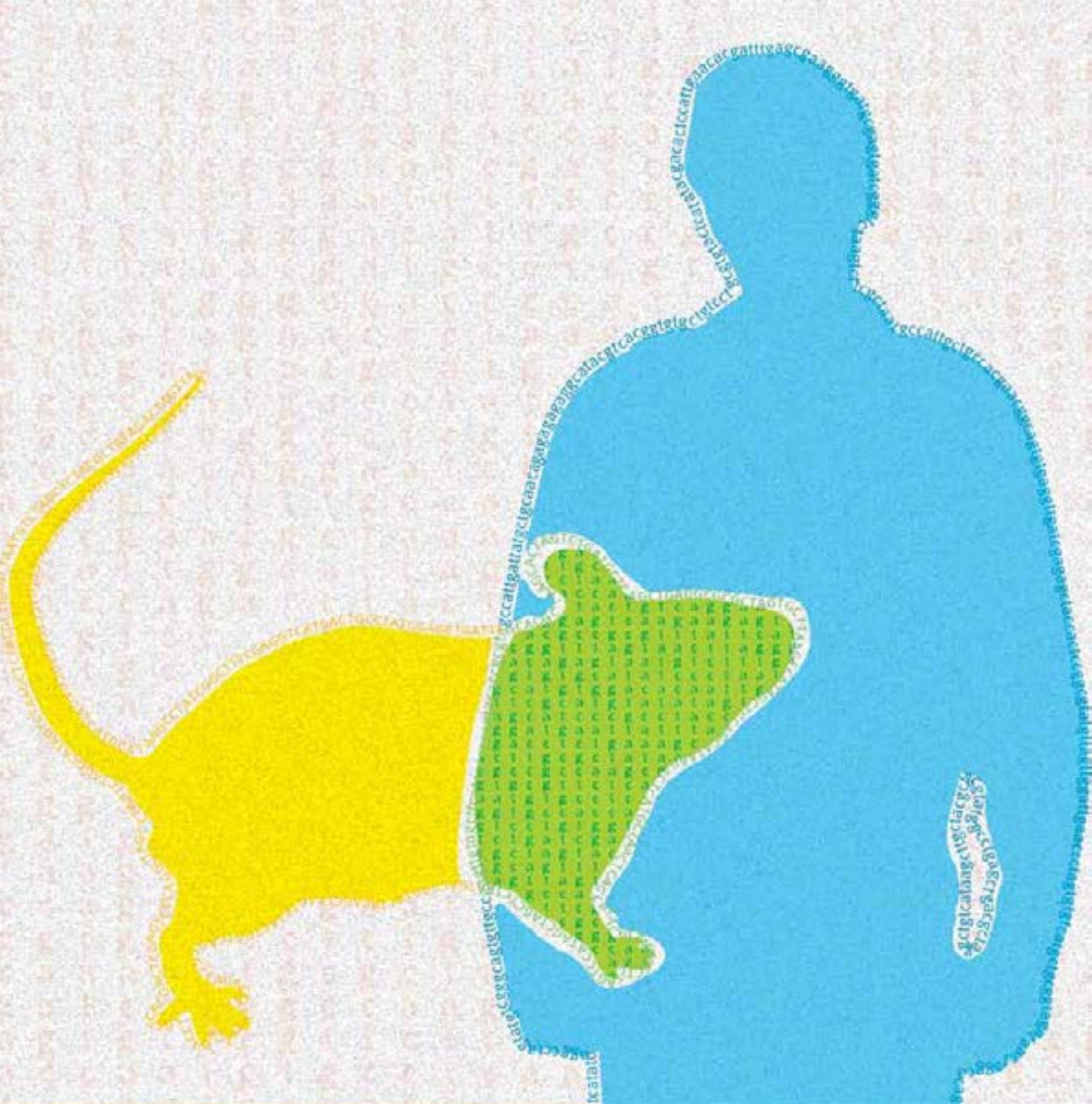




From Mouse to Medicine

**Five years of phenomics
infrastructure investment**



APN PARTNERS

Animal Resources Centre
 Centenary Institute of Cancer Medicine and Cell Biology
 IMVS
 Menzies Research Institute / University of Tasmania
 Monash University
 Queensland Institute of Medical Research
 The Australian National University
 The University of Melbourne
 Walter and Eliza Hall Institute of Medical Research



APN KEY PERSONNEL

Professor Chris Goodnow	Chief Scientific Officer
Dr Steve Winslade	Chief Executive Officer
Ms Adrienne McKenzie	Chief Operating Officer
Professor Moira O'Bryan	Lead Scientist
Professor Doug Hilton	Lead Scientist
Dr Benjamin Kile	Lead Scientist
Professor John Furness	Lead Scientist
Professor Simon Foote	Lead Scientist
Professor Emma Whitelaw	Lead Scientist
Dr Tim Kuchel	Lead Scientist
Professor Warwick Britton	Lead Scientist
Mr Michael Hall	Lead Scientist

ROLE

INSTITUTION

The Australian National University
 The Australian National University
 The Australian National University
 Monash University
 Walter and Eliza Hall Institute of Medical Research
 Walter and Eliza Hall Institute of Medical Research
 The University of Melbourne
 Menzies Research Institute Tasmania
 Queensland Institute of Medical Research
 IMVS
 Centenary Institute of Cancer Medicine and Cell Biology
 Animal Resources Centre

www.australianphenomics.org.au

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Phenomics ~

The systematic study of phenotypes on a genome-wide scale to better understand what genes do.



An Australian Government Initiative
National Collaborative Research
Infrastructure Strategy

THE AMBITION OF PHENOMICS IS TO IMPROVE QUALITY OF LIFE

FIVE-YEAR PHENOMICS PROJECT REPORT

The Australian Phenomics Network
2006 to 2011



In our lives we are both entertained as well as fascinated by the differences we observe in our friends and family. We know instinctively that biology drives these quirks and foibles – we know heredity shapes what researchers now call our “phenotype” – we know that the genes we are born with, and on which historical circumstance and the environment will work, delivers not only our personal successes but also determines our health.

Our individual phenotype makes us similar and different to others – we are governed by how our genes operate over the various stages of our life. The questions we will invariably ask when we are confronted by scientific existential reflections have an inescapable connectivity and direction founded mostly on self-interest. Will we follow the family tendencies or have we created a new combination or trait? What does my DNA really have in common with others? Can knowing our DNA profile really help predict the likelihood of disease? How will I know which of the treatments recommended by doctors are likely to be successful?

This Five-Year Report outlines this exciting phase in the recent history of Australian medical research during the post-genomic era

The ambition of **Phenomics** is to address these individual anxieties in a very detailed, personally accurate way, and in so doing improve quality of life.

The science of Phenomics helps a wide variety of Australian researchers better understand how our personal DNA code interacts with the environment to determine our health and likely response to disease treatment options. Recently it has become relatively simple to determine the sequence of our DNA code – but deciphering that code is an enormous challenge. Given the complexity of how our genetic code functions to shape our phenotype, nothing is likely to be solved in a short space of time and with minimal effort. Disentangling the governing rules of human biology and life at the level of genes and proteins, and looking to improve clinical practice is a long voyage and one Phenomics has embarked upon, making significant inroads through the project this report describes.

With substantial financial support from government, through the **NCRIS** program, the Australian medical research community has laid the intellectual foundations for ensuring our highly informed and responsive medical practitioner community can translate those important discoveries as they are made here and overseas. Phenomics is also integrating the research community with the worldwide effort.

The *quid pro quo* of our links to these large-scale research platforms created in overseas medical research facilities depend on Australia contributing as an equal partner.

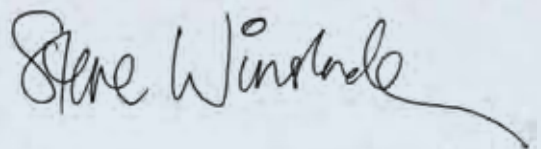
This Five-Year Report outlines this exciting phase in the recent history of Australian medical research during the post-genomic era. It notes the extent of the biological challenges confronting medical research and the responses being made over the past few years. The pace of progress has been astonishingly quick and developed into an exciting journey powered by new and ever more powerful technologies.

The pace of progress has been astonishingly quick and developed into an exciting journey powered by new and ever more powerful technologies

The first three stories in this report set the scene by explaining the complexity of the Phenomics research challenge, and the novel methods in the Phenomics toolbox that the research community are employing. Story four recounts the nature of the international linkages and highlights the increasing importance to work across institutions and national borders to achieve the necessary level of scale and make the breakthroughs. The individual case studies that make up the second half of this report are six stories highlighting the researcher experience both in terms of their individual scientific achievement as well as recognition of the contribution that has come from the public investment.

NCRIS ~

The National Collaborative Research Infrastructure Strategy is an Australian Government initiative to provide researchers with major research facilities, supporting infrastructure and networks necessary for world-class research.



Dr Steve Winslade
CEO Australian Phenomics Network



Phenotype ~

The observable physical and biochemical characteristics that are the product of genes and the environment.



PHENOMICS REVOLUTION

Cracking the code of disease





With about 25,000 genes and over 300,000 proteins, the blueprint of life known as the human genome presents a complex arena for researchers who work in the field. In 1990, the Human Genome Project began the effort to identify and sequence all genes in the human genome. In 2000 the project announced it had successfully sequenced just over 90 per cent of one person's genome. Since then, many more humans, and other organisms, have had their genomes sequenced.

The completion of the Human Genome Project in 2003 precipitated a new era in biomedical research, where scientists in the emerging field of phenomics began investigating the link between our genes and disease. The DNA sequence which constitutes our genome encodes protein, the building blocks of our body. Massive DNA sequence variation exists in the human population – on average, each person has 12,000 protein-changing DNA variants (mutations) spread across their genome. More than 300 of these 'knockout' the protein they encode almost completely, while most of the rest change a single amino acid. There is little or no information about the effect of most of the mutations on people's **phenotypes**, particularly our variability in disease susceptibility and response to treatments.

The power of the mouse phenomics approach is in its ability to bypass much of the genome's complexity by enabling researchers to investigate the genetic causes of disease by initially focusing on a phenotype in a well-defined manner. The phenomics toolbox enables the disease-causing genetic defect to be pinpointed and potential treatments investigated. In this so-called phenotype-driven approach researchers start with the **phenotype** and find which genes are involved. It extends our understanding of how genetic variation produces phenotypic variation and disease.

Mouse models provide a key to understanding the functions of our genetic code

The parallel and complementary effort to sequence the mouse genome by the international Mouse Genome Sequencing Consortium is enabling researchers to make sense of the discoveries in the Human Genome Project. Researchers are able to understand the function of many human genes because the mouse carries a similar set of genes to the human, and the mouse can be used in carefully-controlled laboratory research. Mouse models provide a key to understanding the functions of our genetic code and gain important insights into common illnesses, such as cancer and autoimmune disease.

The Australian Phenomics Network (APN) is focused on creating a catalogue of mice carrying mutations and making this information accessible via web search engines to research teams so that they can find a genetic variant of interest. The infrastructure required for experimental validation of mouse models is beyond the means of single laboratories, departments or institutions and requires national, collaborative infrastructure investment to make Australian medical research cutting edge.

As scientists continue to unlock the secrets of these genetic variants and determine those that have a deleterious effect on people's health, society will increasingly realise the benefits. The phenomics approach seeks to help clinicians to discover gene function, to determine the genetic causes of disease, and to deliver more tailored medicine for individuals. One day, hopefully in the not-too-distant-future, doctors will order a patient's full DNA sequence as easily as ordering a blood test and will review that sequence against cutting-edge scientific and medical advice to determine the best course of treatment. Using mouse models of human disease, Phenomics is enabling excellence in biological research and smoothing the road from gene function discovery to medical application.

