Mouse Phenomics in Australia
September 2011

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John Curtin School of Medical Research
The Australian National University

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Australian Phenomics Network

Outline

- The Australian Phenomics Network
- APN Services
- Phenotyping
- The Missense Mouse Project
- Other APN Activities
- Possible Interactions with IMPC

Nationally Funded Research Infrastructure 2006 - 2009 - 2013

Creation Characterisation Curation

Funding

An Australian Government Initiative

National Collaborative Research Infrastructure Strategy

$35M Australian and State government investment

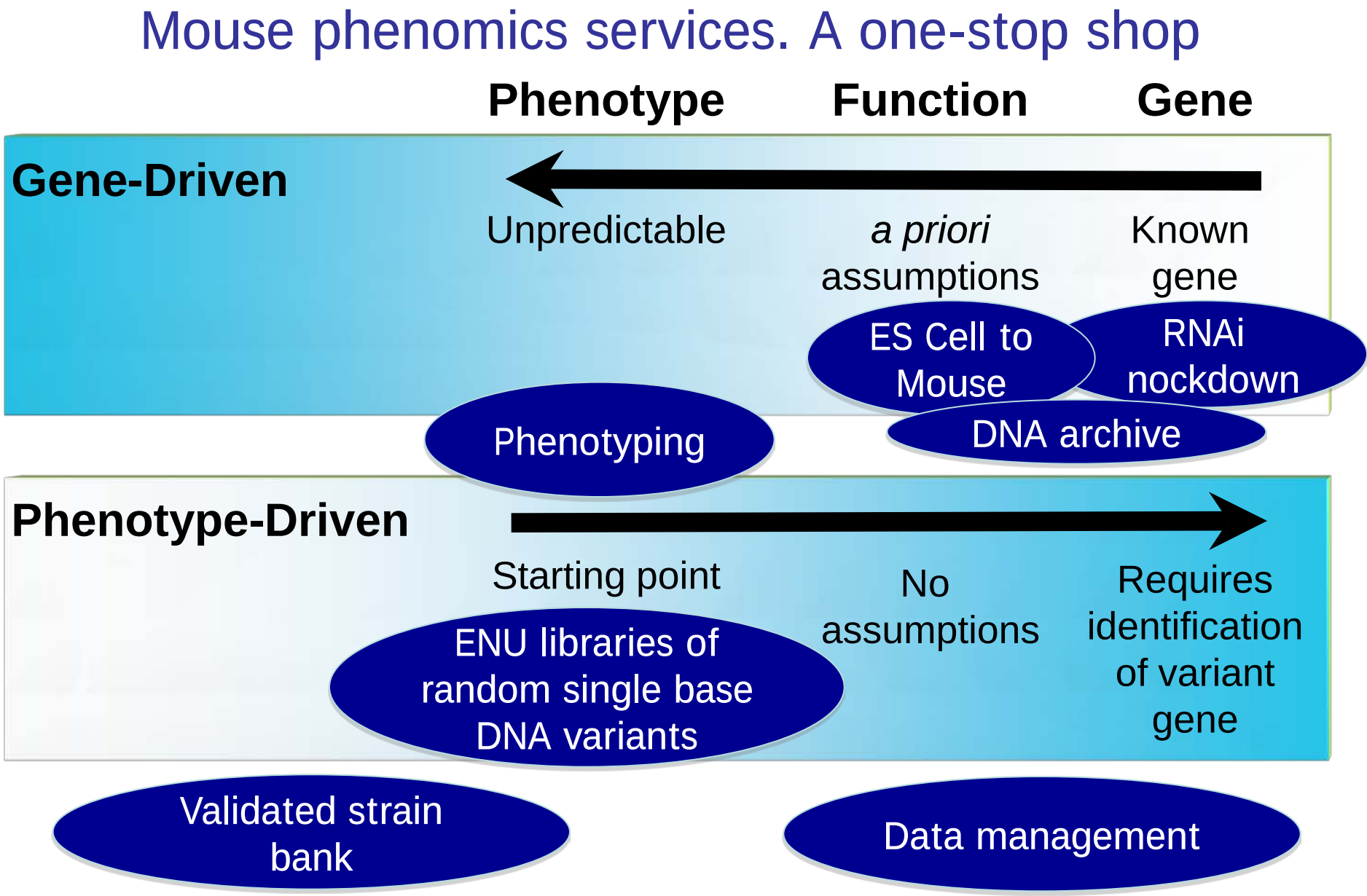
+

$11.5M institution and other cash

+

$27M in-kind

Mouse Phenomics Services: a one-stop shop



CREATION - ENU Variant Collection

FIAT·LUX

The Walter and Eliza Hall Institute of Medical Research

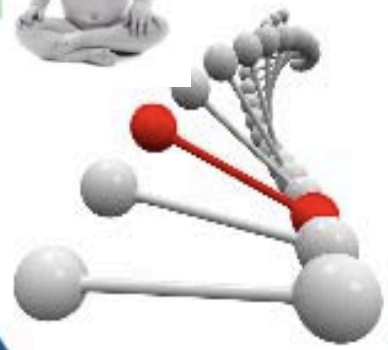
Queensland Institute of Medical Research

