Background Information

April 2006

# Background information: Science in Melbourne briefings April 2006

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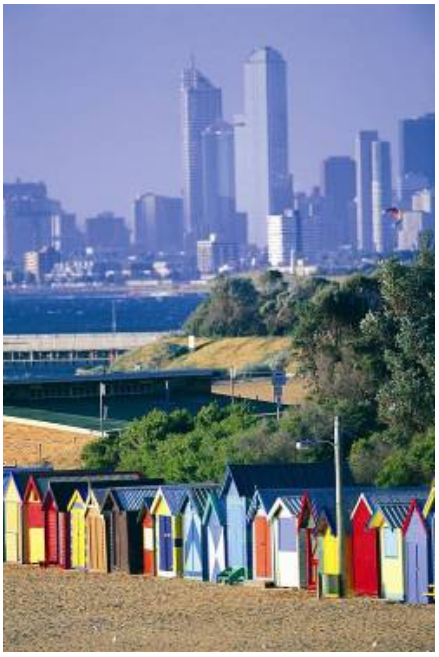


Victoria The Place To Be

# Wallabies: our disappearing Y chromosome, premature babies and milk

*Tammar wallabies – bottom image shows a young joey in the pouch (less than a month old)*
*Photo credit: Australian Genome Research Facility/Vicki Crowley Clough*
*Beta SP footage also available*

Australia and the US National Institutes of Health are collaborating in a multi-million dollar effort to sequence Skippy's[1] genome.

They've chosen the Tammar wallaby to represent kangaroo-kind. It's been the 'model' marsupial for many years and first made headlines in the 1980s when an Australian team reported in Nature that the human male Y chromosome was on the way out – based on their studies of Tammar wallabies.

The Tammar wallaby is a small kangaroo which can do some clever things that humans can't. For example:

- A one day old joey (baby wallaby) weighs less than half a gram. It's roughly the equivalent of a 40 day old human embryo. But even with immature lungs it can breathe unassisted, living in its mother's pouch. Melbourne researchers have visualised baby wallaby lungs using a Japanese synchrotron and hope their research could help develop new treatments for premature babies.
- The baby's development is driven by its mother's milk. Each teat in the pouch can produce a different formula. If a joey gets the wrong milk it dies or grows up deformed. So dairy farmers are supporting research into wallaby, seal and echidna milk to see what they can learn about bioactive compounds in dairy milk.
- Researchers have also discovered a novel antimicrobial protein in wallaby milk and hope that it will lead to new mechanisms for tackling antibiotic resistant bacteria.

These are some of the reasons that the Australian Genome Research Facility has joined with the US National Institutes for Health to sequence the genome of the wallaby – with the Victorian government contributing A$4.5 million to the cost.

## Why is the wallaby genome important?

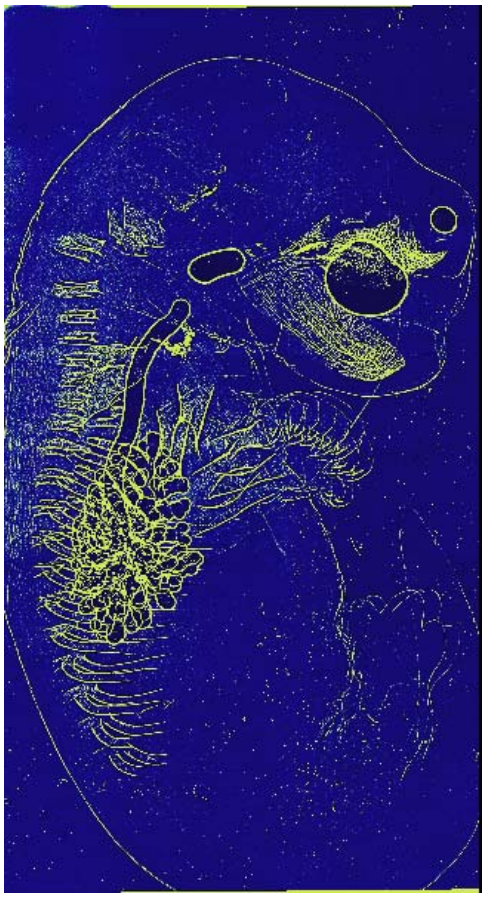
The marsupial genome offers insights into the genetic programming of all mammals – including humans. Because they are such distant relatives in the mammalian family tree, they are sufficiently different

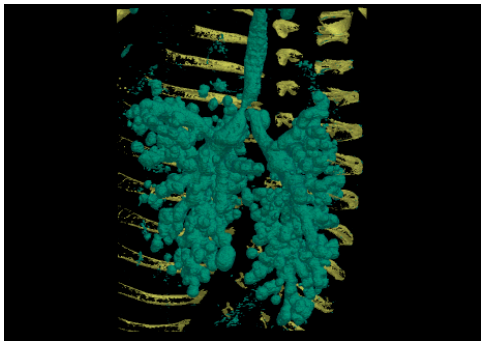
[1] Skippy was the bush kangaroo that could do anything in an Australian childrens' TV s

from humans that we can make useful comparisons which will help us interpret the human genome.

