LYMPHOPROLIFERATIVE SYNDROME II
COLLAGENASE	MMP-13	SPONDYLOEPIMETAPHYSEAL DYSPLASIA
COMPLEMENT C1R,S,2	C1R,S,2	C1R, C1S, C2 DEFICIENCY
COMPLEMENT FACTOR D	DF	DF DEFICIENCY
COMPLEMENT FACTOR I	IF	CFI DEFICIENCY
ECE	ECE1	HIRSCHPRUNG DISEASE
ENTEROPEPTIDASE	PRSS7	ENTEROPEPTIDASE DEFICIENCY
FACTOR VIIa IXa Xa/Xia XIIa	F7,9-12	FACTOR VIIA, IXa Xa Xia XIIa DEFICIENCY, HAEMOPHILIA B
GELATINASE	MMP2	OSTEOLYSIS AND ARTHRITIS
MITOCHONDRIAL INNER	IMMP2L	GILLES DE LA TOURETTE SYNDROME
MEMBRANE PROTEASE 2		
NEUROTYPIN	PRSS12	NONSyndromic MENTAL RETARDATION
NEUTROPHIL ELASTASE	ELA2	CYCLIC NEUTROPENIA
PARAPLEGIN	SPG7	SPASTIC PARAPLEGIA
PLASMA KALLIKREIN	KLKB1	PREKALLIKREIN DEFICIENCY
PLASMIN	PLG	THROMBOPHILIA
PRESENILINS 1,2	PSEN1,2	ALZHEIMER S DISEASE TYPES 3,4
PROTEIN C	PROC	THROMBOPHILIA
THROMBIN	F2	HYPERTHROMBINEMIA, HYPOTHROMBINEMIA
UBIQUITIN C-HYDROLASE 1	UCHL1	PARKINSON S DISEASE TYPE I
X-PRO DIPEPTIDASE	PEPD	PROLIDASE DEFICIENCY

¹Adapted from Puente XS, Sanchez LM, Overall CM, Lopez-Otin C. *Nat Rev Genet.* 2003, 4:544-58.

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APPENDIX 2.

Examples of Protease-Targeting Drugs In Man Or Clinical Trials.

ASPARTIC PROTEASE INHIBITORS IN CLINIC

Protease	Function	Disease	Drug/Status
HIV-1 protease	HIV replication	HIV/AIDS	indinavir,nelfinavir,amprenavir ritonavir, lopinavir, saquinavir atazanavir (pre-reg) fosamprenavir (pre-reg) tipranavir (PhaseIII) (monotherapy unsuccessful)
Renin	Forms angiotensin I	hypertensin	aliskiren (Phase II)
BACE	Forms A β ₄	alzheimers	Elan (preclinical) Actelion(preclinical) Locus (preclinical) TGCN-001 (preclinical) Astex Technology (preclinical) Sunesi s (preclinical) De Novo (preclinical)

Leung et al J.Med.Chem. **2000**, 43, 305-41 Pharmaprojects July **2003****SERINE PROTEASE INHIBITORS IN CLINIC**

Protease	Function	Disease	Drug/Status
Thrombin	blood coagulation	stroke, coronary infarction	Argatroban, Bivalirudin Ximelagatran, Melagatran (pre-reg)
Factor Xa	Blood coagulation		Danaparoid (launched), DX-9065a, CI-1031(PhaseII) DPC-906, JTV-803 (PhaseII) MLN-1021, PMD-3112 (PhaseI) NAPc2 (PhaseII)
Factor VIIa HNElastase	cleaves elastin	SIRS ARDS inflammation inflammation, COPD	sivelestat (Japan only) sivelestat (Phase II, USA) PBI-1101 (Phase II) >27 compounds discontinued
Complement HCV	Inhibition HCV replication	inflammation hepatitis C	nafamostat, FUT-175 (launched) BILN-2061(Phase II) VX-950 (preclinical)
PAI (Urokinase)		cancer	WX-UK1(PhaseII) aminocaproicacid (phaseIII) PAI-2 (PhaseII)
Matriptase Chymase Dipeptidyl Peptidase IV		ulcer, psoriasis prostate cancer restenosis diabetes type II	CVS-3983 NK-3201(preclinical) LAF-237, P32/98 (PhaseII)