Menzies Research Institute

Centenary Institute research for life

Australian National University

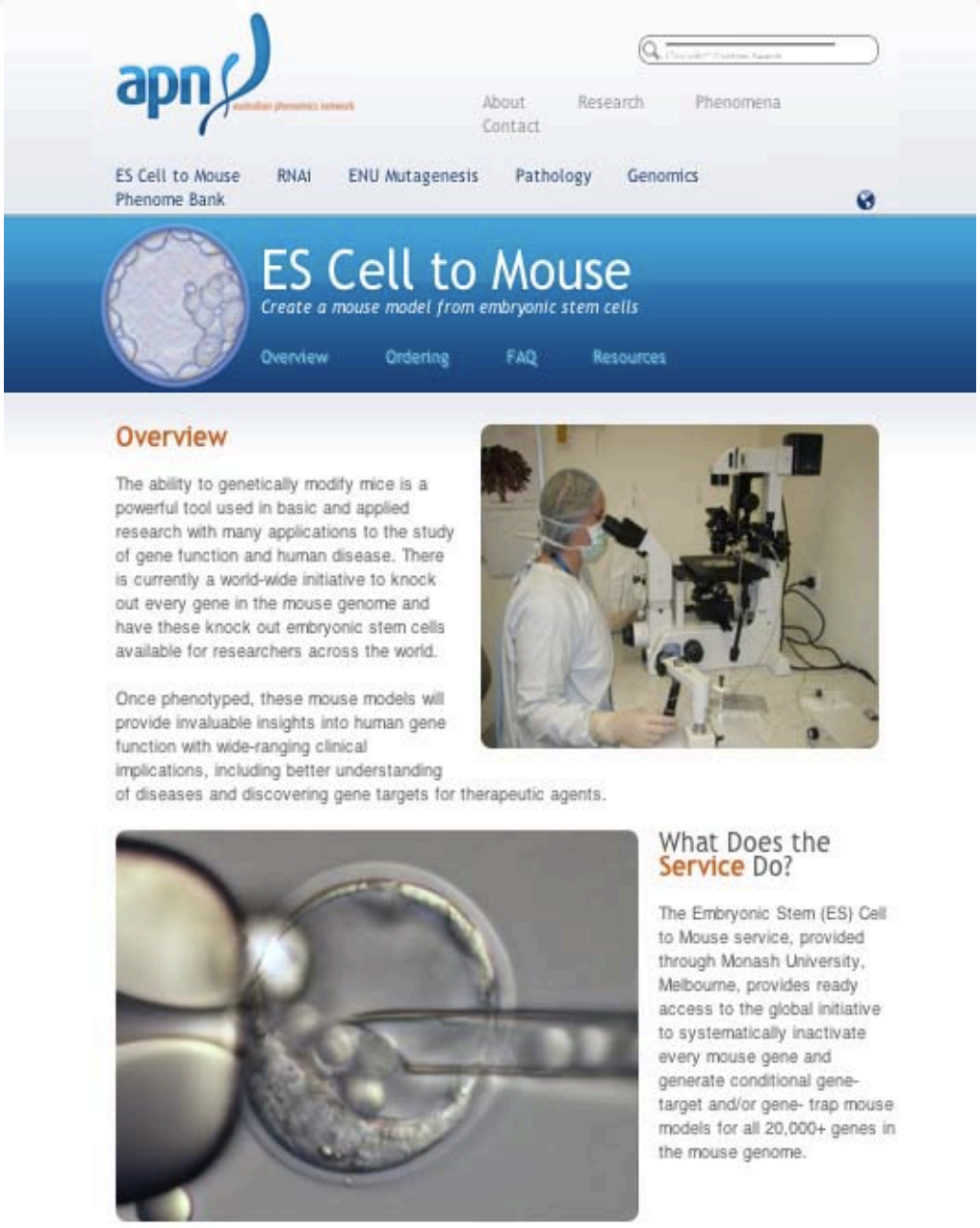
apn australian phenomics network



ENU Variant Collection

Chemically-induced Mouse Models

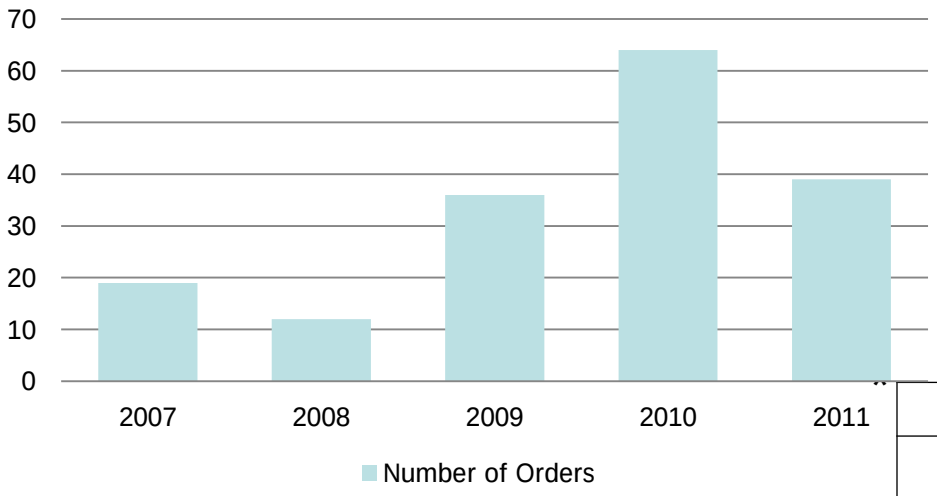
CREATION - ES Cell to Mouse



MONASH University

CREATION - ES Cell to Mouse

APN ES Cell Orders



* 1 July to 27 Sept

Clones (ordered / on order)

Repository	# clones
CMHD/CMMR	6
EUCOMM	104
GGTC	7
KOMP	92
MMRRC	27
TIGM	13
Sanger directly	20
RNAi	18
User Provided	10
Total	**297***

*** for 123 genes**

CREATION - Cell-based Screening and Inducible Models

CREATION - Cell-based Screening and Inducible Models

A. Cell-based Pipeline

Screening of libraries of gene knockdown sequences in tissue culture

1. Genome scale and boutique collections of short hairpin RNAs (shRNA)
   stable, long term, colony formation, long-term drug response