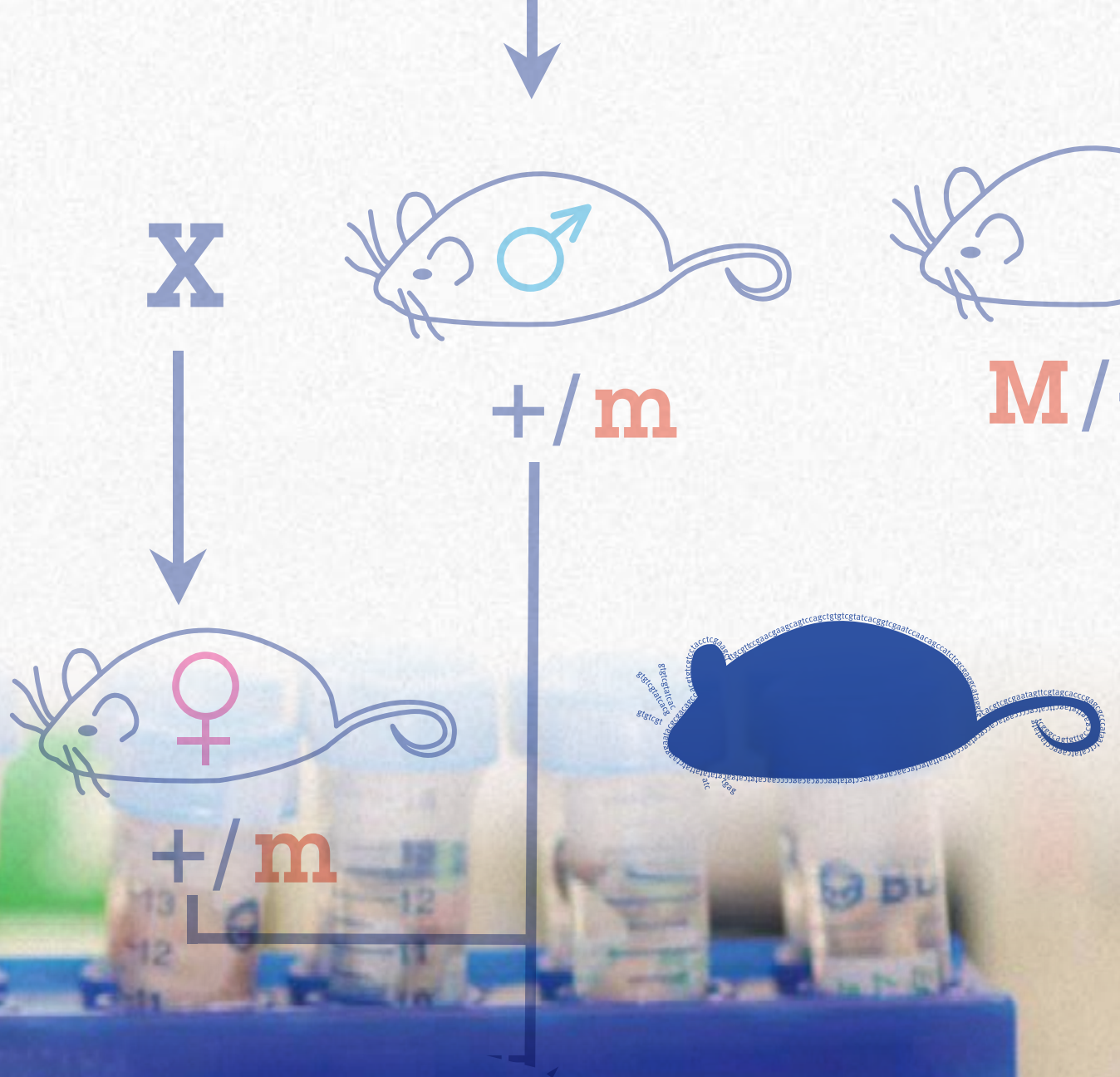
The phenomics approach seeks to help clinicians to discover gene function, to determine the genetic causes of disease, and to deliver more tailored medicine for individuals





Why use mouse models to learn about human disease?





Mice are ideal models for biomedical researchers to better understand the human body, the effects of disease and to determine effective treatments for these conditions. Mice are small, have a fast reproductive rate, have many body systems that are similar to humans and are relatively inexpensive to conduct research on compared with other mammals. Importantly, mice are similar to humans genetically. Almost every human gene is matched by a similar gene arrangement and sequence in the mouse genome. These human-mouse similarities can be found using simple web searches. Researchers now have more power than ever to choose or create a mouse model that is directly relevant to their area of research. Most importantly, for genetic studies, mice provide a well-defined genetic background enabling the biological consequences of specific genetic changes or mutations to be discovered in an efficient manner. By comparison, the enormous genetic diversity between individual people renders it extremely difficult to decipher the important disease-causing mutations.



Of mice and men: Why use mouse models to learn about human disease?



+ / +

Through the phenomics network, researchers are able to gain access to a wide variety of informative mouse models, carrying known mutations, generated both in Australia and around the world. They can create and discover new models by looking for mutant mice showing a particular physical characteristic, access tools to create mice based on the gene they are interested in and they can preserve mouse models for future use.

The network enables all researchers – not just mouse geneticists – to access a range of genomics tools to determine the variation causing the change in physical traits (phenotype). The APN mutation detection pipelines in place at the Australian National University (ANU), Canberra, and the Walter and Eliza Hall Institute of Medical Research (WEHI), Melbourne, provides researchers with an analysis of their sequencing data and points them to the critical change in DNA sequence.

Furthermore, the network provides researchers with pathology expertise to enable them to learn more about the physical characteristics of their mouse model. Histopathology and organ pathology services, based at the University of Melbourne and IMVS in Adelaide, provide whole organ and histological analysis of mouse models and mice at various developmental stages. Veterinary and clinical pathologists working alongside the laboratory staff offer expert analysis of organs, tissues and blood to Australian researchers enabling them to more fully understand their mouse model's phenotype.

Creating valuable collections of mutant mice

Collections of gene variant (mutant) mice fuel the discovery of new functions for genes in an unbiased and cost-effective manner. These collections are skilfully created at four of the APN partner institutions, via propagating male mice that have been treated with the chemical mutagen **ENU**. This chemical accelerates the rate of spontaneous, random mutations that naturally arise in each generation and are inherited by the next generation. This mutagenic process enables us to require fewer mice to build a valuable collection of mutants that model human disease.

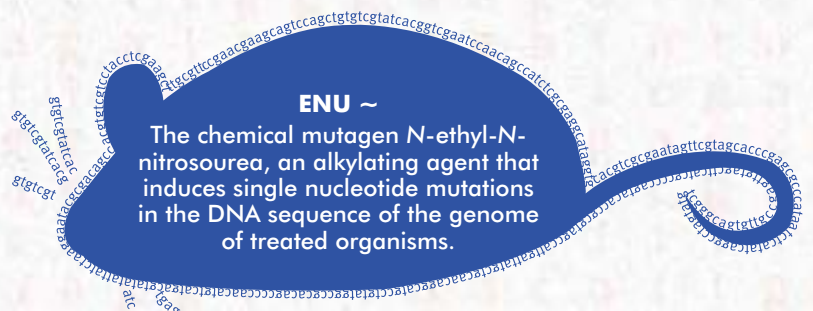
Collections of gene variant (mutant) mice fuel the discovery of new functions for genes in an unbiased and cost-effective manner

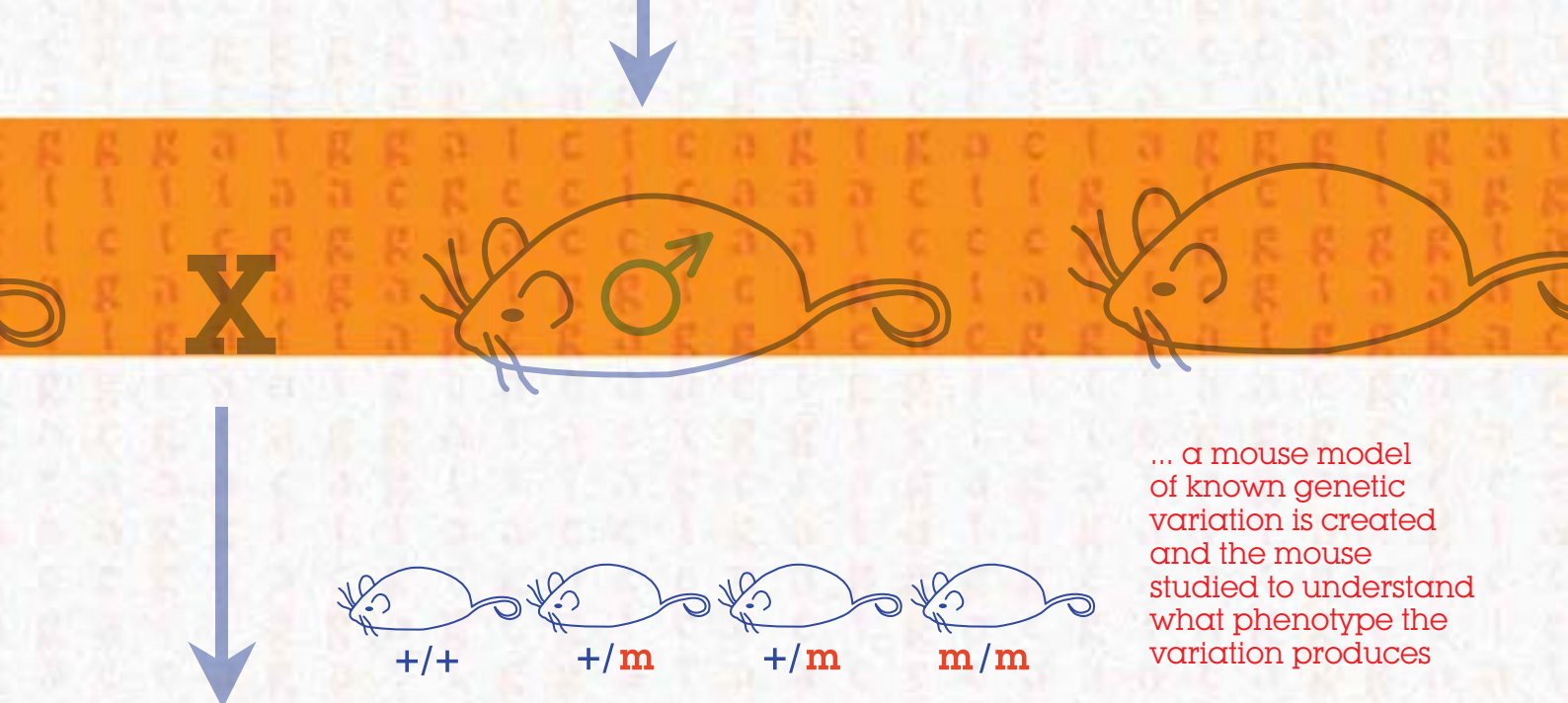
ENU treatment induces genetic point mutations that are 'heterozygous' (carried on one chromosome) in the first generation progeny.

Further breeding to the third generation produces mice with mutations that are 'homozygous' (carried on both chromosomes). The abnormal traits caused by these point mutations are considered by many to be more medically relevant than those caused by removing entire genes, which is a less common cause of human disease. Researchers work with scientists at each of the centres to conduct phenotype-driven screens to identify mice that display characteristics relevant to their area of interest. These are varied and include blood tests, body fat scans and immunological screens. Once a phenotype of interest has been identified, and heritability established, sequencing and gene identification experiments can be conducted to find the variation in the genome that directly caused the phenotypic change.

The random, unbiased nature of the ENU mutagenic action produces the full range of mutations relevant to human disease. By supporting and bringing together the recessive collections (where the mutations are in a homozygous state) at the ANU and the Centenary Institute of Cancer Medicine and Cell Biology, Sydney, and the dominant collections (where the mutations are in a heterozygous state) at the WEHI, the Queensland Institute of Medical Research, Brisbane, and Menzies Research Institute at the University of Tasmania, Hobart, the APN provides researchers with access to one of the largest ENU resources available internationally. These resources increase researchers' chances of finding their phenotype of interest, without the costs and risks of producing the libraries themselves.

Without the APN, few researchers could afford to individually create usefully large collections of mutant mice to screen because the infrastructure is very expensive. Furthermore, the APN has developed the best ways of using current infrastructure and also using new mouse model tools as they become available so that researchers are not burdened with the task of working it all out themselves.





Providing ready access to valuable international genetic tools

The APN's Embryonic Stem Cell to Mouse facility at Monash University allows researchers to create mouse models using a genotype-driven approach. Using this methodology, a mouse model of known genetic variation is created and the mouse studied to understand what phenotype the variation produces. It is a biased approach, so the gene variant is chosen based on prior understanding of biological pathways but the effect of the change is not known. This targeted approach complements the unbiased approach offered through the chemical mutagenesis described above.

The facility provides researchers with access to the embryonic stem cell lines from the International Knockout Mouse Consortium. This global initiative aims to knock out every gene in the mouse genome and have these knockout embryonic stem cells available for researchers across the world. Once phenotyped, these mouse models will provide invaluable insights into human gene function with wide-ranging clinical implications, including better understanding of diseases and discovering gene targets for therapeutic agents. The Monash program provides an international focus and a central pathway for Australian researchers to communicate and engage with overseas researchers. This enables Australian researchers to capitalise on the unrivalled value of this international resource.