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Cysteine	Function	Disease	Drug/Status
Rhinovirus	viral replication	SARS	rupintrivir (Preclinical)
SARS CoV M ^{pro}	viral replication	SARS	AG7088 (Preclinical)
Cathepsin K	bone resorption	osteoporosis	AAE-58, SB-462795(PhaseII)
Caspase 1	Cytokine release	arthritis	VX-765 (Phase I), pralnacasan (PhaseII)
Caspase-3	Apoptosis	cancer, alzheimers	eXegenics (Preclinical)
		ischaemia, sepsis	Locus Pharm, Novartis (Preclinical)
Caspase 8	Apoptosis	sepsis, diabetes	IDN-6556 (PhaseII)
Cruzain	parasite replication	trypanosomiasis	K-777, INPL-022-E7 (Preclinical)
Cathepsins F,L,S			INPL-022-E2, E10, D6 (Preclinical)
Metallo	Function	Disease	Drug/Status
ACE-1	forms angiotensinII	hypertension	trandolapril, enalapril, captopril
NEP	release of ANP	hypertension	candroxatril (Discontinued)
TACE	release of TNF α	arthritis, MS	BMS-561392 (Phase II)
MMP-1	degrades matrix matrix	cancer	marimistat (disc), Neovastat (PhaseIII)
		periodonitis	periostat (Launched)
MMP-2		cancer	Rebimistat (PhaseI)
MMP-8		osteoarthritis	Glucosamine sulfate(Launched)
MMP-9		inflammation	Rega-3G12, Biopharma (Preclinical)
MMP-3,13			Pfizer, Novartis (Preclinical)
Threonine			
Proteosome		ischaemia	Bortezomib, MLN-519 (PhaseI)

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APPENDIX 3 : Summary of Specific Interests in Proteases, Inhibitors, Receptors

QLD		Research Group : Main Protease Interest
Abbenante	UQ	New approaches to inhibitors of aspartic/serine/cysteine/metallo proteases
Alewood	UQ	Chemical synthesis & engineering of proteases, active site mechanisms
Blanchard	GU	Calpains and caspases; protein crystal structure structures
Bottle	QUT	Antioxidants to retard free radical oxidation of proteins and activation of proteases
Brinkworth	UQ	Homology modelling , enzymology, aspartic/serine/cysteine/metallo proteases
Clements	QUT	Genetics, structure and functions of kallikreins, hormone regulation, cancers
Craik	UQ	NMR-derived structures of plant proteases & proteinaceous inhibitors, cyclotides
Deeth	UQ	Proteases in milk : plasmin and cathepsins, extracellular bacterial proteases
Dong	QUT	Kallikreins in ovarian cancer, breast cancer and endometrial carcinomas
Fairlie	UQ	Inhibitors of aspartic/serine/metallo/cysteine/threonine proteases, PAR ligands
Fischer	QIMR	Serine proteases and homologues from scabies parasites
Gorman	UQ	Proteomics, host/viral proteases and viral infection; proteolysis analysis
Harris	QUT	Molecular modelling and expression of kallikreins, phage displays for inhibition
Herrington	QUT	Roles and regulation of ADAMs and involvement in prostate cancer
Hooper	QUT	Molecular/cell biology and enzymology of TTSRs and kallikreins in cancer
Kemp	QIMR	Serine proteases and homologues from scabies parasites
Kobe	UQ	Protease structure/function/genomics; Schisto cathepsin D, latexin, autoregulation
Lavin	QIMR	developmental genetics, novel proteases and inhibitors from snake venoms
Lewis	UQ	Proteases related to generation of toxins (e.g. conotoxins and venom proteases)
Loughlin	GU	Synthesis of beta-strand mimicking molecules as protease inhibitors
Loukas	QIMR	Intestinal hookworm proteases as vaccines and targets for drugs
Martin	UQ	Crystal structures viral proteases, protease-ligand complexes, protein inhibitors
Masci	PAH	Proteases and inhibitors from snake venoms and hemostasis
Odorico	QUT	Regulation of ADAMs and kallikreins in cancer, prostate cancer
Reid	UQ	Protease inhibitors, drug design and synthesis, beta strand mimetics
Stoermer	UQ	Protease inhibitors, drug design and synthesis, viral proteases
Tyndall	UQ	Modelling/structural studies of protease-ligand recognition, inhibitor design
Walsh	QUT	Proteases in biological activation/regulation, prokallikreins, insect proteases
Watters	GU	Caspases and inhibitors associated with tumour resistance to apoptosis
Whiteside	QUT	Metalloproteases and TIMPs in osseointegration and bone remodelling
Young	UQ	Serine proteases as antiviral targets and vaccines; flaviviruses.