2. Genome scale libraries of small interfering RNAs (siRNA)
   transient knockdown (72 to 96 hour post transfection)

B. Inducible shRNA Transgenic Pipeline

Production of mouse strains in which genes identified in the cell-based pipeline (or by other means) can be rendered inactive in a regulated manner at a specific time or in a specific cell type

CHARACTERISATION - Pathology

THE UNIVERSITY OF MELBOURNE

IMVS

apn australian phenomics network

About Research Phenomena Contact

ES Cell to Mouse Phenome Bank | RNAi | ENU Mutagenesis | Pathology | Genomics

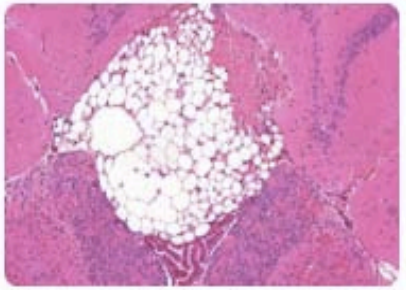
Pathology

Investigate mouse models using clinical and histopathology

Overview Ordering FAQ Resources

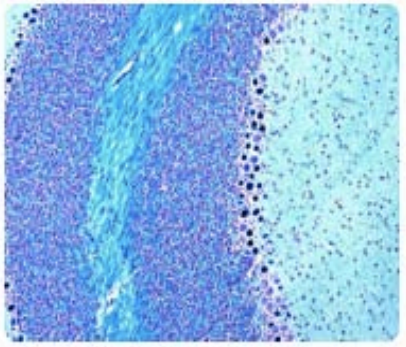
APN Histopathology, Organ Pathology & Clinical Phenotyping

When creating mouse models, many changes to phenotype remain unidentified without further investigations. The APN Histopathology & Organ Pathology, and Clinical Pathology services offer Australian researchers the opportunity to understand their mouse model's phenotype more deeply by providing expert analysis of organs, tissues and blood.



Histopathology & Organ Pathology

The APN Histopathology and Organ Pathology service helps researchers across Australia in whole organ and histological analysis of mouse models and mice at specific developmental stages. The service is based at the Department of Anatomy and Cell Biology at The University of Melbourne and through the Veterinary Service Division at the Institute of Medical and Veterinary Science (IMVS) in Adelaide.



This service offers the latest in high quality capabilities including:

CHARACTERISATION - SNP Analysis and Gene Identification

Exome Sequencing and Bioinformatics Pipeline

1. Increased the sequence depth over the exome
   - Collaboration with Nimblegen and Agilent to develop and test DNA capture kits for the mouse genome
   - DNA sequencing on Illumina platform
2. Developed an efficient analysis pipeline
   - Existing alignment and SNV software tools
   - Unique tools developed by the APN
   - Exploit unique characteristics of ENU in inbred mice

RESULT

- A sequence analysis strategy that reduces the rate of false positive calls by several orders of magnitude such that the majority identified are true breeding, protein-changing DNA variants