The Australian Phenome Bank safeguards value

Mouse models are valuable resources that could be impacted by disasters such as flooding or major disease outbreaks. It would cost millions of dollars and take several years to re-establish the collections if they were destroyed. The Australian Phenome Bank is a collaboration between the ANU, Monash University and the Animal Resources Centre, Perth. It was created to safeguard the value of these resources by securely banking them as cryopreserved sperm samples or embryos using the latest in technology and methodology. Banking is an insurance policy against disaster. Banking also saves husbandry costs by obviating the need to maintain live colonies of all mouse strains regardless of whether they are currently used by researchers. Instead, strains not currently required can be banked for future retrieval when needed. The phenome bank is able to reanimate the genetic stock of the various mouse strains using the same sorts of techniques applied in human fertility.

Banking is an insurance policy

Information on the cryopreserved strains in the bank, and those held at other institutions, is made available via the web-based phenome bank database. This system brings together the information previously held in multiple sites and of varying quality, standardises the nomenclature and display and provides an efficient means of distributing the information to Australian and international researchers. Through the online database, researchers can find strains relevant to their research and, therefore, do not need to recreate the strains from scratch. This, along with the collaboration opportunities that can be realised through the use of the bank, has the potential to progress medical research at a rate greater than seen to date.

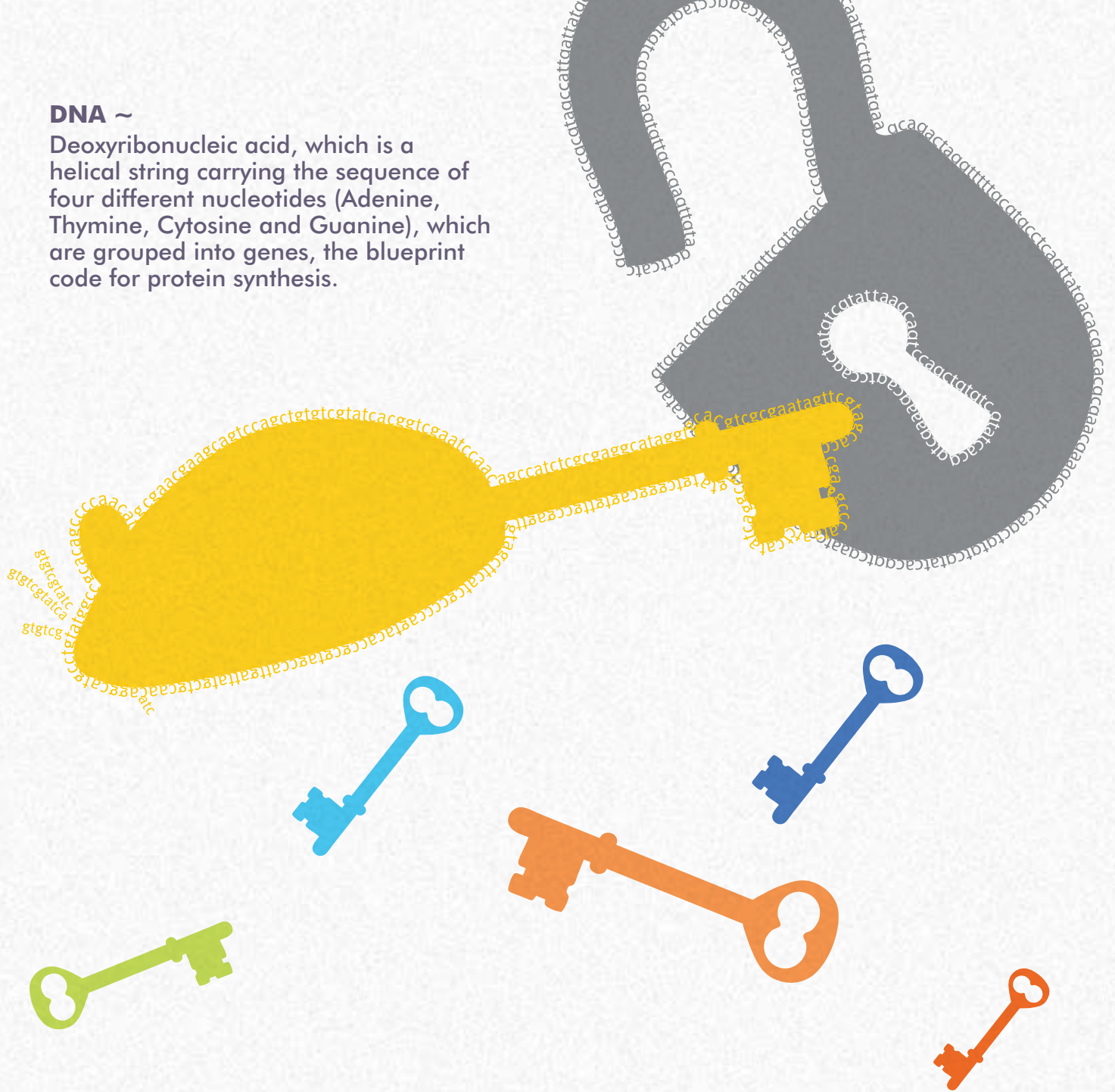
The phenome bank is about one-fifth of the way through archiving the existing mouse strains in Australia, with another 4000 strains to cryopreserve, so there is still much work to be done. As more information about human disease and genetic processes emerge, preservation of these mouse models and the information around them will become increasingly important.

In addition, the Phenome Bank is cryopreserving and banking the mutant mice produced through the chemical ENU mutagenesis program. This will preserve an additional 10,000 mice, thereby securely protecting this large investment in this program.



DNA ~

Deoxyribonucleic acid, which is a helical string carrying the sequence of four different nucleotides (Adenine, Thymine, Cytosine and Guanine), which are grouped into genes, the blueprint code for protein synthesis.



UNLOCKING THE GENOME

Understanding the cause of disease





German physician and ‘father of bacteriology’ Robert Koch argued that it was never good enough to stop at the clinical association stage; the point where a link is made between cause and effect. One must be able to experimentally test that association. Internationally renowned biomedical scientist and the APN’s Chief Scientific Officer Professor Christopher Goodnow ardently subscribes to this view.

Goodnow has been a leader in phenomics for more than 15 years. His groundbreaking research continues to transform our understanding of immunity, tolerance and autoimmunity. Goodnow was one of the pioneers in developing transgenic mouse technology as a tool for revealing the mechanisms of immunological tolerance and memory. He has been a driving force behind international efforts to extend the application of mouse molecular genetics and genetic screens to areas such as tuberculosis, virus resistance, stem cell biology, blood diseases, type 2 diabetes, deafness and infertility. He developed innovative mouse mutagenesis screens to identify new mechanisms of immune regulation and decode how single **DNA** variants affect medically important processes.

In a pioneering step, Goodnow came to the ANU in the late 1990s and established large-scale mouse models for the study of human disease. He used the chemical mutagen ENU to induce genetic variation in thousands of mice in a way that mimics most of the natural variation seen in the human population. By screening each of these mice for physical characteristics (a specific abnormal phenotype) known to be relevant to specific diseases in humans and identifying the disease-causing genetic mutation, Goodnow and his team were able to make inroads into the task of understanding the role of genes in disease and to challenge the associations made through human clinical observations. This approach proved to be effective in yielding results.

... make inroads into the task of understanding the role of genes in disease and to challenge the associations made through human clinical observations

Experimental validation, the process of questioning and challenging the hypothesis that has arisen from the clinical association, is an integral part of the APN’s scientific vision

The yields have become greater, faster, and cheaper with the advent of powerful sequencing technology. Now researchers can rapidly obtain the DNA sequence in mice of interest and zero in on which of the genes actually has a variation. This has dramatically accelerated the rate that researchers can identify all of the DNA variants that change a protein and phenotype of key body systems. “Whereas it took two to four years to get that experimental validation, now it takes two to four months,” Goodnow says. “So it really is a quantum leap. What it often means is that we’ll have the mutation at the same time or even before we have the evidence that it is affecting a disease process.”

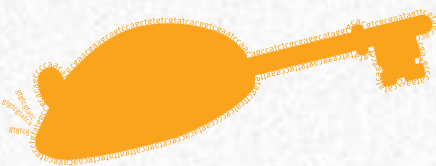
Technological advances in sequencing have enabled clinicians to perform rapid and relatively cheap DNA-sequencing of human genomes or exomes from patients with many different diseases. This is becoming a game-changing technology in biomedical research and personalised medicine and will result in a deluge of data showing possible links or clinical association between diseases and genes. Goodnow is using these new DNA sequencing technologies so that one day he will be able to reveal the full spectrum of genetic variability in immune controlling genes. “What is needed is a way to investigate a substantial list of gene variants in every individual, much in the same way that a physician evaluates a long list of different diagnoses,” Goodnow explains.

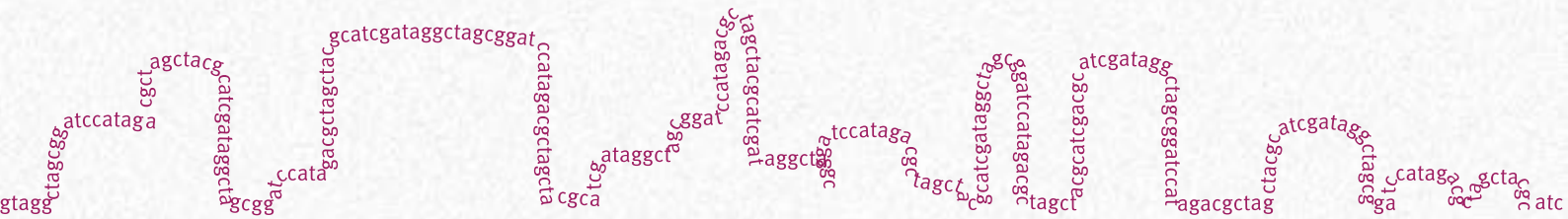
The challenge is to work through the morass to filter out the noise and determine what is significant and should be investigated further. To interpret the human exome sequence data successfully, researchers and clinicians desperately need access to experimental evidence establishing the phenotypic consequences of inheriting a variant in each of the approximately 20,000 to 25,000 genes. The main source of this experimental evidence now, and even more so in the future, is from validated mouse models with defined protein-changing DNA variants and defined phenotypes.

The goal of this work is to enable biomedical researchers to understand the cause of a disease, but the effect of a disease can often confuse matters. Clinical association is the really important smoking gun, but it has to be backed up with experimental validation, says Goodnow. Experimental validation, the process of questioning and challenging the hypothesis that has arisen from the clinical association, is an integral part of the APN’s scientific vision. Goodnow is confident that, with DNA sequence analysis dramatically accelerating the discovery of human gene variants and with the growing Australian expertise in this area of science, researchers will make important discoveries.



Professor Chris Goodnow
Chief Scientific Officer
Australian Phenomics Network





PARTNERSHIPS

Building in the global village

In just five years, the Australian Phenomics Network (APN) has established itself on the international stage and along with researchers using mouse models has formed productive partnerships with several overseas research institutions. The network is bringing its innovative mouse infrastructure to the world and enabling Australian researchers to access what is on offer overseas. Facilitating this two-way engagement has been integral to the APN's success.

Through the support of the phenomics network, Australian researchers have been able to attract major international funding and establish important research partnerships with the US, Canada, Europe, Singapore and China and has become a founding member of the International Mouse Phenotyping Consortium (IMPC).

With these considerable research strengths, Australia has been able to form partnerships with several international consortiums. These are primarily the UK and North American partners of the International Knockout Mouse Consortium, Genome Canada and the Wellcome Trust Sanger Institute in the UK. With further Government support, the capabilities developed by the APN will enable Australia to be a key partner in complementary international research infrastructure projects such as those under the umbrella of the IMPC.

The network is bringing its innovative mouse infrastructure to the world and enabling Australian researchers to access what is on offer overseas

The Phenomics Network has also been able to forge research links with China. Through the Australian Government's International Science Linkages Program, the China-Australia Centre for Phenomics Research was established in 2008. Dr Ed Bertram, the centre's Australian director, is steering this collective effort towards discovering alterations in the genome code that affect the immune system, with a special emphasis on trying to understand various viral infections. These include the influenza virus and chronic infections such as Hepatitis B. China is investing heavily in biomedical research, as well as investing in new buildings and infrastructure and recruiting top scientists to lead the charge. Australian research will benefit greatly from China's rapid progress in the field.