WA		
Bhoola	UWA	Kallikrein-kinin system in immune cells, inflammation, asthma, COPD
Henry	UWA	PARs in the airways and lung function; epithelial proteases; allergens, asthma
Lan	UWA	PARs in the airways
Misso	UWA	Plasma/tissue kallikreins in asthma, chronic obstructive pulmonary disease.
Mitchell	UWA	PARs, proteases, PGE ₂ ; physiology of the airway, development of airway cells
Smith	UWA	Proteases as allergens from dust mites, allergy and asthma
Stacey	UWA	PARs and wound healing
Stewart	UWA	Serine and cysteine proteases as allergens and PARs
Thomas	UWA	Protease allergens from dust mites
Thompson	UWA	Kallikrein-kinin system in immune cells, inflammation, asthma, COPD

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NSW		
Curmi	SYD	NMR-derived structure determination and PAI-II
Dalton	UTS	Protease in parasitology (malaria, schistosomiasis, liver flukes)
Di Girolamo	NSW	UVB-induction of MMPs and pro-inflammatory cytokines in ocular epithelial cells
Gorrell	SYD	Dipeptidyl peptidase IV genes in diabetes, apoptosis, cancer, fibrosis
Guss	SYD	Protein crystallography and Amino peptidases
Hogg	NSW	Fibrinolysis, plasmin/tissuefactor serine proteases, reversible disulfides switches
Hunt	NSW	Mast cell proteases, asthma
Jackson	SYD	Metalloproteases and protein C, wound healing, arthritis, diabetes and pregnancy
Little	SYD	Aggrecan proteolysis; cartilage, disc, tendon degradation; MMPs, ADAMTS
Rodgers	HRI	Proteasomes and lysosomes in proteolysis of oxidised proteins
Russell	NSW	proteases in the invasion and metastases of (particularly bladder, prostate) cancer
Wang	NSW	Urokinase/UPA receptor, serine proteases, cell migration, angiogenesis, metastasis
Wouters	NSW	Bioinformatics and evolution of proteases, design of serine proteases

VIC		
Aguilar	MON	Cardiovascular metalloproteases, beta amino acids in inhibitors, neuropeptides
Anderson	LaTr	Insect/plant proteases/inhibitors, mutated chymotrypsins, crop protection
Bird	MON	Molecular/cell biology of serpins, folding, granzyme B, cathepsin G
Bottomley	MON	Serpins and serine proteases, biophysics, kinetics, folding, enzymology
Chai	MEL	Brain ACE, IRAP, Parkinsons disease, inhibitors/mutations on learning/memory
Coughlin	MON	Bioinformatics & genetics of murine/human serpins, plasmin-antiplasmin
Deadman	AMRD	Inhibitors of thrombin and fibrinolysis proteases
Dougan	LaTr	Chaperones and bacterial/mitochondrial proteases, targeting misfolded proteins
Fosang	MEL	Arthritis – aggrecanase, MMPs, ADAMTS, ADAM 4&5 knockouts
Guipponi	WEHI	Type II Transmembrane Serine proteases in hearing loss; genetics, genomics
Hawkins	MCRI	Human and drosophila caspases and IAPs, apoptosis
Irving	MON	Evolutionary, biochemical, structural aspects of protease inhibitors called serpins
Mackie	MON	Thrombin and PARs in bone and muscle cell biology
Medcalf	MON	Fibrinolysis; gene regulation; serine proteases; PAIs, tPA, uPA, plasmin, draculin
Nie	MON	Endometrial proteases, proprotein convertases, HtrA, contraception, infertility
Perlmutter	MON	Beta amino acids in inhibitors, cardiovascular metalloproteases, neuropeptides
Pike	MON	Enzymology, proteases in fibrinolysis/complement, bacteria & parasites
Pritchard	MON	Functional genomics, ADAMTS, ADAMTR-1 knockout, aggrecan, versican
Salamonsen	MON	Endometrial metalloproteases, activation by serine proteases, chemokines
Scott	WEHI	Type II Transmembrane Serine Proteases; genetics, genomics
Smith	BAK	Cardiovascular and brain Zn proteases, ACE-2 shedding, ECE, Neurolysin
Smooker	RMIT	Cathepsin B- and L- like secreted proteases from liver flukes and in vaccination
Smyth	PMc	Granzymes and viral infections, lymphocyte granule exocytosis and cell death
Thompson	MEL	Membrane type MMPs in breast cancer progression
Trapani	PMc	Cytotoxic T lymphocytes, granzymes in immunopathology, apoptosis, cancer
Truscott	LaTr	Chaperones and bacterial/mitochondrial proteases, targeting misfolded proteins
Villangros	WEHI	Cathepsins and cystatins in dendritic cells, knockouts, pathogen destruction
Waltham	MEL	MMPs and endogenous inhibitors in tumour growth, breast cancer, metastasis
Warner	BAK	Zinc metallopeptidases, cell biology and physiology of ACE-2
Whisstock	MON	Bioinformatics, structures, functions of serpins and interactions with proteases

