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AUSTRALIAN PHENOMICS FACILITY

Phenomena

Recent Discovery from an APF ENU-Gene Variant Pedigree: 'Tiny'

Nijnik et al (2007) Nature 447: 686-690

nature

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ARTICLES

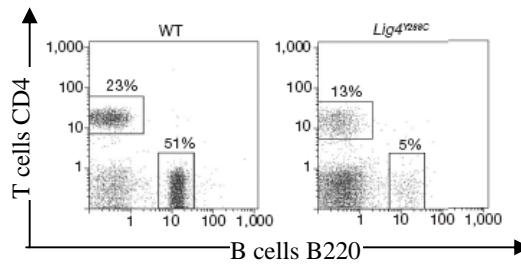
DNA repair is limiting for haematopoietic stem cells during ageing

Anastasia Nijnik¹, Lisa Woodbine², Caterina Marchetti^{2,3}, Sara Dawson⁴, Teresa Lambe¹, Cong Liu², Neil P. Rodrigues⁵, Tanya L. Crockford¹, Erik Cabuy⁶, Alessandro Vindigni³, Tariq Enver⁵, John I. Bell¹, Predrag Slijepcevic⁶, Christopher C. Goodnow^{1*}, Penelope A. Jeggo^{2*} & Richard J. Cornall^{1*}

Accumulation of DNA damage leading to adult stem cell exhaustion has been proposed to be a principal mechanism of ageing. Here we address this question by taking advantage of the highly specific role of DNA ligase IV in the repair of DNA double-strand breaks by non-homologous end-joining, and by the discovery of a unique mouse strain with a hypomorphic *Lig4*^{Y288C} mutation. The *Lig4*^{Y288C} mouse, identified by means of a mutagenesis screening programme, is a mouse model for human LIG4 syndrome, showing immunodeficiency and growth retardation. Diminished DNA double-strand break repair in the *Lig4*^{Y288C} strain causes a progressive loss of haematopoietic stem cells and bone marrow cellularity during ageing, and severely impairs stem cell function in tissue culture and transplantation. The sensitivity of haematopoietic stem cells to non-homologous end-joining deficiency is therefore a key determinant of their ability to maintain themselves against physiological stress over time and to withstand culture and transplantation.

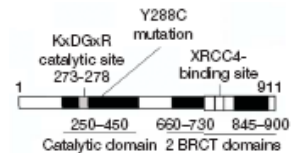
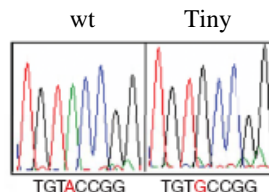
Phenotype:

Reduced lymphocytes in peripheral blood and growth retardation



Genotype:

An A-to-G substitution results in a Tyrosine-to-Cysteine conversion in the DNA Ligase IV protein primary structure



The APF Networks with the Stem Cell Research Community at the 5th ISSCR Conference in Cairns

The APF was represented at the recent 5th International Society for Stem Cell Research (ISSCR) Conference, held in tropical Cairns between 17 - 20 June with a dedicated exhibit hall booth.

The Scientific Programs team disseminated information on the broad range of research opportunities provided by the APF as well as successful outcomes of current researchers including the findings in the recent *Nature* publication on "Tiny" mouse strain (see article above)

You can find us (and try for your chance at winning an Ipod Nano) at booth #15 at the 7th IBRO World Congress of Neuroscience in Melbourne

between 12 - 17 July as well as at booth #53 at ComBio 2007, which will be held in Sydney between 22 - 26 September.



APF Representatives discussing the facility's services to an interested conference participant

The APF Working with the Network in Genes & Environment in Development (NGED)

The aim of NGED is to develop a National Research Capability Plan in "Development", harnessing the resources of leading researchers in epigenetics, developmental biology and developmental physiology (www.nged.adelaide.edu.au).

NGED will generate new insights into the mechanisms by which events in early life determine the risk of adverse outcomes in perinatal and adult life. Through this NGED membership, Dr Michael Dobbie, Scientific Programs Manager for Developmental Projects at the APF, presented at the NGED Forum held at Palm Cove, Queensland, 13 - 15 June,

which was also attended by Dr Ed Bertram (APF Head of Scientific Programs).

Along with Professor Rob Saint (Drosophila) and Dr Peter Currie (Zebrafish), Michael spoke in the Animal Models session. He discussed

the role of the APF in the production of new mouse models of human disease and development through chemical (ENU) mutagenesis, which enables the linking of a phenotype to a point mutation. Information about access to the ENU-mutagenesis discovery projects and the NCRIS-funded infrastructure support was presented.

Contact made during the forum have already lead to discussions aimed towards initiating projects to develop new mouse models. For further details please contact Michael
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Participants of the 2007 NGED Forum at Palm Cove, QLD

APF Gene Variant Strains

The following tables describe the characteristics of some of the gene variant strains held at the APF which are available for further analysis by interested researchers. Each strain carries a point mutation created through ENU mutagenesis with proven heritability. All and more can be on the Phenome Bank: <http://pb.apf.edu.au>.

Please contact us if you require further information on any of these strains.