When you find a gene in humans and kangaroos that has hardly changed in 180 million years of evolution you know you are onto something important to human development.

The wallaby genome initiative offers us the opportunity to exploit a unique natural experiment. Wallabies and kangaroos show extraordinary adaptability to environmental challenges. They have unique features of lactation and reproduction that can help in the dairy industry, in livestock fertility, and in human fertility and infertility.





*A baby joey's lungs visualised using a synchrotron – top image colourised, above – 3D interpretation of lungs from a 3 day old joey – also available as an animation. Photo credit DPI Victoria/Rob Lewis Monash*

An understanding of kangaroo reproduction will:

- help us understand and manage human fertility and infertility problems; and
- help us understand and manipulate sex determination and other aspects of fertility valuable to the livestock industries.

Studies have already revealed that the male Y chromosome in humans used to be the same size as the female X chromosome 300 million years ago. If the Y chromosome keeps losing genes it may disappear in the distant future.

## Who cares about wallaby milk?

Around the world people are looking for bioactive compounds in milk.

Bioactives are specific molecules that have useful, health-giving properties. Bioactives found in milk include proteins, peptides, lipids and carbohydrates. They could be used in the development of medicines and functional foods – foods with components that provide a specific health benefit.

Some bioactives already on the market are:

- Lactoferrin, a minor component of the whey protein in milk, boosts immune capacity in the digestive tract – lactoferrin is included in baby foods and some yoghurts.
- Travelan - colostrum product which improves strength and endurance in athletes and improves immune strength against stomach ailments.
- Recaldent - casein phosphopeptide – used in chewing gum and dental products world wide to repair decayed teeth enamel.

Melbourne scientists are studying the mammary genes of the Australian fur seal and the Tammar wallaby – mammals which have specific lactation characteristics associated with bioactives in their milk.

In most mammals, the majority of the early growth and development occurs inside the uterus with nutrients delivered via the placenta.

Marsupials, such as the Tammar wallaby, however, have only a very brief pregnancy and give birth to a tiny, embryo-like young which then matures inside the pouch. It seems that all the factors required for growth of the young joey are found in the wallaby's milk. The milk changes composition as the joey develops to provide the appropriate nutrition and the bioactives required for growth of the suckled young. The very immature joey needs milk with a high colostrum level, as do premature human babies. There are potential biomedical and veterinary applications for these bioactives in treating premature babies.

Researchers are also working with the milk of the echidna, the spiky, egg-laying, monotreme mammal, and with the Australian fur seal.

The seal has the ability to 'switch off' lactation for up to 50 days when it goes to sea foraging, and resume suckling its young immediately upon returning to land. The females progressively increase the rate of milk production during lactation. This suggests that fur seals have a unique capacity to maintain mammary gland capacity even when not producing milk at sea. A better understanding of the process at work in the seals' mammary glands could potentially lead to ways of increasing the length of the lactation period in dairy cows.

*Big Mama, a 40-year old echidna, is helping Australia's Dairy Cooperative Research Centre learn more about the bioactive compounds in milk that drive the development of puggles (baby echidnas)*
*Photo credit: Rismiller-Mckelvey/Dairy CRC*

## Wallaby antibiotics

Wallabies and kangaroos are born without an adaptive immune system and don't develop antibodies until over 100 days after birth.

Yet somehow the young in pouches manage to avoid infection.

Melbourne scientists have used a genomics approach to search for factors in

wallaby milk that might protect the young from bacteria in wallaby milk.

They've found a novel antimicrobial protein, AGG01, with a broad-spectrum of antimicrobial activity. This may aid the pouch young in adaptation to the environment and increase resistance to potential pathogens. This finding may provide new mechanisms for tackling antibiotic resistant pathogens.

