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Publication: Recent APF Gene Variant, "Nessy"

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A mutation in a chromosome condensin II subunit, kleisin β , specifically disrupts T cell development

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Communicated by Gerald R. Crabtree, Stanford University School of Medicine, Stanford, CA, May 31, 2007 (received for review February 20, 2006)

Condensins are ubiquitously expressed multiprotein complexes that are important for chromosome condensation and epigenetic regulation of gene transcription, but whose specific roles in vertebrates are poorly understood. We describe a mouse strain, *nessy*, isolated during an ethylnitrosourea screen for recessive immunological mutations. The *nessy* mouse has a defect in T lymphocyte development that decreases circulating T cell numbers, increases their expression of the activation/memory marker CD44, and dramatically decreases the numbers of CD4⁺CD8⁺ thymocytes and their immediate DN4 precursors. A missense mutation in an unusual alternatively spliced first exon of the kleisin β gene, a member of the condensin II complex, was shown to be responsible and act in a T cell-autonomous manner. Despite the ubiquitous expression and role of condensins, kleisin β ^{ness/ness} mice were viable, fertile, and showed no defects even in the parallel pathway of B cell lymphocyte differentiation. These data define a unique lineage-specific requirement for kleisin β in mammalian T cell differentiation.

tion; and Dnmt-1, a protein responsible for the propagation of DNA methylation patterns during cell division (10). In addition, the polycomb group proteins Bmi1, M33, and me118, which maintain silencing of genes by combining with histone deacetylases or blocking nucleosome remodeling, have also been shown to cause defects in thymocyte differentiation (11). In most of these examples, knockout of the protein is embryonic lethal or causes poor viability in mice, and conditional knockouts are used to study the T cell-specific effects of the gene.

Knockout mice have been invaluable in understanding T cell differentiation, with >100 genes shown to be important in this process. However, this technology has the disadvantage of only being applied to genes already suspected to play a role in T cell development. Knocking out a gene of interest to see whether a phenotype is observed is an example of a reverse-genetics approach. Forward-genetics approaches, which start with a phenotype, have the advantage of not presupposing which genes

ES to Mouse Service

The Australian Phenomics Network provides a number of cutting edge services available to all academic researchers across Australia. One such service is the ES to mouse service.

At the request of researchers, mouse ES cells lines containing a single gene modification will be imported into our facility from the European Conditional Mouse Mutagenesis (EUCOMM), North American (NORCOMM) and NIH Knockout Mouse Project (KOMP) programs.

These collaborative programs will collectively generate knockouts of every gene in the genome (approx 25,000) over the next 5+ years. As part of the ES to mouse service, our facility will generate heterozygote mice carrying the gene modification and distribute it to the researcher. The aim of the ES to mouse service is to provide Australian biomedical researchers with access to this wonderful resource.

The facility is located at Monash University and includes capabilities in molecular biology, tissue culture, embryology and animal husbandry.

The scientists in the facility have several years experience in producing genetically modified mice, providing excellent expertise for this operation.

As this service is subsidised by both the Federal and Victorian state government through the National Collaborative Research Infrastructure Strategy (NCRIS) initiative, we are able to offer this service at a heavily discounted fee to academic researchers.

Gene trap, targeted or knockout mice constitute a sophisticated and cost-effective means of proving a cause-effect relationship between a gene and biological or pathological outcome *in vivo*. Thus this initiative is expected to have a major impact on biomedical research and ultimately on human health.



MONASH INSTITUTE
OF MEDICAL RESEARCH

For more information, contact Debbie Bianco at Monash Institute of Medical Research, Monash University:

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Useful Links:

www.sanger.ac.uk/PostGenomics/genetrap

<http://norcomm.phenogenomics.ca/>

www.eucomm.org

www.genetrap.org

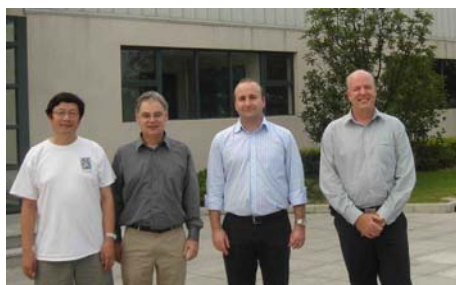
www.komp.org

www.mmrrc.org

The APF Establishes New Linkages in China

In July 2007 Ed Bertram, Head of Scientific Programs travelled to China for 19 days on the Young Investigators Exchange Program hosted by the Australian Academy of Technological Science & Engineering and China's Ministry of Science & Technology.

Taking the opportunity to engage in collaborations for APF projects, developmental biologists from ANU Dr Ruth Arkell, Professor Rob Saint and APF's CEO Dr Steve Winslade also travelled to China for the first week.