Science is global, collaborative and large-scale. The world's leading biomedical research funding bodies have recognised the critical need for mouse models that map specific genetic variations to phenotypes. The rate of investment internationally is staggering and we need to engage and bring the products of that investment to Australia. As a direct result of the APN's government funding, Australia has developed world-class capabilities in importing stem cells that are generated overseas and converting them into mice, as well as mouse phenotyping in areas such as immunology and infectious disease. The impact of the Australian phenomics capabilities established under the National Collaborative Research Infrastructure Strategy is that Australia now leads the world in producing validated mouse models for use in medical research through the phenotype-driven approach. Ultimately, the network is keen to contribute where it can to the global effort to advance biomedical research and bring together the capabilities in human and mouse phenomics.

The impact of the Australian phenomics capabilities established under the National Collaborative Research Infrastructure Strategy is that Australia now leads the world in producing validated mouse models for use in medical research



UNIVERSITY
OF MANITOBA

From Mouse to Medicine
australian phenomics network



APN INTERNATIONAL LINKAGES

CONSORTIUM / ACTIVITY	PARTNER ORGANISATION	LOCATION
International Knockout Mouse Consortium (IKMC)	European Conditional Mouse Mutagenesis Program (EUCOMM)	Europe
	North American Conditional Mouse Mutagenesis Project (NorCOMM)	Canada
	Texas A&M Institute for Genomic Medicine (TIGM)	Texas
	Knockout Mouse Project (KOMP)	Children's Hospital Oakland Research Institute; University of California at Davis, USA; Wellcome Trust Sanger Institute
International Mouse Phenotyping Consortium (IMPC)	MRC Mammalian Genome Unit	Harwell, UK
	National Institutes of Health	USA
	Toronto Centre for Phenogenomics	Canada
	German Mouse Clinic, Infrafrontier	Munich, Germany
	Institut Clinique de la Souris (ICS)	Strasbourg, France
	Wellcome Trust Sanger Institute (WTSI)	Cambridge, UK
	RIKEN BioResource Center	Japan
	CNR Monterotondo	Rome, Italy
	Model Animal Research Center	Nanjing, China





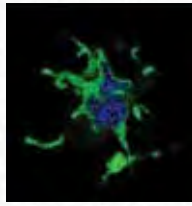
CONSORTIUM / ACTIVITY	PARTNER ORGANISATION	LOCATION
Mouse strain repositories	International Mouse Strain Resource (IMSR)	USA & UK
	Mouse Mutant Resource Regional Centres (MMRRC)	Various, USA
	Mouse Genome Informatics, The Jackson Laboratory	Maine, USA
	European Mouse Mutant Archive (EMMA)	Germany
Other	China-Australia Centre for Phenomics Research (CACPR)	Beijing, China
	BGI	Shenzen, China
	University of Manitoba	Winnipeg, Canada
	Genome Canada	Canada
	Mutagenetix	The Scripps Research Institute, California



SERENDIPITY ROAD

**Harnessing the power
of discovery-based
research**





Almost every illness, from cancer and diabetes to malaria and stroke, involves blood. All blood cells start from stem cells, mostly in bone marrow, where problems can occur. For instance, leukaemia is a form of blood cancer that causes hundreds of thousands of deaths worldwide each year. Understanding how blood cells are created, regulated and terminated is critical to the development of new therapies for blood-related diseases.

Dr Benjamin Kile and his colleagues at the Walter and Eliza Hall Institute of Medical Research (WEHI), Melbourne, have made strides towards such an understanding and are renowned internationally for their research into cancer, stem cells and blood cell production. Kile was awarded the 2010 Science Minister's Life Scientist of the Year prize for his groundbreaking work in the field. The prize is awarded annually for outstanding achievements in science that advance, or have the potential to advance, human welfare.

... awarded the 2010 Science Minister's Life Scientist of the Year prize

The biology of platelets, which play a key role in blood clotting, is one of Kile's major research interests. Dysregulation of these small cells leads to blood clots forming where they should not, conversely, with too few one bleeds uncontrollably. In 2007, Kile and his team uncovered a longstanding mystery in platelet biology by revealing the molecular program that regulates platelet life span. The Bcl-xL protein, which keeps platelets alive, is counteracted by a protein, called Bak, which kills them. The two are in balance in a healthy platelet, but Bcl-xL slowly runs out until Bak kills the platelet. This research could lead to the development of drugs to extend the shelf-life of platelets stored in blood banks, which in turn would benefit cancer patients and others in danger of serious bleeding disorders. The finding also has potential implications for our understanding of conditions where platelets trigger pathological blood clots, such as heart attack and stroke.

Kile's team recently made a discovery that has led them to a new scientific endeavour

As part of their ongoing research into blood cell biology, Kile's team recently made a discovery that has led them to a new scientific endeavour. They isolated a mouse with several abnormal physical characteristics from the mutant mouse collection held at the WEHI and thought it was worth investigating further. The pathology report revealed that the mouse not only had an irregular blood cell count but also had cardiomyopathy, pancreatitis and meningitis. "It turned out that this mouse had a mutation in a gene that had not been previously characterised, that gene regulates a whole series of inflammatory responses," Kile explains. "It's a microbial sensor that usually acts as an alarm system for the body to alert it to the presence of specific microbes. When it misbehaves the result is a very severe autoinflammatory disease".

Determining what this gene does in human disease is the next step and Kile believes it could potentially lead to the development of new anti-inflammatory drugs. These kinds of insights are "pure gold" and required the expertise of a pathologist, Kile says. Gaining access to mouse pathologists in Australia is very difficult were it not for the approach taken by the Australian Phenomics Network (APN) to bring together expertise in many aspects of mouse model characterisation. There is a dearth of qualified vets or doctors who have the requisite expertise in mouse pathology and so the average researcher does not have direct access to these highly sought after people. "Pathologists can look at mouse tissues and diagnose a myriad of conditions, for example cancer, arthritis or cardiomyopathy."

Kile believes more and more researchers are becoming aware of the Phenomics Network and its potential for facilitating groundbreaking and innovative discoveries. Those who are not mouse geneticists, such as clinical researchers who specialise in epilepsy or cardiac disease, could potentially benefit and also greatly advance scientific research. "The Phenomics Network does not just provide access to infrastructure and services, it also connects researchers with other people in their field who are using mouse genetics" Kile says. "These collaborations can be very useful for progressing research."

Collaborative and discovery-based research, which is supported by the APN, complements hypothesis-driven research because it produces unpredictable results, Kile says. "Hypotheses are very important in science, but the unexpected genetic insight is a wonderful thing," he explains. "It is often a classic case of serendipity: you look for one thing and you find another".

Ultimately, Kile is committed to translating his research from the laboratory to the clinic so that Australian patients and the health system benefit from his work. "My team is focused on making fundamental and clinically important discoveries in blood cells."

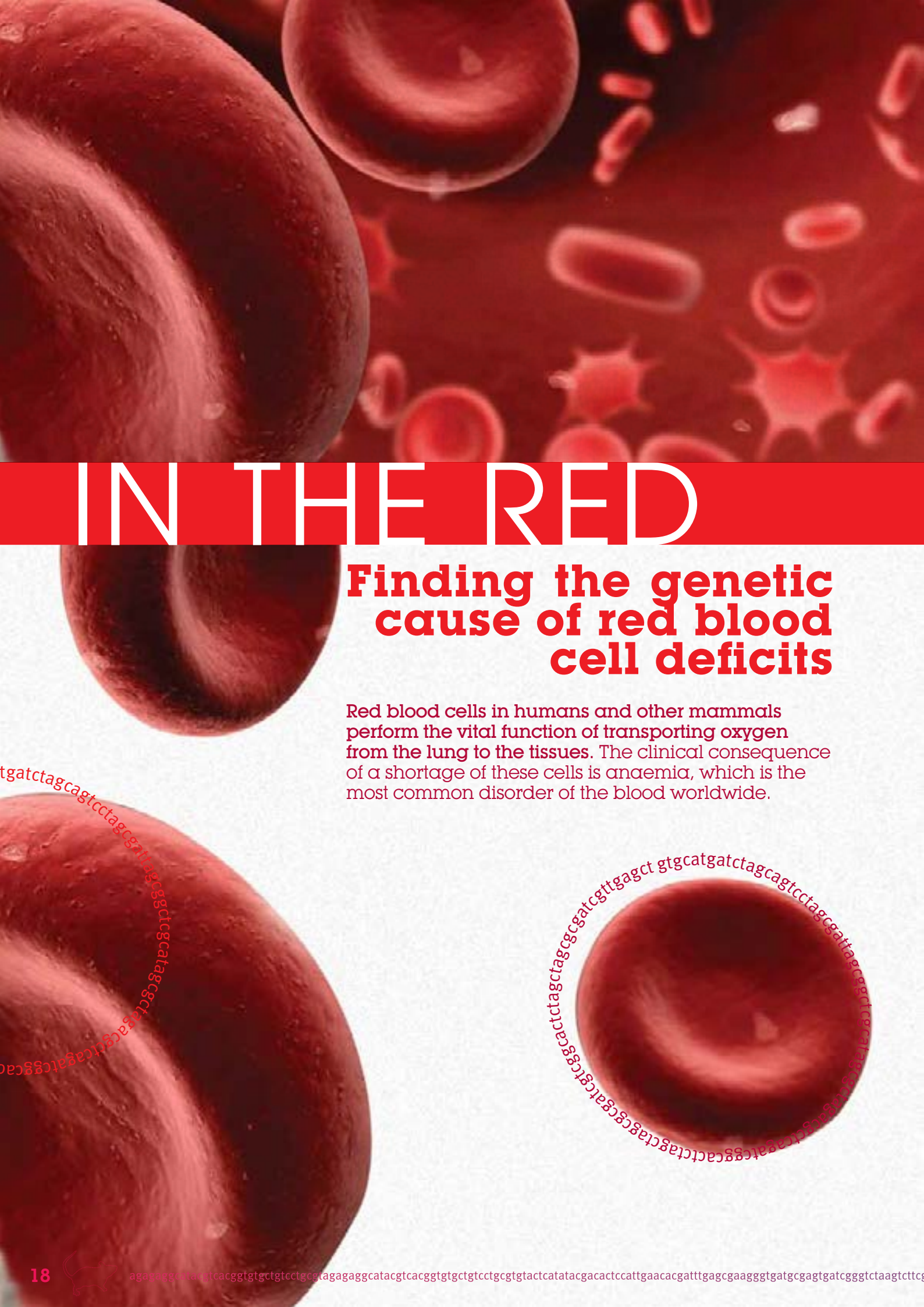


Dr Benjamin Kile

Walter and Eliza Hall Institute of Medical Research, Melbourne



From Mouse to Medicine
australian phenomics network



IN THE RED

Finding the genetic cause of red blood cell deficits

Red blood cells in humans and other mammals perform the vital function of transporting oxygen from the lung to the tissues. The clinical consequence of a shortage of these cells is anaemia, which is the most common disorder of the blood worldwide.

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Professor Steve Jane, a clinician who heads research at the Alfred Hospital and the Department of Medicine at Monash University, is investigating the genes involved in red cell production and diseases such as thalassaemia and sickle cell anaemia. Collectively, these genetic disorders of red blood cells, involving a failure of haemoglobin production, are a catastrophic global health burden. About 10 per cent of the world's population has a disorder of the haemoglobin genes.

Jane works closely with Dr Benjamin Kile and Professor Doug Hilton at the Walter and Eliza Hall Institute of Medical Research, Melbourne, where they create mouse lines carrying a dominant mutation, using the chemical mutagen, ENU. Kile and Hilton investigate mice with white blood cell and platelet abnormalities and refer those with red blood cell irregularities to Jane. "We have become the repository for red blood cell abnormality for anyone using mutagenesis strains," Jane explains.

... to identify genes that confer malarial resistance in mice that can be translated into potential strategies to eradicate malaria in humans

The Australian Phenomics Network (APN)-supported mutant mouse program at the WEHI has enabled Jane and his team to identify novel regulators of haemoglobin that will improve our understanding of these diseases and potentially lead to new treatments. "The program has had tremendous importance to our understanding of red blood cell biology and why anaemia occurs in the context of genetic disorders," Jane says.

One of the genes discovered is a transporter of iron into the red blood cell that is essential for the production of haemoglobin. Iron-deficiency anaemia affects hundreds of millions of people, with problems ranging from malnutrition and blood loss to parasitic infection in the gut.

Many red blood cell disorders that are genetically unfavourable have survived in the global population because they protect against malaria. The countries where thalassaemia and sickle cell disease are endemic overlap with a map of malarial prevalence in the world. Jane is collaborating with Professor Simon Foote at the Menzies Research Institute Tasmania to identify genes that confer malarial resistance in mice that can be translated into potential strategies to eradicate malaria in humans.