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ACT		
Baker	ANU	Ubiquitin-specific cysteine proteases (USPs), proteasome
Dean	CAN	Cellular disposal of oxidised proteins, proteasomes and lysosomes
East	CSIRO	Insect serine proteases and digestion
Hulett	ANU	Heparanase and cancer
Ollis	ANU	Protein crystal structure of Hydrolyse

SA		
Abbott	FLIN	Dipeptidylprolinases (IV, 8, 9), metalloproteases, betacellulin shedding
Kelly	UA	Genetics and ubiquitin pathways
Khew-Goodall	IMVS	Neutrophil proteases and inhibitors, serpins, inflammatory diseases
Kumar	IMVS	Drosophila caspases, Nedd4 mediated ubiquitin regulating Na ⁺ channels
Roberts	USA	Ubiquitin pathway and tumour suppressors
Wood	UA	Roles of deubiquitinating enzymes and intracellular trafficking

APPENDIX 4 : Summary Of Researcher Activity On Categories Of Peptidases, Protease Activated Receptors, or Inhibitors.

QLD	Institution	Aspartic	Serine	Metallo	Cysteine	Receptors	Inhibitors
Abbenante	UQ	*	*	*	*		*
Alewood	UQ	*					
Blanchard	GU				*		
Bottle	QUT			*			*
Brinkworth	UQ	*	*		*		
Clements	QUT		*				
Craik	UQ		*				*
Deeth	UQ		*		*		
Dong	QUT		*				
Fairlie	UQ	*	*	*	*	*	*
Fischer	QIMR		*		*		
Gorman	UQ		*		*		
Harris	QUT		*				
Herington	QUT		*	*			
Hooper	QUT		*			*	
Kemp	QIMR		*		*		
Kobe	UQ	*					*
Lavin	QIMR		*				*
Lewis	UQ		*		*		
Loughlin	GU						*
Loukas	QIMR	*	*		*		
Martin	UQ	*	*				*
Masci	PAH		*				*
Odorico	QUT		*	*			
Reid	UQ	*					*
Stoermer	UQ	*		*			*
Tyndall	UQ	*	*	*	*		*
Walsh	QUT	*	*				*
Watters	GU				*		
Whiteside	QUT			*			*
Young	UQ		*				*

WA	Institution	Aspartic	Serine	Metallo	Cysteine	Receptors	Inhibitors
Bhoola	UWA		*				
Henry	UWA		*			*	
Lan	UWA					*	
Misso	UWA		*				*
Mitchell	UWA		*			*	
Smith	UWA		*		*		
Stacey	UWA					*	
Stewart	UWA		*		*	*	
Thomas	UWA		*		*		
Thompson	UWA		*		*		

SA	Institution	Aspartic	Serine	Metallo	Cysteine	Receptors	Inhibitors
Abbott	FLIN		*	*			*
Kelly	UA		*		*		
Khew-Goodall	IMVS		*				
Kumar	IMVS		*		*		
Roberts	USA		*		*		
Wood	UA				*		

ACT	Institution	Aspartic	Serine	Metallo	Cysteine	Receptors	Inhibitors
Baker	ANU				*		
Dean	CAN		*				
East	CSIRO		*				
Hulett	ANU		*				
Ollis	ANU		*				