## Wallaby contacts

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Antibiotics and wallaby lungs: Ben Cocks, Research Director, Animal Genetics and Genomics, Department of Primary Industries Victorian Institute of Animal Science, +61 (3) 9217-5644, ben.cocks@dpi.vic.gov.au

Kangaroo genomics and the fate of the Y chromosome: Jenni Graves, ARC Centre for Kangaroo Genomics, +61 (2) 6125-2492, graves@rsbs.anu.edu.au

## Web links

- http://www.agrf.org.au
- http://www.hgsc.bcm.tmc.edu/projects/wallaby/
- http://www.genomealliance.org.au/projects/Wallaby/Wallaby.htm
- http://www.dairycrc.com/www/163/1001127/displayarticle/1001509.html

# Hay fever relief

Relief may be close for the more than two million Australians who suffer from seasonal allergies to the pollen of perennial ryegrass, a crop widely grown in Australia and elsewhere as a feed or forage crop for dairy cattle and other animals. Their plight is shared by twenty million US allergy-sufferers.

In an innovative use of biotechnology, a new ryegrass with significantly reduced levels of pollen allergens that cause the sneezing and itchy eyes of hay fever has been developed by Melbourne researchers.

*An end to ryegrass allergies?*
*Photos: credit Molecular Plant Breeding CRC*

The major allergens in ryegrass pollen are two proteins known as Lol p1 and Lol p2. Using 'antisense' gene-silencing technology, where a complementary strand of DNA to the gene of interest is used to inactivate the gene so that the protein is not expressed, the researchers have created new strains of ryegrass that do not express the Lol p1 and Lol p2 proteins.

"The genes are almost fully silenced – it's very effective," says Professor German Spangenberg, from the Molecular Plant Breeding Cooperative Research Centre, based at the new $20 million Victorian Agribiosciences Centre (VABC) at La Trobe University in Bundoora, near Melbourne.

Field trials of the new grasses have been conducted in the US.

As well as reducing the allergen load, the researchers are improving several other traits, making the grass easier to digest and giving it a higher nutritional value. These traits can now be mixed and matched to create a variety of low allergen grasses suitable for different purposes.

In addition, the same technology can be used to improve the quality and remove allergens from other species of grasses including tall fescue, which is widely grown in the US.

A new company, Gramina, has been established to commercialise the grasses both in Australia and worldwide.

## Key facts

Ryegrass and other pollen allergies affect about 2 million Australians and 20 million

Americans every year, causing hay fever and asthma.

The main allergy-causing proteins in ryegrass, known as Lol p1 and Lol p2, are very similar to proteins found in other grass pollens.

Although the role of Lol p1 and Lol p2 in the pollen is not fully understood, silencing the proteins does not have an effect on the fertility of the ryegrass.

Other programs involving pasture grasses at VABC include the development of grasses with lower lignin content, making them softer and more digestible and hence more palatable for the cows that eat the grasses. Conversely, grasses with a higher lignin content may be suitable for use in situations where tough turf is required – such as on playing fields.

More nutritious grasses are also in development, utilising the genetic pathways that control the production of fructan, a carbohydrate that provides an excellent source of energy for dairy cattle.

Techniques to transform ryegrass with all of the desired traits simultaneously are being developed to speed up the process.

The improved traits can then be bred into a variety of elite ryegrass cultivars to create low allergen grasses suitable for many uses.

The first low - allergen grasses are likely to be released for commercial use in 2013 – there are still field trials to complete for final cultivar development and seed to be grown up in sufficient quantities.

The VABC, which was funded by the Victorian State Government and by La Trobe University, is intended to be a one stop shop for academic, commercial research and development groups, according to Spangenberg, and comprises a consortium including La Trobe University, Department Of Primary Industries Victoria (DPIV), RMIT University, Monash University, Florigene Ltd - a division of Suntory, Molecular Plant Breeding CRC and GE HealthCare Biosciences.

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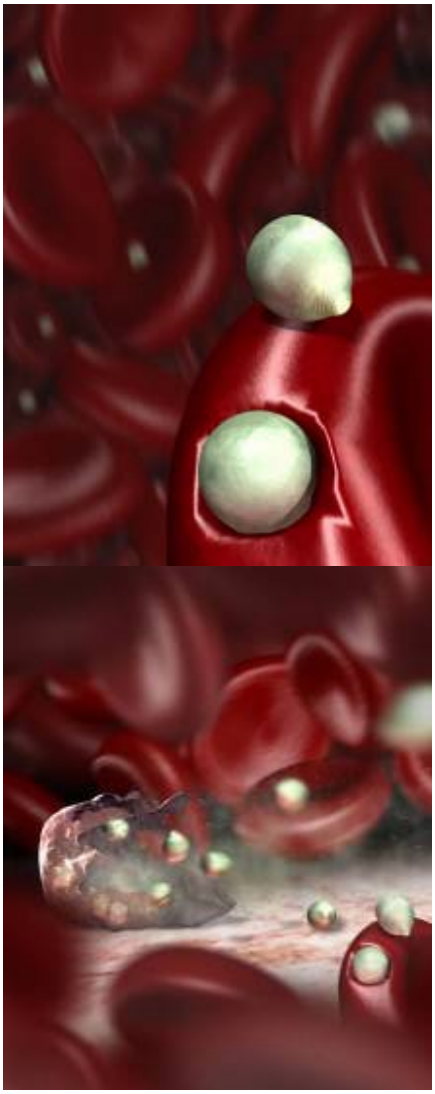
## Web links