Because mice are so biologically similar to humans, particularly in relation to blood development, the findings that Jane is making in the animal model are likely to translate directly to the human patient. "I'm a translational scientist, so I'm not interested in the minutiae for its own sake; I'm more interested in how it can assist us to improve our patient care and management."

Capabilities that are being developed at the APN for identifying and analysing the genetic variation are speeding up the process

Capabilities that are being developed at the APN for identifying and analysing the genetic variation are speeding up the process, according to Jane. Many of the 18 independent mouse lines that Jane identified were difficult to solve and some had intervals with no clear candidate genes. "We've been able to solve a number of them very rapidly using this new mutation detection strategy, which has really revolutionised the whole process," he says. "It's taken a lot of that non-productive downtime out of the equation completely, which is brilliant."

The Phenomics Network has allowed researchers like Jane to address the bigger picture without the need to have an in depth understanding of mouse genetics. "I'm interested in understanding red blood cell biology and the genesis of anaemia, and thanks to the network I don't have to do this on a piecemeal basis," Jane explains. "I can take a much broader genome-wide approach by using this ENU screening strategy."

Jane's research program has led to a better understanding of red blood cell biology and also why anaemia occurs in the context of genetic disorders. "The discoveries in relation to malarial resistance, for instance, have enormous implications from a global health perspective," Jane says. "Further research will hopefully determine why certain red blood cell disorders provide protection against malaria and lead to improved therapies."

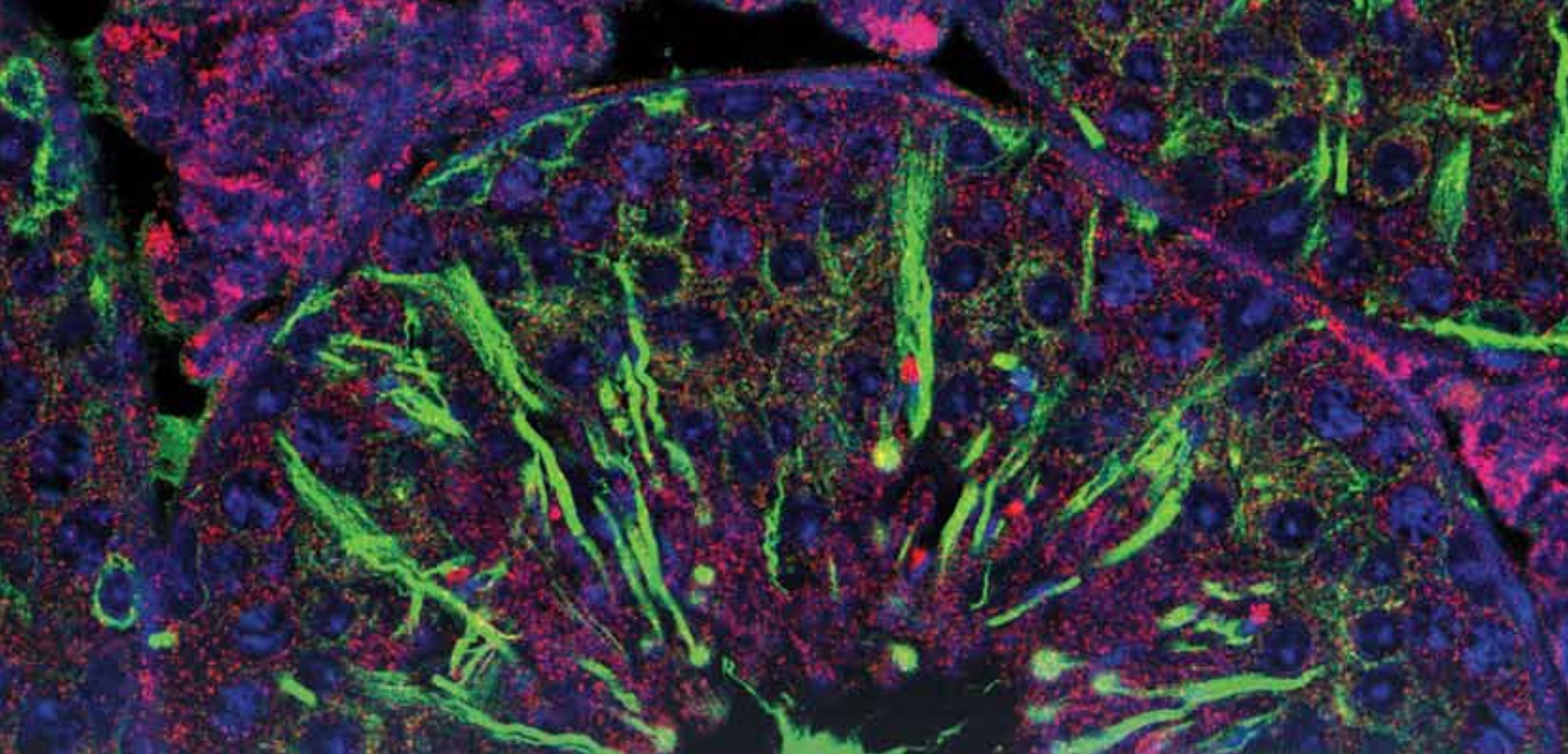
"I'm more interested in how it can assist us to improve our patient care and management"



Professor Steve Jane

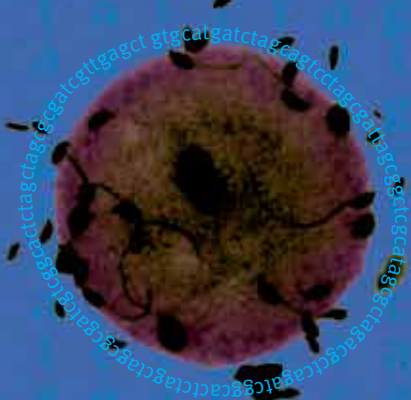
Alfred Hospital and the Department of Medicine at Monash University





SINK OR SWIM

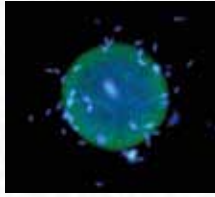
The perilous genetics of male infertility



Genome ~

The total sequence of nucleotides (A, T, C, and G) in an individual's DNA, and therefore the complete set of genes.





In Australia and other developed countries, about one in 25 men are infertile. Functional male sperm are produced through complex processes that take place in the male reproductive system and female reproductive tract. A breakdown during any of these processes can cause male infertility. In at least 30 per cent of sufferers, the underlying cause of their inability to produce sperm remains unknown, which makes the provision of treatment difficult. To complicate matters further, other potentially dangerous conditions could be linked to these unexplained cases of infertility. However, medical scientist Professor Moira O'Bryan believes a series of genetic malfunctions could be responsible.

"About 2300 genes are involved in the process of creating sperm and each need to be activated at precisely the right time to make a sperm that is capable of fertilisation," explains O'Bryan, who is a Professor in the Department of Anatomy and Developmental Biology at Monash University. "It is difficult, therefore, to determine which genes are causing the condition because many of the associated proteins, encoding genes, and regulatory pathway functions are unknown."

Sperm development, known as spermatogenesis, occurs within the testes of the male. Upon leaving the testes, sperm need to undergo two additional processes before they can achieve fertilisation. The first occurs during transit through the epididymis, which collects sperm from the testes and confers upon them the ability to swim forward and fertilise. The second phase occurs within the female reproductive tract and enables the sperm membrane to bind to the egg.

Men are infertile if they do not have enough sperm, their sperm do not swim properly or their sperm are grossly malformed. Artificial reproductive technologies such as Intra Cytoplasmic Sperm Injection (ICSI) that are used in the case of male infertility produce about 1.5 per cent of births in developed countries. ICSI does not cure the infertility and can transmit genetic defects that could cause infertility in future generations, O'Bryan says.

Through the Australian Phenomics Network (APN)-supported mutant mouse collection at Australian National University, O'Bryan's research team has identified mouse lines with a range of abnormalities caused by single gene mutations that are relevant to human male fertility. O'Bryan believes her team's thorough screening process and archiving of sperm will be useful in identifying new genetic mechanisms involved in spermatogenesis. Many of the mouse lines, including those with abnormal reproductive systems, have been cryopreserved at the Australian Phenome Bank. O'Bryan believes this collection will form a valuable resource for the identification and analysis of key regulators of multiple aspects of male fertility. Furthermore, she is confident that international efforts to inactivate every gene in the mouse **genome** will assist her team and other researchers in the field to identify causes of infertility more quickly.

... this repository will form a valuable collection for the identification and analysis of key regulators of multiple aspects of male fertility

The pathology service operated through the APN has helped O'Bryan identify not just infertility-related phenotypes in mice, but also some potentially dangerous associated anomalies that could have implications for patients. Three out of the seven infertile mice in her project also had lung problems and one had hydrocephalus, which is known as 'water on the brain'. Hydrocephalus is caused by a build-up of cerebrospinal fluid that puts pressure on the brain, causing cells to die. Thankfully the condition is quite rare and is usually picked up early in childhood due to observed learning difficulties.

The common factor among the brain, lung and infertility problems is a structure called a cilia, which is a complex cell organelle involved in sensory perception and fluid or cell movement. O'Bryan thinks that the same problems occur in humans. "Male infertility seems to be like a canary in the coal mine – it could be prescient of disease later in life," she says.

Each of these discoveries will help improve our understanding of the genes involved in male infertility and the potentially dangerous knock-on effects that infertility could have, according to O'Bryan. "Hopefully, the insights we gain will lead to better treatments of infertility and these other serious conditions."



Professor Moira O'Bryan

Department of Anatomy and
Developmental Biology, Monash University

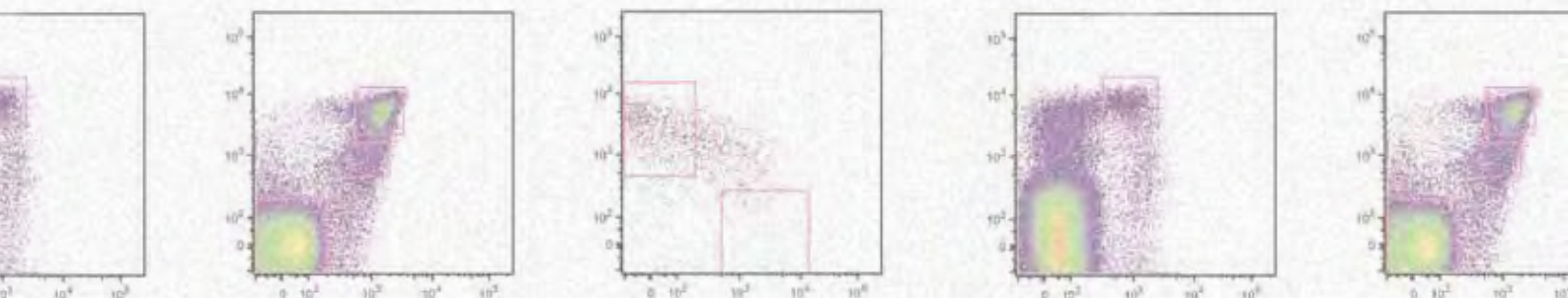


From Mouse to Medicine
australian phenomics network



CANCER

New treatments may stem from mutant mice





Cancer can have a detrimental impact on a person's life and, depending on its nature and stage of development, could result in a prolonged and painful death. Treatments are often expensive and rarely curative. New discoveries capitalising on the expanding phenomics toolbox, however, could change all that. Australian researchers have uncovered a new mutation that alters the behaviour of stem cells, which has implications for the development of new drugs to improve outcomes from chemotherapy and to treat leukaemia and bone marrow failure disorders.

Clinical researcher Associate Professor Andrew Perkins from the Institute for Molecular Bioscience at the University of Queensland, Brisbane, and Dr Peter Papathanasiou from the John Curtin School of Medical Research at the Australian National University (ANU), Canberra, have identified genes that control the development and turnover of stem cells. Stem cells can grow into any other kind of cell in the body, so they potentially hold the key to new treatments for various medical conditions including cancer and degenerative diseases.

The research team searched the collection of mutant mouse embryos created by the Australian Phenomics Network (APN) at the ANU for aberrant stem cell behaviour. Pinpointing the mutated genes responsible is enabling them to learn more about how these genes regulate normal embryonic and adult stem cell behaviour. The researchers have found new genetic pathways involved in the development of stem cells and their self-renewal.