Table 1: The following four strains have undergone mapping to determine the exact location of the causative mutation. These strains are being held as live mice at the APF and sperm from at least 10 mice of each strain have been cryopreserved. If we receive no expressions of interest for these strains by **31 July 07**, we will no longer house live mice.





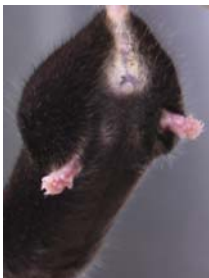
Strain Name	Phenome Bank ID	Phenotype	Affected Gene	Area of Research
Armidilo 	28	Sparse hair covering, wrinkly, smaller than littermates	Dsg4	This strain is useful for studying skin disorders
Leukyswalker	51	Partial block in thymocyte differentiation. Phenotype is less severe than in knockouts.	Eed	This strain is useful for studying cancer and developmental biology
Polly 	63	Polycystic kidney disease	NPHP3	This strain is useful for studying nephrology
Vibes	88	Tetanic ataxia at weaning, shaking	Kcnv1	This strain is useful for studying neuromuscular disease

Table 2: The affected gene for these more recently discovered strains has not yet been determined; strains are at different stages of the mapping process, as indicated.

Strain Name	Phenome Bank ID	Phenotype	Status
Dorian 	1227	Coat Colour Change. Affected mice undergo dramatic greying/whitening of their coat from about 4 weeks of age.	First generation mapping cross
Pinky (Video available upon request)	1236	Limb deformity. Shortening and angular deformity of hindlimbs with extra digits present in some cases.	Chromosomal Mapping
Hipster 	1235	Coat abnormality. Mice develop a white stripe transverse across abdomen or a large white spot in the same location	Chromosomal Mapping
Eddie	1237	Generalised Shaking, mild hypermetric, jerky movements at weaning, non progressive.	Fine Mapping. 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
T-Bird	1228	Mice develop a dull, sparse and greasy coat at ~60 days of age	First generation mapping cross

ANU To Adapt APF Mouse Handling Training Program

The ANU is adopting a proposal put forward by Irene Whiting from the APF Training Team to create an ANU-wide training program for people working with animals.

The program will be based on the mouse handling training program currently offered for users and staff of the APF. This training program is currently being developed further by a committee which actively involves members of the APF. Stage 1 of the training program is to be

implemented early next year.

The current APF Mouse Handling program aims to ensure a high standard of animal welfare and safety, as well as facilitate good research practices using competency based assessment.

The program promotes correct handling techniques and provides instructions on common procedures such as euthanasia, identification of animals, injections and sample collection. The program is conducted

by a team of specially trained animal technicians.

The APF training program is currently available on the AEEC Research Office Website at www.anu.edu.au/ro/ORI/animal_documents.php.

Please contact us at Training@smtp.apf.edu.au if you would like more information about the APF Mouse Handling Training program.

APF Mapping & Genotyping Update

The APF mapping & genotyping team provide accurate, high-throughput genotyping of mice housed within the facility. Our experienced staff design and optimise new assays for your project with more than 100 genotyping assays currently available. Mouse tissues are collected and processed by highly trained APF technicians offering clients an efficient, trouble-free service.

The Facility offers a number of technologies and resources for mapping. These include Microsatellite

or Amplifluor (SNP) proximal/distal and genome wide (10-20Mb) panels for various mapping crosses.

For a much denser panel of markers the APF offers the Affymetrix 5K Mouse SNP chips (AGRF) with approximately 2500 SNPs available between any 2 inbred strains giving a marker density of >1 per Mb.

To complete the mapping service the APF now offers resequencing of exons within a mapped interval. We have the ability to perform gene and exon annotation including candidate

gene searches through OMIM and JAX files and efficiently design primers for resequencing candidate genes or all exons within a defined interval. The sequencing assays are run at the AGRF, Brisbane and then expertly analysed at the APF to locate the causal mutation.

For more information regarding our services, contact our Genotyping and Mapping manager Belinda Whittle:

E: Belinda.Whittle@anu.edu.au
P: 61 2 6125 7756

The NHMRC Australian Phenome Bank

The NHMRC Phenome Bank is central database of genetically modified mice held in Australia either live or as cryopreserved material.

An internet accessible database, the Phenome Bank allows you to search for murine strains carrying mutations in particular genes, strains with

transgenic alterations or mice with particular phenotypes.

To realize the full potential of this venture, the database needs your input. To have your mouse strain information made available on the Phenome Bank database, simply provide your strain information to the database curator, Dr Stuart Read (stuart.read@anu.edu.au)

To access the database visit:
<http://pb.apf.edu.au>



Mouse Sperm Cryopreservation Service

To complement the Phenome Bank, we offer **free of charge** cryopreservation of sperm from all mouse strains distributable to other researchers. Sperm from 10 animals of each strain are cryopreserved, with duplicate samples stored at the ANU and at Monash University.

For more information on the NHMRC Phenome Bank or our mouse sperm cryopreservation service, please contact our Phenome Bank Curator Dr Stuart Read: E: Stuart.Read@anu.edu.au; P: +61 2 6125 1324

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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:
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