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Prestigious Ramaciotti Research Award Granted to Chris Goodnow and Anselm Enders

This year the prestigious Ramaciotti Research Award was granted to Chris Goodnow and Anselm Enders from the John Curtin School of Medical Research at the Australian National University. The award is valued at \$1 million and represents one of Australia's largest private research grants. Since 1970 the Ramaciotti Foundation, established by Clive and Vera Ramaciotti has distributed more than \$40 million dollars to over 3,000 biomedical research initiatives throughout Australia.



Chris Goodnow and Anselm Enders, accepting the Ramaciotti Research Award on behalf of the John Curtin School of Medical Research, ANU

laboratory is to research genetic issues surrounding vaccine development for various infectious and autoimmune diseases.

More specifically, the work will endeavour to work out the 'nuts and bolts' of how to build the correct immune response, guiding our understanding of why traditional vaccine design does not work with all diseases. It is hoped that ultimately the research outcomes from this venture will provide the research community with the groundwork upon which new approaches for vaccine design can be applied.

Congratulations Chris and Anselm!

The funding awarded to the John Curtin School of Medical Research this year will be

dedicated towards the establishment of the Ramaciotti Immunisation Genomics Laboratory. The aim of this new

Nature Publication: Roquin Indirectly Represses Autoimmunity

Yu et al (2007) Nature 450: 299-304

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nature

LETTERS

Roquin represses autoimmunity by limiting inducible T-cell co-stimulator messenger RNA

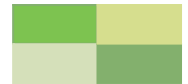
Di Yu¹, Andy Hee-Meng Tan², Xin Hu¹, Vicki Athanasopoulos^{1,3}, Nicholas Simpson¹, Diego G. Silva¹, Andreas Hutloff⁴, Keith M. Giles⁵, Peter J. Leedman^{5,6}, Kong Peng Lam², Christopher C. Goodnow^{1,7*} & Carola G. Vinuesa^{1*}

Immune responses are normally targeted against microbial pathogens and not self-antigens by mechanisms that are only partly understood. Here we define a newly discovered pathway that prevents autoimmunity by limiting the levels on T lymphocytes of a co-stimulatory receptor, the inducible T-cell co-stimulator (ICOS). In *sanroque* mice homozygous for an M199R mutation in the ROQ domain of Roquin (also known as R3h1¹), increased Icos expression on T cells causes the accumulation of lymphocytes that is associated with a lupus-like autoimmune syndrome. Roquin normally limits Icos expression by promoting the degradation of Icos messenger RNA. A conserved segment in the unusually long ICOS 3' untranslated mRNA is essential for regulation by Roquin. This segment comprises a 47-base-pair minimal region complementary to T-cell-expressed microRNAs including miR-101, the repressive activity of which is disrupted by base-pair inversions predicted to abrogate miR-101 binding. These findings illuminate a critical post-transcriptional pathway within T cells that regulates lymphocyte accumulation and autoimmunity, and highlights the therapeutic potential of partially antagonising the ICOS pathway.

lymphadenopathy, splenomegaly, total T- and B-cell numbers, T_{HH} cell expansion and germinal-centre B-cell numbers in *sanroque* mice (Fig. 1b-e and Supplementary Fig. 3a, b). This effect is unlikely to reflect a nonspecific reduction in co-stimulation because halving the gene dose of *Cd28* in *sanroque* mice using a similar strategy did not reduce spleen nor lymph node size (Supplementary Fig. 4a, b). Furthermore, the severity of the lymphadenopathy correlated closely with the levels of Icos expressed on naive T cells across the different groups of genetically manipulated mice (Supplementary Fig. 4c). These results indicate that Icos overexpression caused by Roquin (M199R) is an essential contributor to the lupus phenotype, and demonstrate that tight regulation of Icos expression by Roquin is crucial to prevent T- and B-cell accumulation.

Because ectopic expression of Roquin in CD4⁺ T cells reduces endogenous Icos protein expression¹, we tested whether it regulated endogenous Icos mRNA abundance by overexpressing Roquin in stimulated EL4 T cells. In cells expressing wild-type Roquin, the quantity of Icos mRNA was halved compared to cells transfected with empty vector, whereas Roquin(M199R) was a less potent repressor of Icos mRNA (Fig. 2a). Manual annotation of ICOS mRNA by a BLAST

A Snapshot of Mouse Mutagenesis and Phenotyping Activities Worldwide



Dr Michael Dobbie, Scientific Programs Manager at the Australian Phenomics Facility, recently attended this annual gathering of mammalian geneticists (www.imgc2007.com). The Kyoto meeting was organised by the International Mammalian Genome Society, and the local organiser was Dr Yoshihide Hayashizaki, RIKEN Yokohama Institute. The IMGC provided an update on worldwide efforts to understand human physiology and pathophysiology through genotype-phenotype linkage, predominantly using the mouse as a model organism. From a phenomics perspective, a conference highlight was the Mutagenesis Session, which included news from the following mouse mutagenesis and phenotyping programs.