A major finding of the project was the discovery of a mutation in the c-Myb gene. This gene has been previously linked to a number of different cancer types with disordered stem cell biology. The researchers have also identified five other genes that could be targeted for novel therapies to treat patients with stem cell failure syndromes.

The research has unearthed some unexpected results, according to Perkins. One of the mutant mice has limb and facial deformities, as well as a blood stem cell problem, which suggests the gene responsible might be involved in cleft palate, one of the most common human disorders of development. Perkins is screening mutant mice to identify phenotypic traits that occur when both the alleles of specific genes are faulty – a condition not ordinarily compatible with life. “We screened at the stage that the first blood stem cells are made in the mouse embryo which is about two thirds of the way during their normal gestation period or about 14 days in the mouse,” Perkins explains.

The phenomics network is at the cutting-edge internationally with respect to the detection of genetic variation

His team has been very careful to select that particular timeframe due to our understanding of the developmental biology of stem cell generation. They can screen pregnant mothers and all the babies in the uteri rather than waiting until they are adults – hence the animal labour and other associated costs are significantly reduced. “The real strength of the screen we ran is that it is an unbiased phenotype-driven screen, so things jump out at you that you would never have expected,” Perkins says.

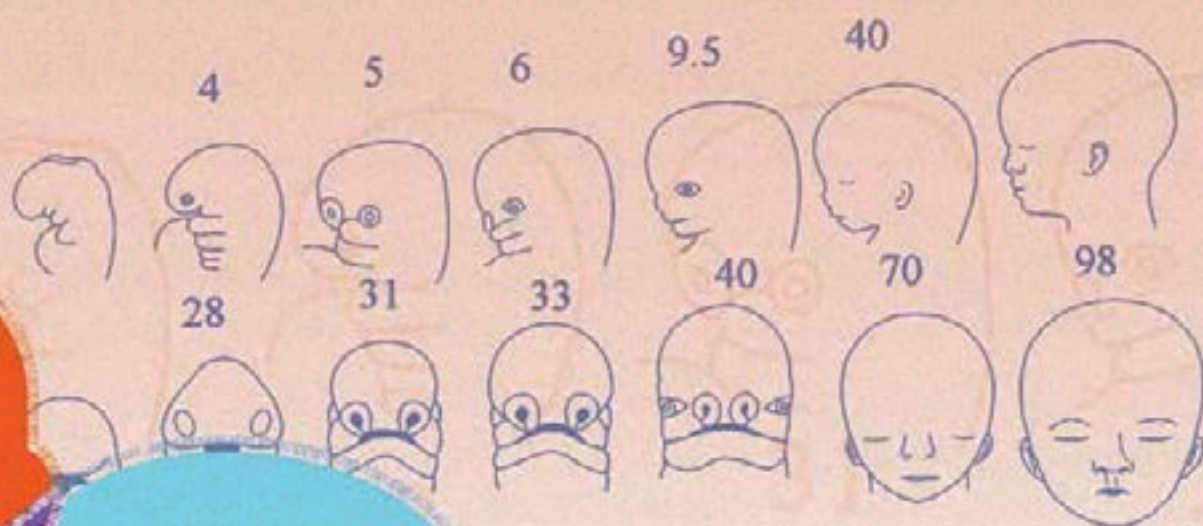
The phenomics network is at the cutting-edge internationally with respect to the detection of genetic variation, Perkins says. Without access to a large collection of mice, phenotyping expertise and capabilities to identify the causative mutation to fast-track the discovery of the gene responsible for an abnormal phenotype, his research would not be possible. “Most the time I can follow the progress online and know what’s going on all the time,” Perkins says. “Professor Chris Goodnow is a leader in the field and is a very forward-thinking person; none of this would have happened without his support and his vision.”

As a clinician, as well as a scientist, Perkins is keen to progress his team’s research towards translational outcomes. “This research is exciting and it’s going to have numerous tangible translational benefits,” he says. “There are some safe drugs on the market that could be used now to target the genetic pathway we have discovered, so I’m confident we will have the potential to advance quickly through safety issues in humans and start clinical trials within the next few years.”

 **Associate Professor Andrew Perkins**
Institute for Molecular Bioscience,
University of Queensland, Brisbane

 **Dr Peter Papathanasiou**
John Curtin School of Medical
Research, Australian National
University, Canberra





PHENOMICS

**The new face of
solving human
disease**



Treacher Collins Syndrome is a congenital condition that affects the development of a person's head and face before birth. Common features include down-slanting eyes, underdeveloped cheekbones and eye sockets and deformed or protruding ears. In addition to abnormal physical characteristics, people with this syndrome could have breathing and eating difficulties, hearing loss and a cleft palate.

This condition is rare, but congenital anomalies or dysmorphology syndromes collectively affect up to 5 per cent of births and are the leading cause of infant illness and death. They place a significant burden on government health care budgets due to the complex and prolonged nature of treatment required. Abnormalities caused by Treacher Collins typically require complex medical and surgical management over many years costing upwards of \$24,000 per annum. Furthermore, the functional and physical impairment of craniofacial and limb anomalies extends well into adulthood, often impacting upon a patient's social interactions, relationships, mental health, self-esteem and academic and vocational achievement.

Dr Peter Farlie, of the Murdoch Childrens Research Institute, Melbourne, is conducting craniofacial research using mouse models to gain a better understanding of these congenital defects. His research team has complementary skills in developmental biology, biochemistry and clinical genetics to drive fundamental new discoveries at the biological and clinical level. Characterisation of the developmental processes and signalling mechanisms disturbed in the five strains mined from the Australian Phenomics Network (APN)-enabled mutant mouse collection at the Australian National University, Canberra, have the potential to dramatically advance our understanding of normal craniofacial and limb development. Each of the strains appear to exhibit traits similar to human dysmorphology syndromes and provide Farlie's team with powerful tools to help determine the cause of a range of congenital malformations in humans.

The major advantage offered by the APN is access to world-class mouse infrastructure, Farlie says. "Federal government funding covered the cost of generating the collections of mutant mice; I would never have launched into a project like that on my own because it's too complicated and time-consuming to set up. With the help of the network, I was able to launch a screen with very little start-up money."

The major advantage offered by the APN is access to world-class mouse infrastructure

Farlie's team began searching for disease-causing genes using conventional genetic mapping techniques but made the switch to next-generation sequencing halfway through their investigations. He would not even think about doing it the old way anymore. He believes the APN is enabling researchers to take advantage of next-generation sequencing, which is having a huge impact. "Financially, this new platform is better because it is much quicker and, therefore, much cheaper – the longer you have to breed mice the more it costs you."

... the animal models and capabilities being established through the phenomics approach are helping to fast-track gene discovery in this area

The various services provided through the phenomics network have been integral to Farlie's research. The network's technical expertise and strategic advice have helped him make important decisions throughout the research process. Farlie is also using the Embryonic Stem Cell to Mouse facility at Monash University to confirm one of his mutagenesis models. "Mice that have a mutation in that particular gene have a very profound birth defect with limb and craniofacial features that are quite severely malformed," he says. "But we just don't know why yet."

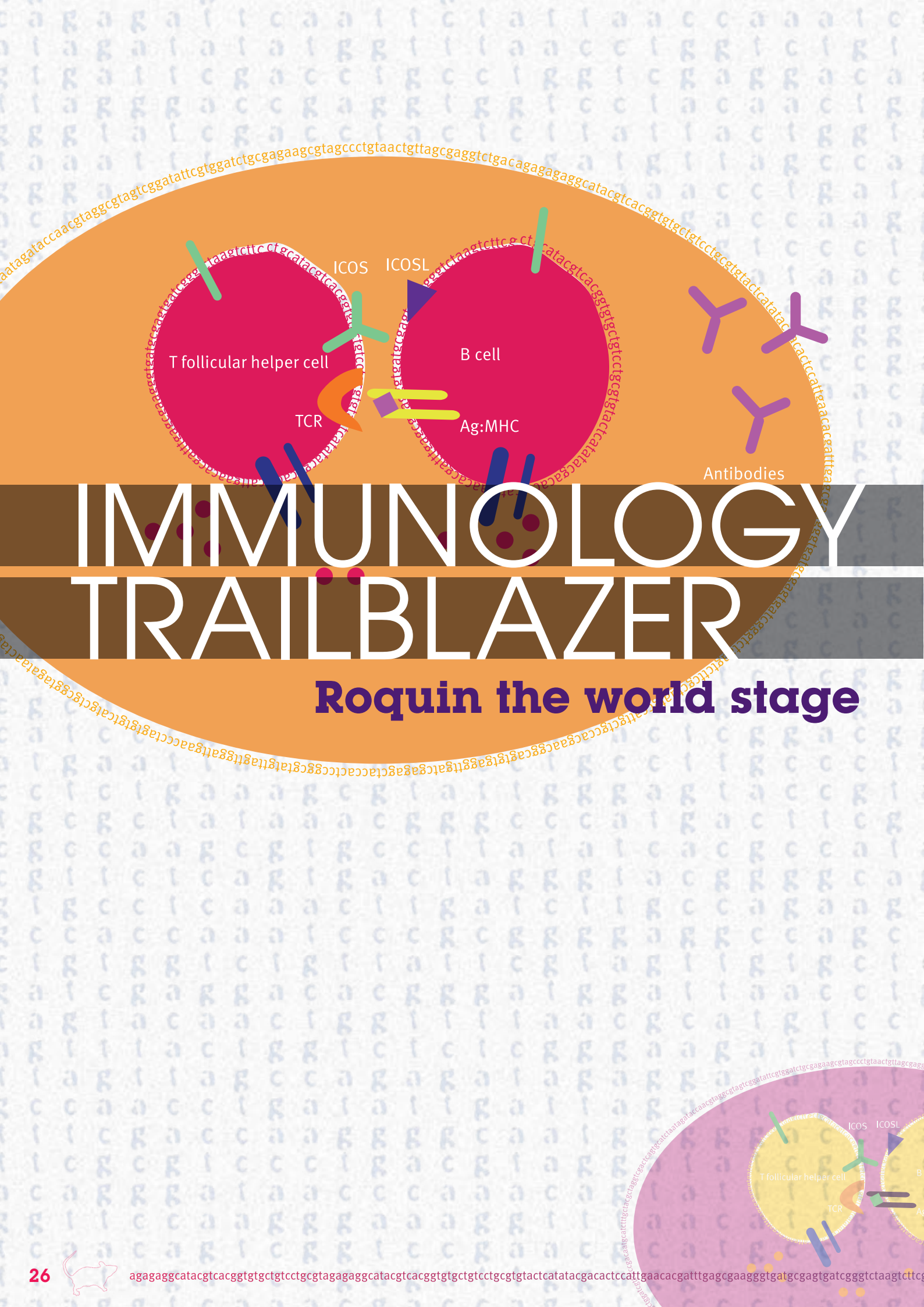
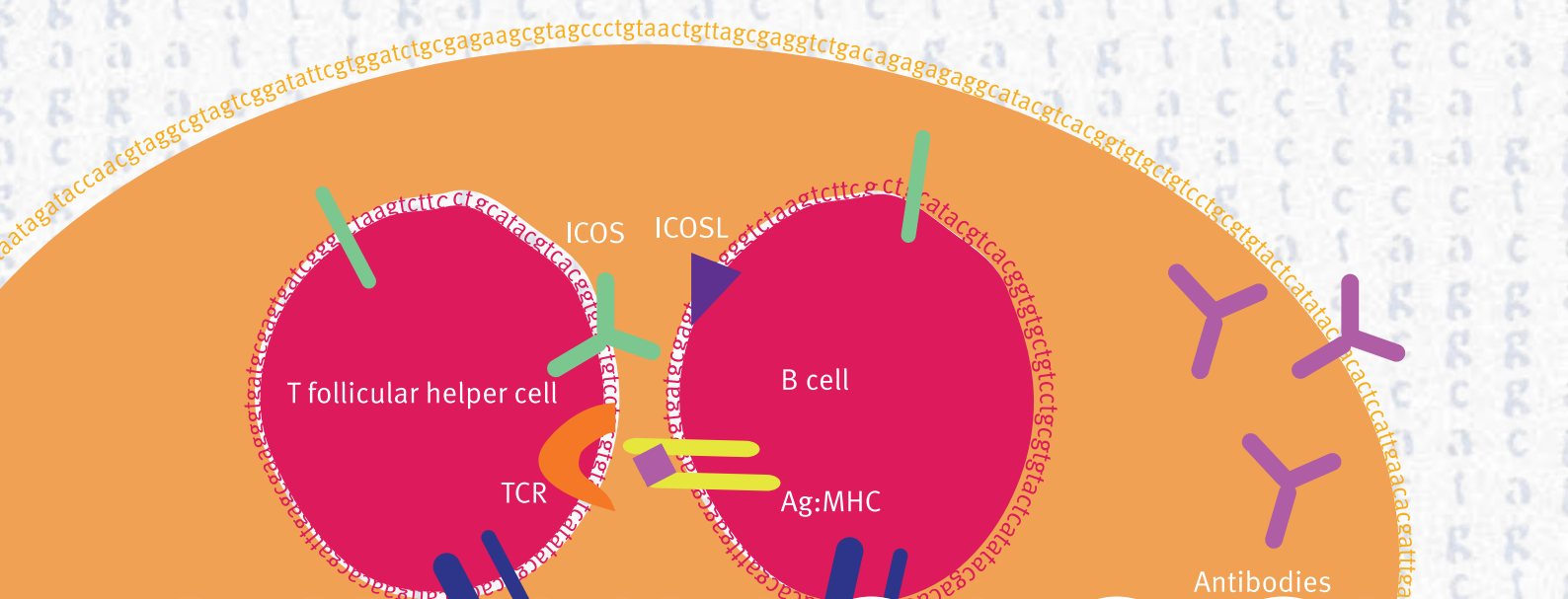
Researchers still have much to learn in the field, Farlie explains. "We don't really understand how our faces and bodies are put together genetically, so it's very hard to understand how birth defects occur. I think the animal models and capabilities being established through the phenomics approach are helping to fast-track gene discovery in this area."