NSW	Institution	Aspartic	Serine	Metallo	Cysteine	Receptors	Inhibitors
Curmi	USYD		*				*
Dalton	UTS	*		*	*		*
Di Girolamo	NSW			*			
Gorrell	USYD			*			
Guss	USYD			*			
Hogg	UNSW		*				
Hunt	UNSW		*				
Jackson	USYD		*	*			
Little	USYD			*			
Rodgers	HRI		*				
Russell	NSW	*	*	*	*		
Wang	UNSW		*			*	*
Wouters	VC			*			*

VIC	Institution	Aspartic	Serine	Metallo	Cysteine	Receptors	Inhibitors
Aguilar	MON			*			*
Anderson	LaTr		*				*
Bird	MON		*				*
Bottomley	MON		*				*
Chai	MEL			*			*
Coughlin	MON		*				*
Deadman	AMRAD		*				*

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Dougan	LaTr		*				
Fosang	MEL			*			*
Guipponi	WEHI		*				
Hawkins	MCRI				*		
Irving	MON						*
Mackie	MEL		*			*	
Medcalf	MON		*				*
Nie	MON		*				
Perlmutter	MON			*			*
Pike	MON		*		*	*	*
Pritchard	MON			*			
Salamonsen	MON			*			*
Scott	WEHI		*				
Smith	BAK			*			*
Smooker	RMIT				*		
Smyth	PMc		*				
Thompson	MEL			*			
Trapani	PMc		*		*		*
Truscott	LaTr		*				
Villadangos	WEHI				*		*
Waltham	MEL		*	*			*
Warner	BAK			*			
Whisstock	MON		*				*

APPENDIX 5 : Summary Of Interdisciplinary Areas Of Expertise.

Area of Expertise														
Name	Institution	immunology	neurobiology	cancer biology	bioinformatics	structural biology	genomics	genetics	proteomics	transcriptomics	molecular biology	cell biology	developmental biol	microbiology
QLD														
Abbenante	UQ	*	*										*	
Alewood	UQ							*					*	
Blanchard	GU				*						*			*
Bottle	QUT													*
Brinkworth	UQ			*									*	
Clements	QUT		*			*			*	*	*			
Craik	UQ		*		*								*	
Deeth	UQ							*					*	
Dong	QUT									*	*			
Fairlie	UQ	*	*	*	*						*	*	*	*
Fischer	QIMR	*		*								*		
Gorman	UQ							*			*	*	*	*
Harris	QUT				*				*	*			*	*

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Herington	QUT			*						*	*								
Hooper	QUT			*	*		*			*	*		*		*			*	
Kemp	QIMR	*			*														
Kobe	UQ				*	*	*			*									
Lavin	QIMR	*		*			*	*		*	*			*					
Lewis	UQ					*			*		*			*		*			
Loughlin	GU																*	*	
Loukas	QIMR				*					*			*	*			*		
Martin	UQ					*	*		*	*	*		*	*			*		
Masci	PAH	*												*					
Odorico	QUT			*						*	*								
Reid	UQ					*											*	*	
Stoermer	UQ																*	*	
Tyndall	UQ				*	*							*				*	*	
Walsh	QUT			*		*				*	*								
Watters	GU			*							*								
Whiteside	QUT	*								*			*						*
Young	UQ	*								*			*	*			*		
														*					
ACT																			
Baker	ANU			*	*		*		*	*			*						
Dean	CAN									*			*						*
East	CSIRO									*	*		*						
Hulett	ANU			*		*													
Ollis	ANU					*													
SA																			
Abbott	FLIN						*			*	*			*					
Kelly	UA							*		*	*								
Kumar	IMVS									*	*			*					
Roberts	USA			*						*	*								
Wood	UA									*	*	*							
WA																			
Bhoola	UWA	*								*		*				*			
Henry	UWA	*								*		*				*			
Lan	UWA	*								*		*				*			
Misso	UWA	*								*		*				*			
Mitchell	UWA	*								*						*			
Smith	UWA	*								*		*				*			
Stacey	UWA	*								*		*				*			
Stewart	UWA	*										*				*			
Thomas	UWA	*								*		*				*			
Thompson	UWA	*								*		*				*			
VICTORIA																			
Aguilar	MON																*	*	
Anderson	LaTr						*			*		*		*					