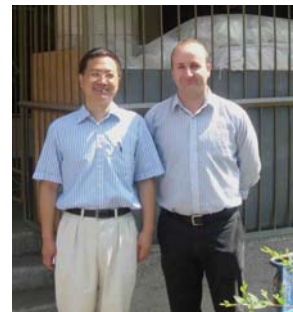


Tian Xu (Fudan University) Rob Saint, Ed Bertram & Steve Winslade

technology to complement the APF's ENU mutagenesis approach.

A visit to the National Resource Centre for Mutant Mice and Model Animal Research Centre (MARC) at Nanjing University was also featured in the trip's agenda. The discussions here covered the facility's direction as a provider of mouse resources to Chinese researchers as well as discussions on a number of other animal models used at the facility, including *Drosophila* and *Xenopus*.

Australian government provided assistance to this facility to establish a SPF poultry breeding facility to produce influenza vaccines.



ZhiGao Bu (Harbin Veterinary Research Institute) and Ed Bertram

Following on from the series of successful research institutions in China, Ed joined 5 other young investigators from Australia, who's research areas together cover a broad cross section of Australian science.

Each gave a formal presentation to distinguished guests from Australia and China, including from Australia Dr Mike Sargent AM FTSE, Chairman of Australian Academy of Technological Sciences and Engineering International Relations Committee; Dr Jim Peacock, Australian Chief Scientist and Dr Geoff Garrett, CEO of CSIRO.

These series of visits were successful to the APF in establishing a new program of research with Professor Hong Tang from the Institute of Biophysics and Prof Hualen Chen at the Harbin Veterinary Research Institute. New linkages with Prof Tian Xu at Fudan University have also been established.



Members of the Young Scientist Exchange Scheme

The first day in Beijing was spent meeting representatives from China's Ministry of Science & Technology, Chinese Academy of Sciences and the Natural Science Foundation of China to discuss the current funding programs for researchers.

The following week featured visits to a number of research facilities in Beijing, Nanjing, Shanghai and Harbin. These included a visit to Professor Hong Tang, Director of the Centre of Infection and Immunity at the Institute of Biophysics in Beijing to discuss the possibilities of a joint research programme.

The team also visited Fudan University to meet Professor Tian Xu, Director of the Institute of Molecular Medicine and Development. The topic of discussion during this meeting focused on using Professor Xu's PiggyBac transposon m u t a g e n e s i s



Jion Chen, Zhongzhou Yang, Qingshun Zhao, Rob Saint, Ruth Arkell, Steve Winslade and Ed Bertram

Finally, Steve and Ed travelled to the northern city of Harbin to visit the Harbin Veterinary Research Institute, where they met with Professor Zhigao Bu to discuss influenza related research. In 1990, the



Dinner with members of the Institute of Biophysics. L-R: Hongyu Deng, Ed Bertram, Steve Winslade, Hong Tang, Ruth Arkell and Zhijie Liu

The APF would like to thank the Australian Academy of Technological Sciences and Engineering and China's Ministry of Science and Technology for their support and organisation of the visit especially Elizabeth Meier and Min Gu.

China-Australia Symposium on Sustaining Global Ecosystems

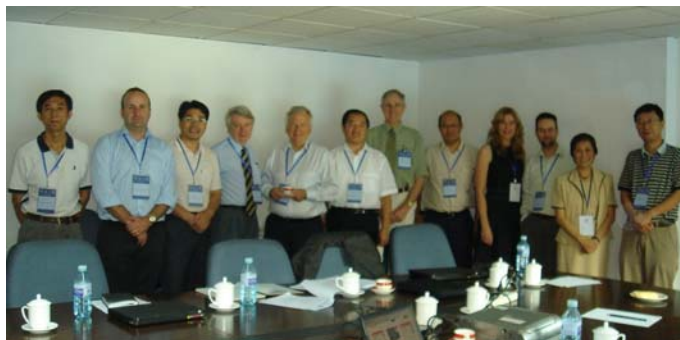


Following on from the series of visits in China (described in previous article), Ed went on to speak about the APF at the Health and Environment Workshop, part of the China - Australia Symposium on Sustaining Global Ecosystems that was held in Beijing from 8-10 August.

The Health and Environment workshop was hosted by Professor Philip Kuchel, Head of

Biochemistry from the University of Sydney and included talks from Professor Perry Bartlett, Director of the Queensland Brain Institute, Dr

Glen King, Institute of Molecular Biosciences and Dr Rachel Huxley, Director of Nutrition and Lifestyle Division, The George Institute for International Health.



Researchers Presenting in the Health and Environment Workshop

This Symposium was organised by the Australian Academy of Science and Chinese Academy of Science and covered 5 themes including sustainable water, land, air, energy and health.