As reported in the previous Phenomena newsletter in the "ES to Mouse Service" article, KOMP (www.knockoutmouse.org), EUComm (www.eucomm.org), and NorCOMM (norcomm.phenogenomics.ca) are consortia dedicated to collectively producing a null allele, a conditional allele and a point mutation in each of the ~25,000 mouse genes within the next 5 years. Of the 18,000 genes on the KOMP Master Gene List, nearly 10,000 genes have been prioritised for targeting (contact KOMP or EUComm to nominate your favourite genes). 167 ES cell lines are currently available for distribution from the KOMP repository. EUComm has produced 198 mutant strains, with the production rate set to rapidly increase.

The enormous progress made by these targeted mutagenesis projects has set the new challenge - to provide detailed phenotype data to determine which mutants will usefully model specific diseases. Several consortia are providing this functional annotation through systematic phenotyping of the new mouse lines. The MRC Mammalian Genetics Unit, UK (www.mgu.har.mrc.ac.uk/mutagenesis/) is coordinating the phenotypic characterisation of 650 EUComm lines, through the

EUMODIC (www.eumodic.org) mouse clinics (using EMPReSS slim primary phenotyping screen; empress.har.mrc.ac.uk) and specialist centres (see the EuroPhenome www.europhenome.eu). Prof. Steve Brown, Director of the MRC Mammalian Genetics Unit, visited the Australian Phenomics Facility in August to discuss these new tools and programs. Currently there are over 150 phenotyping SOPs



Attendees of the 21st International Mammalian Genome Conference

available through EMPReSS (empress.har.mrc.ac.uk). Novel phenotypes have been found in over 90% of the mutant lines examined to date. Additionally, the complex relationship between environment and genes will be studied by a new phenotyping platform at the German Mouse Clinic, GMC II (www.gsf.de/ieg/gmc).

The Sanger Institute Mouse Genetics Programme (www.sanger.ac.uk/Teams/Team109/) aims to phenotype 250 mutant mouse lines each year. Researchers will be able to request a mutant based on a particular gene, expression pattern or phenotype. The program is currently calling for suggestions for genes to prioritise and phenotyping tests to include. To date, 50 researchers have requested a total of 633 genes. In addition, the "Young Investigator Guest Screening Programme" provides an opportunity to develop screening protocols related to your research interest. Any disease models that you discover with your screening protocols will be available to you for further characterization.

Infrafrontier (www.infrafrontier.eu) provides high-

throughput phenotyping (phenomefrontier) and archiving (archivefrontier) of European mouse strains, aiming to archive over 4,000 lines by 2012 from 15 European laboratories. EMMA (European Mutant Mouse Archive; www.emmanet.org) provides links to these and other mouse resources.

The Texas Institute of Genomic Medicine (TIGM, www.tigm.org) is developing a new archive of 350,000 gene-trapped mouse ES cell lines on a C57BL/6 background, covering 10,000 genes. TIGM also has limited access to a privately held 129/SvEvBrd gene trap library, covering over 9,000 genes, which should be available for distribution to the academic research community on a subsidised basis.

Finally, two new genetic search tools have been developed and distributed by RIKEN Genomic Sciences Centre, Japan (omicspace.riken.jp/db/genome.html). The **OmicBrowse** genome browser is a free, open source tool for sequence alignments. It can be installed onto personal computers and integrates hundreds of genome databases, and can integrate public data with private data. **PosMed** is a database that performs a full-text search of document databases (e.g. MEDLINE) and produces a ranked list of genes within a specified genomic region according to phenotypic keywords, thereby achieving "in silico positional cloning" to identify candidate genes. This is a powerful tool to connect phenotypes and genes since it considers not only gene-gene interactions but also drug-protein and orthology data.

Any queries or questions about any information provided in this article, contact Michael Dobbie at the APF on:

Michael.dobbie@anu.edu.au

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>. Many of these strains will be frozen down and live stock discontinued in the near future, so if you would like the opportunity to further characterise live mice, please contact Anusha Subramaniam, Anusha.subramaniam@anu.edu.au.