- http://www.molecularplantbreeding.com
- http://www.gramina.com.au

# Malaria

A drug that costs just 12 cents a dose may provide a dramatic reduction in the number of deaths due to malaria.

Researchers led by Dr Louis Schofield at Melbourne's Walter and Eliza Hall Institute of Medical Research (WEHI) are about to start testing long-established anti-malarial drug Fansidar as an immune system protector. The drug, which has been around for 20 years, is no longer very effective as an anti-malarial due to the development of resistance by the parasite, but the researchers have discovered that even a single dose of the drug can boost a person's immune response the next time it encounters malaria, reducing the deaths, debilitation and complications of malaria by a massive 50 percent.



*Artists impresson of malaria parasites entering blood cell (top); bursting out of a dead red blood cell*
*Photo credit Drew Berry/WEHI*
*Also available as a broadcast quality animation*

"There seems to be a totally unexpected residual immunological effect when children are given this tablet as a preventative rather than as a post-infection treatment for malaria. While the drug itself dissipates in the bloodstream over a few days, it appears to enable the immune system to re-energize and more successfully combat any subsequent malarial infection. We suspect that many toddlers who seem reasonably healthy might actually have low level malarial infections that are eliminated by Fansidar, allowing the immune system to develop to its full potential," Schofield says.

A trial of the drug is due to start in Papua New Guinea this year, in collaboration with the Papua New Guinea Institute of Medical Research and the University of Melbourne.

It's just one of several approaches to combating the disease, which infects 10 percent of the world's population and kills 2-3 million people a year, being investigated by Melbourne researchers.

Last year, Schofield was one of two recipients at WEHI of a grant from the Bill and Melinda Gates Foundation Grand Challenges in Global Health initiative. The US$8 million grant to Schofield with his collaborators in Canada and France is for investigating methods for boosting the immune system in people with malaria by looking at how the body combats infections to other parasites.

The second grant of US$13 million to Professor Alan Cowman in collaboration

with researchers at the Seattle Biomedical Research Institute and the University of Heidelberg will fund the development of genetically engineered malarial parasites that have been crippled by switching off critical genes, which can be used to study whether an immune response can be generated against the parasite – the first step in getting a successful vaccine.

Two gene targets have already been identified, and genetically altered parasites are expected to be tested in humans in 3-4 years by the US Army at the Walter Reed Army Medical Center.

But these are not the only malaria projects underway at WEHI or even in Melbourne. Last year, six Melbourne scientists including Schofield, Cowman and three other researchers from WEHI and one from the University of Melbourne were named Howard Hughes Medical Institute International Research Scholars, and given grants from that organisation to continue their work on malaria. And there are also malaria research efforts at Monash University, La Trobe University and elsewhere.

## Contacts

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## Other malaria projects

Some of Melbourne's malaria researchers and their projects:

- Prof Leann Tilley and Dr Nick Klonis (La Trobe University) – understanding of the interactions of the malaria parasite with the erythrocytes of its human host, with a view to developing new anti-malarial strategies.
- Prof Robin Anders (La Trobe University) – focused on potential vaccine antigens from the asexual blood stages of *Plasmodium falciparum*.
- Assoc Prof Mick Foley (La Trobe University) –using the powerful phage display approach to identity peptides that interact with a number of important malaria proteins.
- Prof Alan Cowman (WEHI) – investigating how *Plasmodium falciparum* invades mature red blood cells. This information will be important in determining the potential of proteins involved in the process as vaccine and drug candidates.
- Dr Brendan Crabb (WEHI) – study of merozoite surface proteins, the prime targets of immune responses and the leading vaccine candidates for control of the deadly malarial parasite, *Plasmodium falciparum*.
- Prof Simon Foote (WEHI and the Menzies Research Institute, Hobart) – determination of how the host defends itself against malaria resistance by infecting genetically similar mice carrying rare mutations and studying the mutations that allow animals to survive infection. This research will yield insights into host response to malaria.
- Dr Louis Schofield (WEHI) – study of the role of innate immunity and the parasite toxin in susceptibility and resistance to severe malaria. It is hoped that determining the role of the toxin and innate responses in disease, and the role of anti-toxin antibodies and counter-regulatory mechanisms in

clinical immunity to malaria, will provide a rational basis for the development of interventions that prevent malaria fatalities.