APF Gene Variant Strains



The following ENU Gene Variant Strains are available to interested researchers for further characterization.

All these strains and more can be found on the NHMRC Phenome Bank at <http://pb.apf.edu.au>.

Please refer to the contact information at the end of this newsletter if you would like to know more about any of these strains.

| Strain Name | Phenome Bank ID | Phenotype | Status |
|--|-----------------|--|--|
| Hipster  | 1235 | Coat abnormality. Mice develop a white stripe transverse across abdomen or a large white spot in the same location | Gene ID recently discovered! Gene ID: Adamts20 |
| Pinky (Video available upon request) | 1236 | Limb deformity. Shortening and angular deformity of hindlimbs with extra digits present in some cases. | Gene ID recently discovered! Gene ID: plzf |
| Armidilo  | 28 | Sparse hair covering, wrinkly, smaller than littermates. We will discontinue housing live stock of this strain at the end of October 2007 if no expressions of interest for this strain are received. | Gene ID: Dsg4 |

(more variant strains on next page)

| Strain Name | Phenome Bank ID | Phenotype | Status |
|--|-----------------|--|--|
| T-Bird (video available upon request)  | 1228 | Mice develop a dull, sparse and greasy coat at ~60 days of age. Video available upon request | Mutation has been mapped to Chromosome 18 |
| Jaffa  <p><i>Four affected Jaffa mice alongside an unaffected sibling</i></p> | 1639 | Coat colour defect. Affected mice are born with a brown-coloured coat. Mice appear otherwise healthy | Strain expansion |
| Eddie (video available upon request) | 1237 | Generalised Shaking, mild hypermetric, jerky movements at weaning, non progressive. | Mutation has been mapped to Chromosome 18. |
| Pengu  | 1231 | Limb deformity. Four shortened limbs with angular deformity, most pronounced in hindlimbs. Some have kinked tail. | First generation mapping cross |
| Delficio  <p><i>Affected Delficio (right) next to unaffected sibling</i></p> | 2164 | Progressive hindlimb weakness and ataxia with stiff gait. Develops sensory deficits and shows periods of increased muscular tone/tetany. | Mutation has been mapped to Chromosome 6 |
| Dorian  | 1227 | Coat Colour Change. Affected mice undergo dramatic greying/whitening of their coat from about 4 weeks of age. | Chromosomal mapping |

The APF Spreads the Word at ComBio 2007

The APF featured as one of the exhibitors at the ComBio conference this year, held by the waters of Darling Harbour, Sydney.

The 800 registrants of ComBio 2007 represented students and researchers from a wide range of research backgrounds.

This provided the APF booth representatives with the opportunity to discuss the broad applications of the ENU mutagenesis program as a

vehicle for developing animal models of disease with the conference attendees.

The response received at this conference was very encouraging, and the APF team hopes to continue to spread the word of this valuable resource that is now available to Australian and international researchers.



The APF's exhibition booth at ComBio 2007

Free Sperm Cryopreservation Service at the APF & Monash

To complement the NHMRC Australian Phenome Bank - a database of genetically modified mouse strains held in Australia- the Australian Phenomics Network offers **free of charge** cryopreservation of sperm from all mouse strains distributable to other researchers.

The depositing researcher maintains ownership of the strains and can request signing of MTAs prior to distribution.

Cryopreservation is conducted at the Monash Institute of Medical Research, Monash University and at The Australian Phenomics Facility, at the ANU. Mice are shipped to the closest facility.

The cryopreservation of strains allows researchers to preserve strains that are no longer required, freeing up money used to pay for cage costs. In addition, cryopreservation of all strains acts as an insurance policy

against disaster including disease outbreak, building damage, as happened recently during a storm, breeding failure or mismanagement.

For more information on the NHMRC Phenome Bank database or the mouse sperm cryopreservation service, please contact our Phenome Bank Curator Dr Stuart Read:

E: Stuart.Read@anu.edu.au

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The APF is a Major National Research Facility that is openly accessible to all Australian and International Researchers, both academic and commercial.

The APF is dedicated to providing the national and international academic and commercial scientific community access to genome scale collections of mice with informative point mutations.

Our mission is to:

- ◆ provide access to state-of-the-art facilities, technologies, resources and expertise for analysing connections between mammalian genes and physiological processes,
- ◆ foster interdisciplinary linkages between the mammalian genome and phenome, and promote invention and uptake of new genome-phenome analysis tools by Australian and International research and industry in health, agriculture, the environment and biotechnology.

For further information or enquiries, please email:

anusha.subramaniam@anu.edu.au

If you do not wish to receive the Phenomena newsletter, please send an email to anusha.subramaniam@anu.edu.au with 'Unsubscribe' in the subject line.

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