Dr Peter Farlie

Murdoch Childrens Research Institute, Melbourne





IMMUNOLOGY

TRAILBLAZER

Roquin the world stage



Our immune system ordinarily protects us from diseases

by destroying invading pathogens and other harmful agents. However, the body can develop an overactive immune response that results in autoimmune conditions such as type 1 diabetes, which occur when our bodies produce autoantibodies, rogue antibodies that attack our own cells and tissues. Around one in eight Australians suffer from these diseases, which are often chronic, complex to treat and potentially life-threatening.

Award-winning Australian scientist Dr Carola Vinuesa has discovered a genetic cause for autoimmunity that could ultimately pave the way for a new approach to treat autoimmune diseases. Working with Professor Christopher Goodnow and other researchers at the John Curtin School of Medical Research at the Australian National University, she discovered a mouse strain from the Australian Phenomics Network mutant mouse collection that developed a syndrome similar to human lupus. Lupus causes women of child-bearing age to suffer swollen lymph nodes, sore joints, rashes and kidney trouble. Further research uncovered a mutation in a novel gene, and Vinuesa determined the protein that it was encoding and was then able to understand its function.

... awarded the Science Minister's Life Scientist of the Year Award in 2008 and the 2009 Australian Academy of Science Gottschalk medal for her significant contribution to the field

The gene – which they named *Roquin* after the patron saint of plague victims – is now understood to play a critical role in the quality control of antibodies. When the immune system detects an invading pathogen, antibodies against the foreign invader are produced by white blood cells known as B cells. This healthy immune response is dependent on a particular group of T helper cells known as T follicular helper cells. If these T cells are not working properly the result is production of antibodies against self.

... research uncovered a mutation in a novel gene, and Vinuesa determined the protein that it was encoding and was then able to understand its function

The activated *Roquin* gene controls the production of the protein ICOS, which in turn is important in promoting the formation of T follicular helper cells. It only takes the mutation of one letter in the genetic code of the *Roquin* gene to cripple this critical pathway and lead to increased production of ICOS and the consequent accumulation of faulty T follicular helper cells. Vinuesa discovered that accumulation of these cells leads to the presence of rogue B cells that make autoantibodies thereby leading to disease.

In collaboration with Dr Matthew Cook, a clinical immunologist at The Canberra Hospital, she went on to show some lupus patients have faults in this helper T cell-mediated process and that this correlates with disease severity. "The discovery of the roles of proteins such as ICOS and T follicular helper cells opens up opportunities for developing new drugs," Vinuesa explains. "It may one day be possible to use antibodies targeting the T helper cells or molecules such as ICOS to treat autoimmune diseases such as lupus, type 1 diabetes and rheumatoid arthritis."

Vinuesa's research is gaining increasing relevance internationally; she believes it could even help in the field of infectious diseases. She was awarded the Science Minister's Life Scientist of the Year Award in 2008 and the 2009 Australian Academy of Science Gottschalk medal for her significant contribution to the field.

The diagnostic mouse pathology services provided through the APN at the University of Melbourne have been particularly useful to her research. "You get a very detailed diagnostic service and histopathological analysis of the organ and tissue that you are interested in, and then you are put in contact with an expert, such as a vascular tissue specialist, for example."

Vinuesa's team have used the Australian Phenome Bank to cryopreserve several strains with interesting phenotypes that they will investigate in the future. She is excited by the fact that others could potentially use these strains and that she could use somebody else's stored lines. "I think having access to lots of potentially interesting strains from around the world is really useful for researchers."

Vinuesa is certain that there are further exciting discoveries in the pipeline. "I think I'll be working in this area for many years to come because we've got many exciting projects and it seems to be going very well. I've got a fantastic, motivated team that keeps making new discoveries."



Dr Carola Vinuesa

John Curtin School of Medical Research,
Australian National University

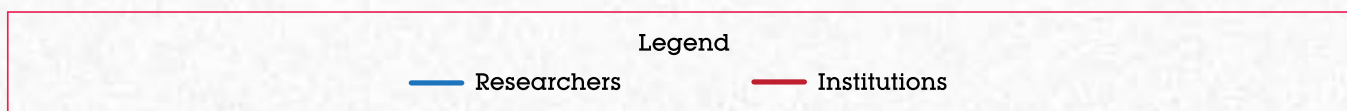


From Mouse to Medicine
australian phenomics network

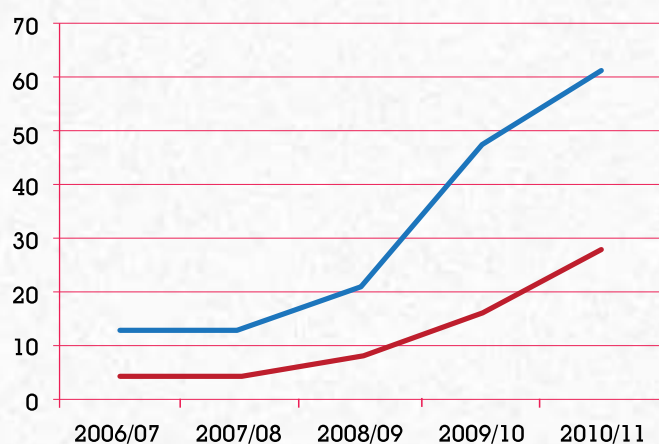
Growth in APN Service Usage

During the 5-year project a total of 335 researchers (including five NHMRC Australia Fellows) representing a total of 70 institutions employed at least one of the APN services.

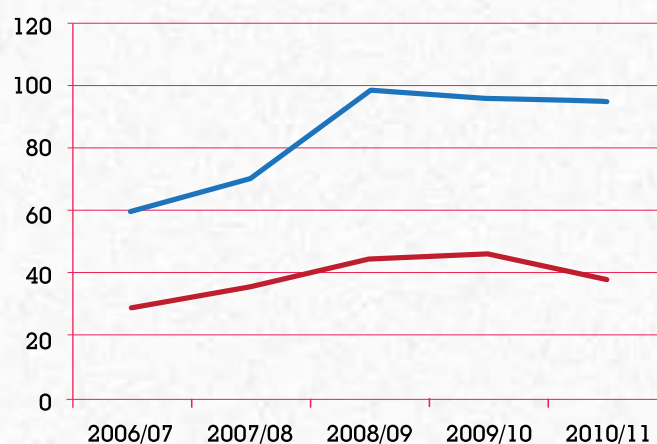
Use of APN services by researchers and institutions



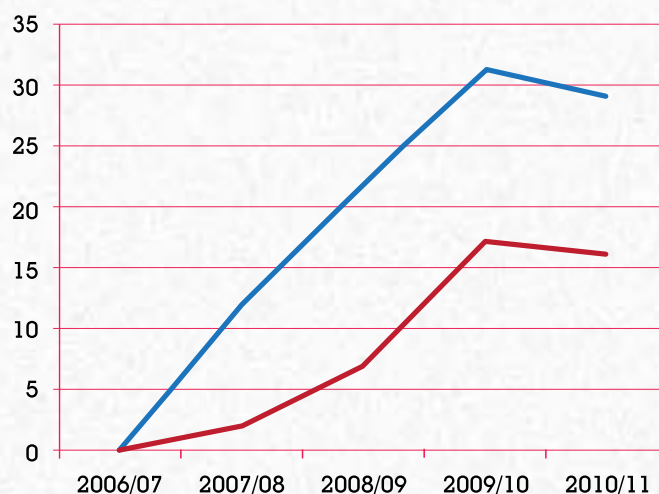
ES Cell to Mouse Service



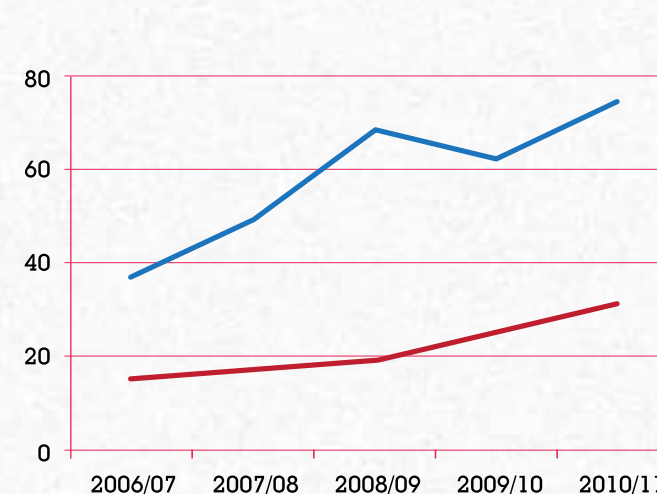
ENU Mutant Collections



Histopathology Service



Australian Phenome Bank

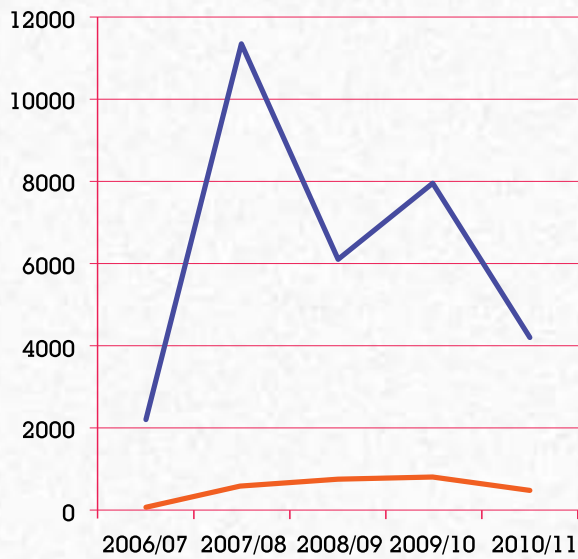


The graphs show the total number of individual researchers and institutions that used the service during each financial year of the 5-year project. The numbers are non-cumulative for each financial year.

Annual numbers of users of the services stabilised as the services achieved full capacity.