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Bird	MON									*	*				*				
Bottomley	MON					*									*				
Chai	MEL	*								*					*				
Coughlin	MON				*		*			*	*				*				
Deadman	AMRAD														*			*	*
Dougan	LaTr										*			*	*				
Fosang	MEL					*			*	*	*			*			*		*
Guipponi	WEHI						*	*											
Hawkins	MCRI									*	*				*				
Irving	MON				*	*				*	*		*	*	*				
Mackie	MEL										*	*							*
Medcalf	MON		*							*	*								
Nie	MON											*							
Perlmutter	MON																	*	
Pike	MON				*	*				*	*		*	*	*				
Pritchard	MON	*		*			*			*	*								
Salamonsen	MON	*		*								*							
Scott	WEHI						*	*											
Smith	BAK		*							*	*								*
Smooker	RMIT									*					*			*	
Smyth	PMc	*		*						*	*				*				
Thompson	MEL								*	*	*				*				
Trapani	PMc	*		*						*	*				*			*	
Truscott	LaTr	*								*			*		*				
Villadangos	WEHI	*								*	*								
Waltham	MEL			*			*			*	*								
Warner	BAK									*	*								
Whisstock	MON				*	*				*	*								
NSW																			
Dalton	UTS												*		*				
Di Girolamo	NSW	*		*											*		*		*
Gorrell	USYD						*			*					*				
Guss	USYD					*									*				
Hogg	UNSW										*				*				
Hunt	UNSW	*								*	*							*	
Jackson	USYD	*								*							*		*
Kurmi	USYD					*													
Little	USYD	*								*	*						*		*
Rodgers	HRI									*							*		*
Russell	NSW			*						*	*				*				
Wang	UNSW			*			*	*		*	*								
Wouters	VC				*										*				

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Appendix 6: Researchers Categorized By State With Web Links To Their Detailed Protease Research Profiles.***National Node Coordinators******National Convenor****QLD**

John Abbenante
 Steven E Bottle
 David Craik
 David P Fairlie**
 Jonathan M Harris
 David J Kemp
 Richard J Lewis
 Jennifer L Martin
 Martin J Stoermer
 Dianne J Watters

Paul F Alewood*
 Ross I Brinkworth
 Hilton C Deeth
 Katja Fischer
 Adrian C Herington
 Bostjan Kobe
 Wendy Anne Loughlin
 Dimitri M Odorico
 Joel D A Tyndall
 Eliza Whiteside

Helen Blanchard
 Judith Clements
 Ying Dong
 Jeffrey J Gorman
 John D Hooper
 Martin Lavin
 Alex Loukas
 Robert C Reid
 Terry Walsh
 Paul R Young

Vic

Mibel Aguilar
 Stephen P Bottomley
 John Deadman
 Christine Hawkins
 Robert L Medcalf
 Robert N Pike*
 Hamish S Scott
 Mark John Smyth
 Kaye N Truscott
 Fiona Warner

Marilyn A Anderson
 Siew Yeen Chai
 David A Dougan
 James A Irving
 Guiying Nie
 Melanie Pritchard
 A. Ian Smith
 Erik Thompson
 José A Villadangos
 James C Whisstock

Phillip I Bird
 Paul Coughlin
 Amanda J Fosang
 Eleanor J Mackie
 Patrick Perlmutter
 Lois A Salamonsen
 Peter M Smooker
 Joe Trapani
 Mark Waltham

NSW

Paul Curmi
 Mark Gorrell
 John E Hunt
 Kenneth J Rodgers
 Merridee A Wouters

John P Dalton
 J Mitchell Guss
 Christopher John Jackson
 Pamela J Russell

Nick Di Girolamo
 Philip J Hogg*
 Christopher B Little
 Yao Wang

SA

Cathy Abbott
 Stephen A Wood

Yeesim Khew-Goodall

Sharad Kumar*

WA

N Asokanathan
 Howard Mitchell
 Wayne R Thomas

Peter J Henry
 Wendy-Anne Smith

Neil L Misso
 Geoffrey A Stewart*

ACT

Rohan T Baker*
 Mark Hulett

Roger T Dean

Peter East

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- (5) The Network will be active in areas of research that can potentially contribute to various degrees to all four current National Priorities :
National Research Priority 1 : An Environmentally Sustainable Australia
National Research Priority 2 : Promoting and Maintaining Good Health
National Research Priority 3 : Frontier Technologies for building and transforming Australian Industries
National Research Priority 4 : Safeguarding Australia
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