- Causative variant ID down from 2-4 yrs -> less than 6 months

CURATION - Australian Phenome Bank

apn australian phenomics network

MONASH University

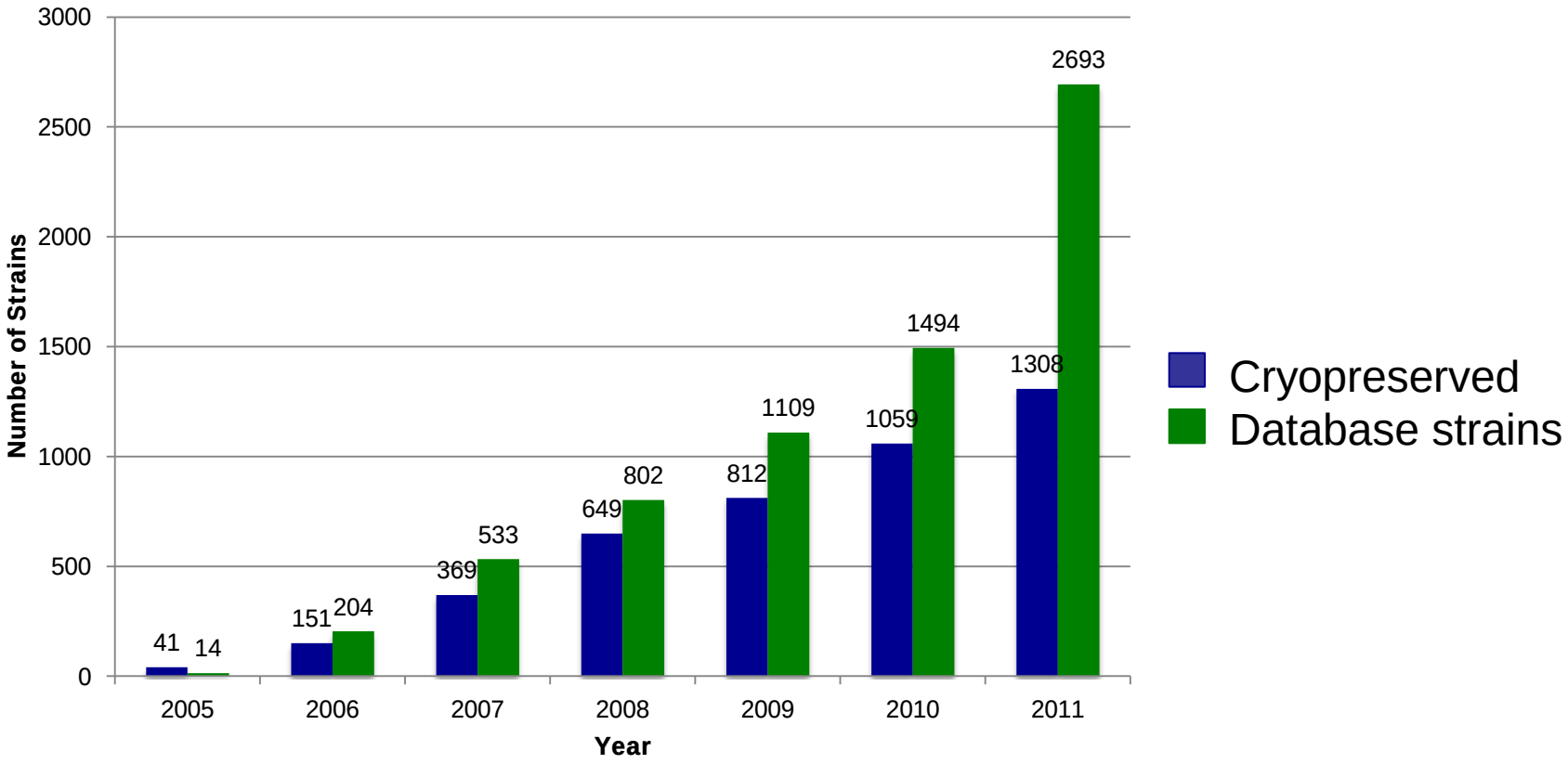
Australian Government
National Health and Medical Research Council

Australian Phenomics Facility

An Australian Government Initiative
National Collaborative Research Infrastructure Strategy