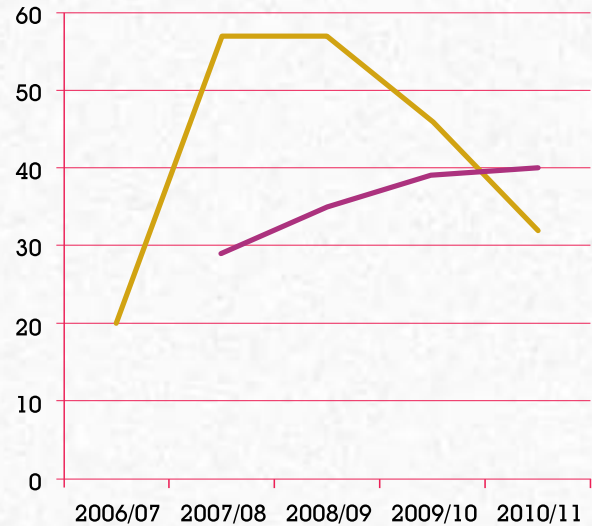
ENU Mutant Production



Legend

- Recessive pedigrees produced
- Dominant lines produced

Uptake of ENU Mutant Discovery Projects and Mutants Discovered

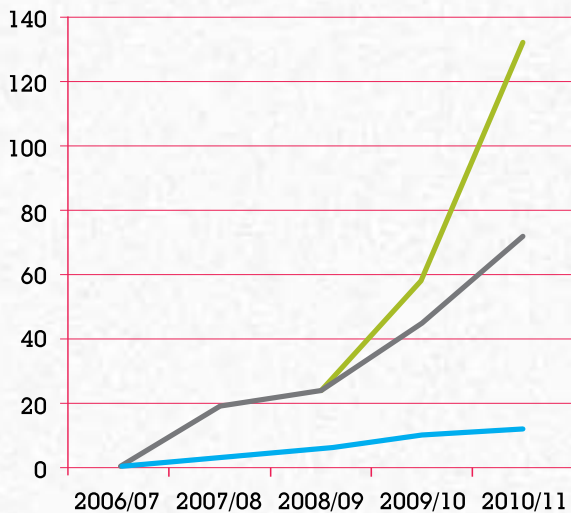


Legend

- Mutant discovery projects
- ENU mutants discovered

ENU projects have a long start-up phase and were accelerated leading up to 2008/09. Beyond that, both the number of ENU mutants produced and the number of research projects declined as individual research projects entered wind-down phases and completed towards the end of the NCRIS project.

Uptake of ES Cell to Mouse Service by Output

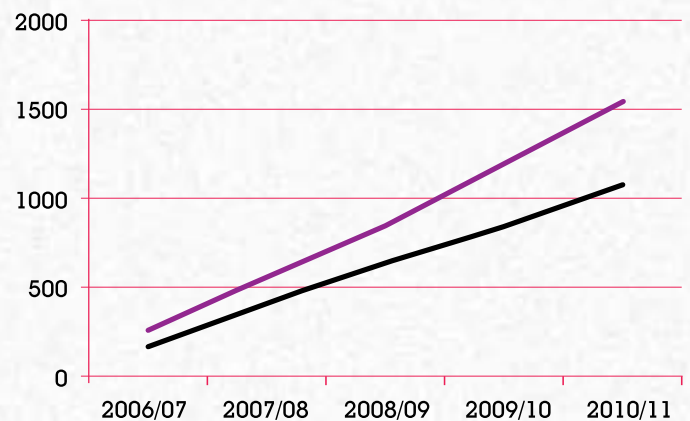


Legend

- Cell lines/ES cell clones imported
- ES cell orders (multiple clones/order)
- New mouse strains produced

Growth in number of mutant mouse strains safeguarded in the Australian Phenome Bank

Cumulative number of mouse strains banked.



Legend

- Database
- Cryobank



Publications that have capitalised on APN services

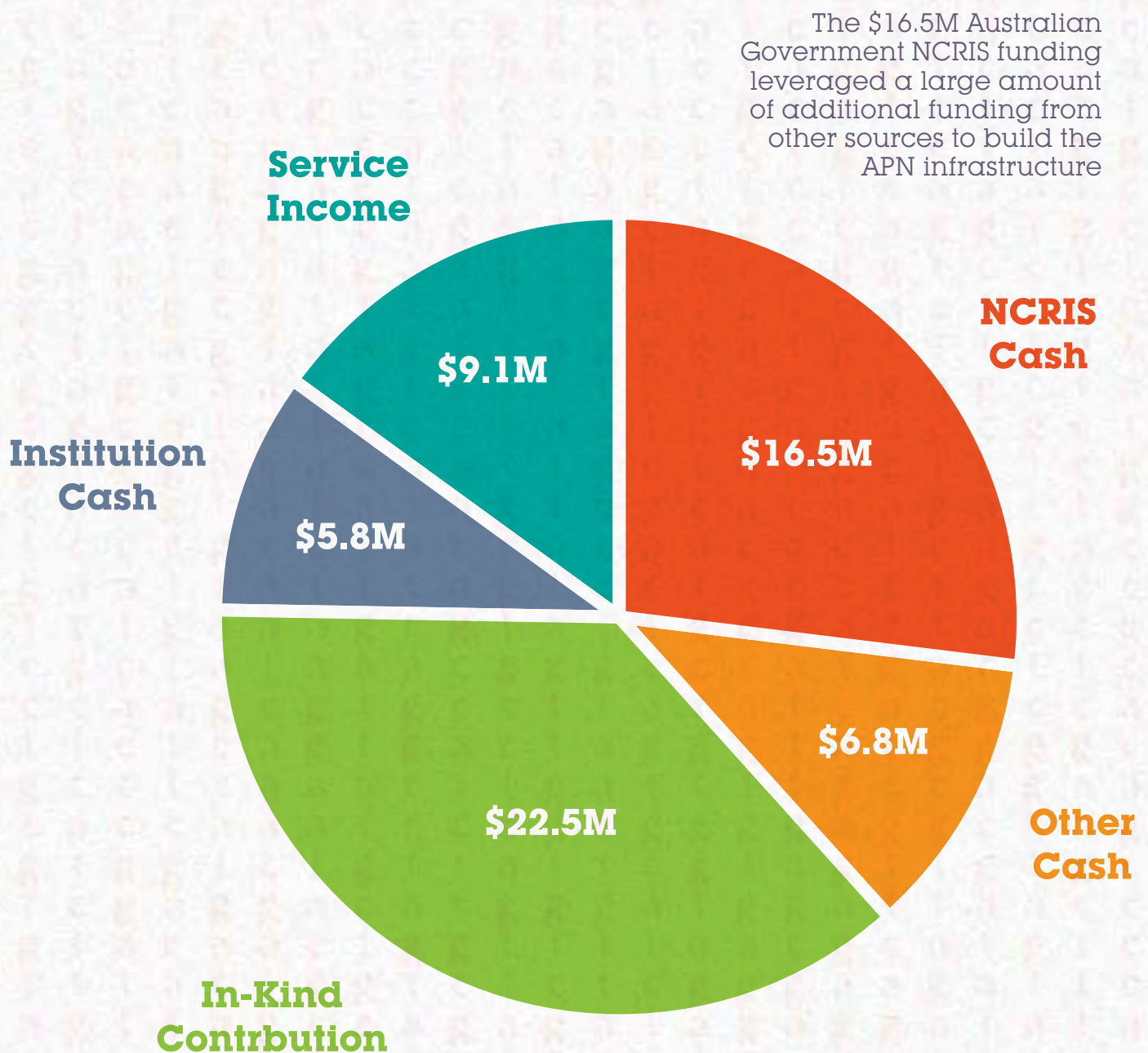
FIRST AUTHOR	YEAR	TITLE	JOURNAL	VOL	PAGES
Yu D	et al. 2007	Roquin represses autoimmunity by limiting inducible T-cell co-stimulator messenger RNA.	<i>Nature.</i>	450(7167)	299–303
Siggs OM	et al. 2007	Opposing functions of the T cell receptor kinase ZAP-70 in immunity and tolerance differentially titrate in response to nucleotide substitutions.	<i>Immunity.</i>	(6)	912–26
Goodnow CC	2007	Nossal and Pike 1975: a turning point in the effort to define self-tolerance mechanisms.	<i>Immunology.</i>	179(9)	5617–8
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Kile BT	et al. 2007	Mutations in the cofilin partner Aip1/Wdr1 cause autoinflammatory disease and macrothrombocytopenia.	<i>Blood.</i>	110(7)	2371–80
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Yu D	et al. 2008	Axon growth and guidance genes identify T-dependent germinal centre B cells.	<i>Immunol Cell Biol.</i>	86(1)	1–2
Blewitt ME	et al. 2008	SmcHD1, containing a structural-maintenance-of-chromosomes hinge domain, has a critical role in X inactivation.	<i>Nat Genet.</i>	40(5)	663–9
Liu M	et al. 2008	Two levels of protection for the B cell genome during somatic hypermutation.	<i>Nature.</i>	451(7180)	841–5
Keys JR	et al. 2008	A mechanism for Ikaros regulation of human globin gene switching.	<i>Br J Haematol.</i>	141(3)	398–406
Heazlewood CK	et al. 2008	Aberrant mucin assembly in mice causes endoplasmic reticulum stress and spontaneous inflammation resembling ulcerative colitis.	<i>PLoS Med.</i>	5(3)	e54
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Gosling KM	et al. 2008	Defective T-cell function leading to reduced antibody production in a kleisin-beta mutant mouse.	<i>Immunology.</i>	125(2)	208–17
Shiow LR	et al. 2008	The actin regulator coronin 1A is mutant in a thymic egress-deficient mouse strain and in a patient with severe combined immunodeficiency.	<i>Nat Immunol.</i>	9(11)	1307–15
Wu Z	et al. 2008	Memory T Cell RNA rearrangement programmed by heterogenous nuclear ribonucleoprotein hnRNPL.	<i>Immunity.</i>	29(6)	863–75
Youngson NA	et al. 2008	Transgenerational epigenetic effects.	<i>Annu Rev Genomics Hum Genet.</i>	9	233–57
Morgan DK	et al. 2008	The case for transgenerational epigenetic inheritance in humans.	<i>Mamm Genome.</i>	19(6)	394–7
Whitelaw NC	et al. 2008	Transgenerational epigenetic inheritance in health and disease.	<i>Curr Opin Genet Dev.</i>	18(3)	283–9
Ashe A	et al. 2008	A genome-wide screen for modifiers of transgene variegation identifies genes with critical roles in development.	<i>Genome Biol.</i>	9(12)	R182
Rank G	et al. 2009	Novel roles for erythroid Ankyrin-1 revealed through an ENU-induced null mouse mutant.	<i>Blood.</i>	113(14)	3352–62
Lambe T	et al. 2009	Identification of a Steap3 endosomal targeting motif essential for normal iron metabolism.	<i>Blood.</i>	113(8)	1805–8
Chu J	et al. 2009	A mouse forward genetics screen identifies LISTERIN as an E3 ubiquitin ligase involved in neurodegeneration.	<i>Proc Natl Acad Sci USA.</i>	106(7)	2097–103
Linterman MA	et al. 2009	Roquin differentiates the specialised functions of duplicated T cell costimulatory receptor genes CD28 and ICOS.	<i>Immunity.</i>	30(2)	228–41
Verhagen AM	et al. 2009	A kinase-dead allele of Lyn attenuates autoimmune disease normally associated with Lyn deficiency.	<i>Immunology.</i>	182(4)	2020–9
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Schoenwaelder SM	et al. 2009	Two distinct pathways regulate platelet phosphatidylserine exposure and procoagulant function.	<i>Blood.</i>	114(3)	663–6
Nijnik A	et al. 2009	Impaired lymphocyte development and antibody class switching and increased malignancy in a murine model of DNA ligase IV syndrome.	<i>J Clin Invest.</i>	119(6)	1696–705
Hilton DJ	et al. 2009	Mutational inhibition of c-Myb or p300 ameliorates treatment-induced thrombocytopenia.	<i>Blood.</i>	113(22)	5599–604
Pontell L	et al. 2009	Structural changes in the epithelium of the small intestine and immune cell infiltration of enteric ganglia following acute mucosal damage and local inflammation.	<i>Virchows Arch.</i>	455	55–65
Johnson AL	et al. 2009	Themis is a member of a new metazoan gene family and is required for the completion of thymocyte positive selection.	<i>Nat Immunol.</i>	10(8)	831–9
Jenne CN	et al. 2009	T-bet-dependent S1P5 expression in NK cells promotes egress from lymph nodes and bone marrow.	<i>J Exp Med.</i>	206(11)	2469–81



FIRST AUTHOR	YEAR	TITLE	JOURNAL	VOL	PAGES
Randall KL	et al.	2009	Dock8 mutations cripple B cell immunological synapses, germinal centers and long-lived antibody production.	<i>Nat Immunol.</i>	10(12) 1283–91
Pontell L	et al.	2009	Structural changes in the epithelium of the small intestine and immune cell infiltration of enteric ganglia following acute mucosal damage and local inflammation.	<i>Virchows Arch.</i>	455 55–65[1]
Theodoratos A	et al.	2010	Mouse strains with point mutations in TAP1 and TAP2.	<i>Immunol Cell Biol.</i>	88(1) 72–8
Zikherman J	et al.	2010	JCD45-Csk phosphatase-kinase titration uncouples basal and inducible T cell receptor signalling during thymic development	<i>Immunity.</i>	32(3) 342–54
Gibbs GM	et al.	2010	Glioma pathogenesis-related 1-like 1 is testis enriched, dynamically modified, and redistributed during male germ cell maturation and has a potential role in sperm-oocyte binding.	<i>Endocrinology.</i>	151(5) 2331–42
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