- Dr William Heath (WEHI) – investigation of the effects of the interaction between malarial parasites and dendritic (antigen-presenting) cells, which initiate immunity, on the ability of malaria to overcome the efforts of a competent immune system.
- Prof Geoff McFadden (The University of Melbourne) – investigation of a tiny and vital organelle, the apicoplast, within the malaria parasite. The aim is to understand how drugs that disrupt the apicoplast work and how the apicoplast is powered.
- Prof Bill Charman (Monash University/Victorian College of Pharmacy) – development of synthetic anti-malarial drug.
- Dr Ross Coppel (Monash University) - understanding facets of the basic biology of the parasite and its relationship to the human host, together with studies to identify components of the parasite, that may be used in vaccines.

## Web sites

- http://parasite.org.au/arcnet/index.shtml
- http://www.wehi.edu.au/index.html
- http://www.med.monash.edu.au/microbiology/research/coppel/rsch-rlc.html
- http://www.latrobe.edu.au/biochemistry/index.html

# Diabetes

A weekly nasal insulin spray is being tested by Melbourne scientists as a weapon to prevent the development of type 1 diabetes.

Type 1 diabetes is an autoimmune disease where a person's own immune system turns on itself and destroys the insulin-producing cells in the pancreas. With no insulin, blood glucose levels are not controlled which can lead to severe complications including kidney failure, blindness, nerve damage, amputation, heart attack and stroke.

The treatment is based on inducing immune tolerance, where the immune system is re-educated to ignore insulin and its precursor proinsulin, and the cells that produce them. A preliminary study of 38 children at risk of developing diabetes demonstrated that the spray prevented the onset of diabetes in the children who started the trial with some insulin function for a period of at least three years.

The Melbourne team, lead by Prof Len Harrison from the Walter and Eliza Hall Institute of Medical Research (WEHI) and Assoc Prof Peter Colman from the Royal Melbourne Hospital, are recruiting for a larger trial which will screen more than 12,000 children and young adults with diabetic relatives to identify a cohort of more than 200 with a high risk of developing the disease.

These participants will be given nasal insulin or a placebo over the course of a year, and then followed for several years to see whether diabetes develops.

The study is being supported by the Diabetes Vaccine Development Centre, a joint venture between the Juvenile Diabetes Research Foundation and Australia's National Health and Medical Research Council.

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## Websites

- http://www.wehi.edu.au/index.html
- http://www.diabetestrials.org/

## VivaGel

A Melbourne-based company, Starpharma, has developed a unique microbicidal gel that is being tested as a preventative against HIV and genital herpes in women.

To date no drugs have been approved for the prevention of HIV infection.

Last year Starpharma received a US$20 million grant from the National Institute of Allergy and Infectious Disease, part of the US National Institutes of Health, to accelerate the clinical development of the gel which is a polyvalent, polylysine dendrimer.

Starpharma is working with a team of internationally recognised leaders in the development of new HIV treatment and prevention measures including the Burnet Institute (Melbourne, Australia), The National Centre for HIV Epidemiology and Clinical Research at the University of New South Wales (Sydney, Australia) and the Thai Red Cross AIDS Research Centre (Bangkok, Thailand) to take the drug through clinical development. Phase I trials completed so far indicate that VivaGel is safe and well tolerated.

In January, VivaGel was awarded fast-track status from the US Food and Drug Administration (FDA), recognising that the product addressed an unmet medical need, and significantly expediting the review process.

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## Deadly fungus under investigation

A fungus that is infectious at the human body temperature of 37 $^{o}$C but harmless at 25$^{o}$C is being investigated by a Howard Hughes Biomedical Research Scholar at the University of Melbourne.

Dr Alex Andrianopoulos from the Department of Genetics received a five-year $400,000 grant last year to study the dimorphic fungus *Penicillium marneffei*, which is endemic in South East Asia. The fungus lives in immune system cells and can be fatal to people with weakened immune systems. While the infection can be treated with anti-fungal drugs, it can't be cured and continued treatment leads to resistance.

Dr Andrianopoulos hopes that by studying the genes responsible for the dimorphic behaviour of the fungus, new drugs can be designed that cure infections by dimorphic fungi such as *P. marneffei*.

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