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: Adams20 Strain to be frozen down soon
Pinky (Video available upon request)	1236	Limb deformity. Shortening and angular deformity of hindlimbs with extra digits present in some cases.	Gene ID: Plzf Strain to be frozen down soon
Kenny	N/A	Diarrhoea before or at weaning; lymphomegaly. Pathology: Multiple plaques in GI tract.	Gene ID: Muc2
Jaffa	1639	Coat colour defect. Affected mice are born with a brown-coloured coat. Mice appear otherwise healthy	Strain expansion
 <p><i>Four affected Jaffa mice alongside an unaffected sibling</i></p>			
Pengu	1231	Limb deformity. Four shortened limbs with angular deformity, most pronounced in hindlimbs. Some have kinked tail.	Gene ID Recently Discovered! Gene ID: Gdf5
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 Strain will be frozen down in January
Metallic	N/A	Silver/grey coloured coat. Appears otherwise healthy	Strain expansion
			
Trembles (video available upon request)	85	Mild to moderate ataxia evident at weaning and non-progressive, some with shaggy fur	Mutation mapped to Chromosome 4
Tipsy	83	Weak and ataxic hindlimbs evident close to 6 months of age; has splayed hindlimbs.	Mutation mapped to Chromosome 8

A Saturation Screen for Modifiers of Epigenetic Reprogramming, or “MOMMEs”



Professor Emma Whitelaw and a team of researchers at the Queensland Institute of Medical Research are carrying out a sensitised screen to identify genes that affect expression of a variegating GFP transgene. This transgene is exquisitely sensitive to changes in the cell's capacity to carry out epigenetic gene silencing. It is a dominant screen and extends a pilot screen initiated in 2002.

The pilot screen identified twelve mutants after screening approximately 1,000 F1 offspring. Of these twelve, the point mutation has been identified in four cases: two are in novel genes and two are in genes already known to be involved in

epigenetic regulation, a DNA methyltransferase and a chromatin remodeller (Blewitt et al, *PNAS*, 2005; Chong et al, *Nature Genetics*, 2007 and unpublished data).



The resultant mutant mice show interesting and varied phenotypes and are helping to elucidate the role of epigenetic processes in various aspects of mammalian development. NCRIS funding will enable the production of 2,500 F1 offspring from

mutagenised males per year for the next four years.

The transgene is driven by a globin promoter and as such is active in cells of the erythroid lineage. This should provide an opportunity for scientists with a particular interest in erythropoiesis to piggy-back for genes involved in this pathway. Similarly, since epigenetic processes play a critical role in differentiation and development, the screen may provide opportunities for developmental biologists.

Any questions or queries about this screen, contact Emma Whitelaw:

emma.whitelaw@qimr.edu.au

Getting to Know the Team: The Scientific Programs Division at the APF



This is the first in a series of articles providing a brief description of the various divisions that together contribute to the running of the Australian Phenomics Network. The featured department this edition is the Scientific Programs division at the Australian Phenomics Facility (APF), Canberra.

The Scientific Programs division at the APF is responsible for the overall management and coordination of research projects run through the facility. The team acts as the primary contact between the external researcher and the facility, communicating requests and progress of the project between the internal departments of the APF and



Scientific Programs Team L-R: Jessica Armstrong, Anusha Subramaniam, Michael Dobbie, Lisa Miosge, Ed Bertram, Teresa Morgan and Geoff Sjollem

the external researcher. The team also works closely with the animal husbandry staff to ensure effective communication on issues relating to

colony management and pedigree screening.

With their experience in phenotypic screens and pedigree design as well as project management, the team will manage your project from the very early stages of screen design right through to mutation identification. This way, researchers can be assured of an efficient, hassle-free service.

Any questions or queries about this service, please contact Anusha Subramaniam on:

Anusha.subramaniam@anu.edu.au

AUSTRALIAN PHENOMICS NETWORK NEWSLETTER

Any questions or queries about articles or information in this newsletter, or the APN in general, please contact us on:

Phone: +61 2 6125 0596

Fax: +61 2 6125 1381

E-mail:

contact@australianphenomics.org.au

Our website is currently under construction. Watch this space!

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

The APN provides access to the following research infrastructure:

- International sources of new mouse models and phenotype data derived from gene-trap Embryonic Stem (ES) cells or similar and phenotyping infrastructure;
- Australian collections of new mouse models and phenotype data from ethyl nitrosourea (ENU) mutant mouse collections or similar and phenotyping infrastructure; and
- Infrastructure for archiving and exchange mouse models as frozen sperm or embryos and an integrated e-science infrastructure for capturing, annotating and disseminating data on mouse models and phenotypes.

If you do not wish to receive the Phenomena newsletter, please send an email to contact@australianphenomics.org.au with 'Unsubscribe' in the subject line.