CURATION - Australian Phenome Bank

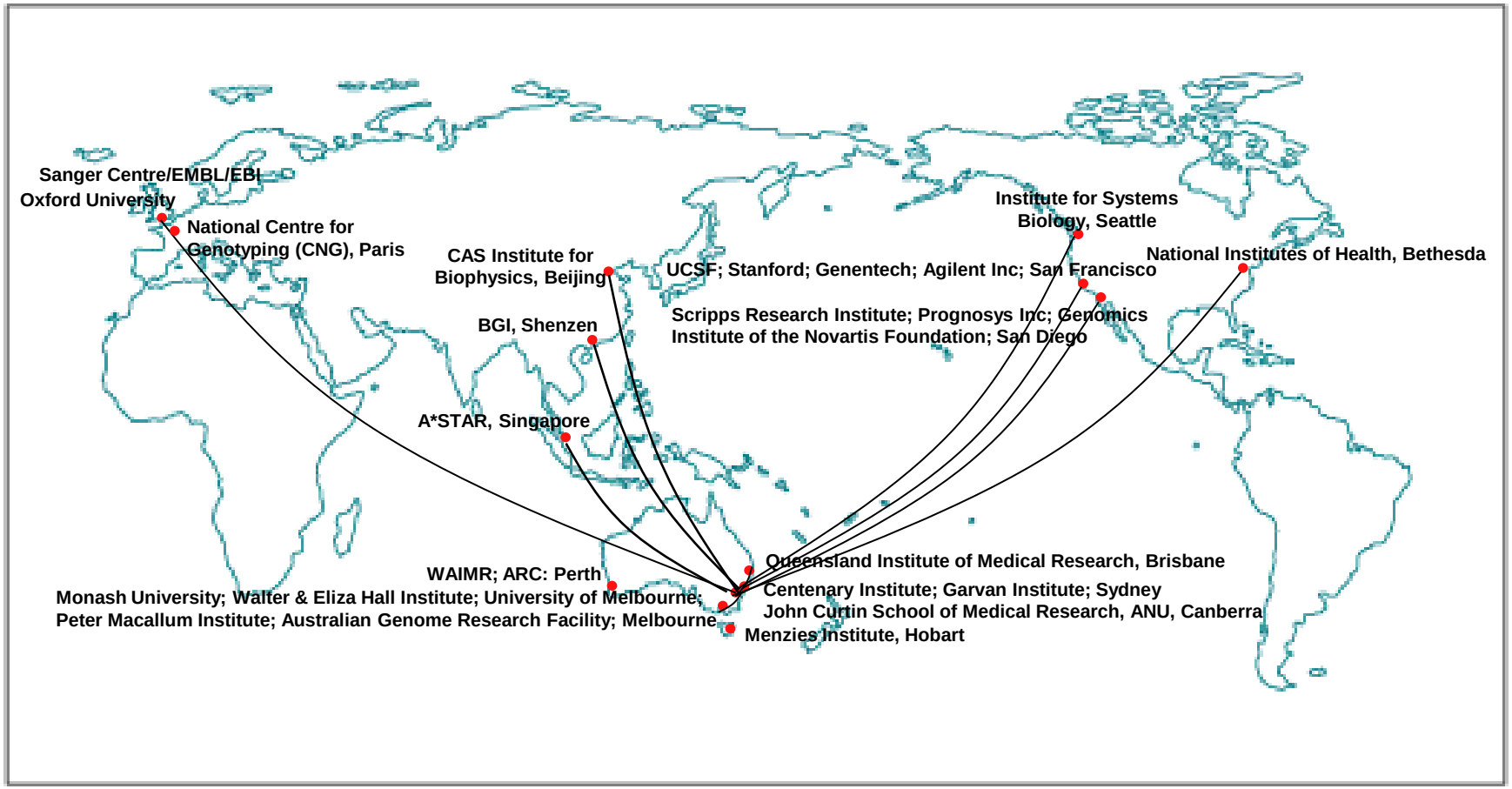
Australian Phenome Bank



Sperm Cryopreservation conducted at ANU and Monash University
Sperm and Embryo cryopreservation conducted at Animal Resources Centre, Perth

Partnerships

The Australian Phenomics Facility & Network: Partnering with world-class teams to discover body processes and new strategies to counter disease



John Curtin School of Medical Research & ANU

- Immunogenomics Laboratory
- Genome Discovery Unit
- ANU Super Computer
- Mouse facilities

Australian National University

www.jcsmr.edu.au

Phenotyping - Spleen Screen

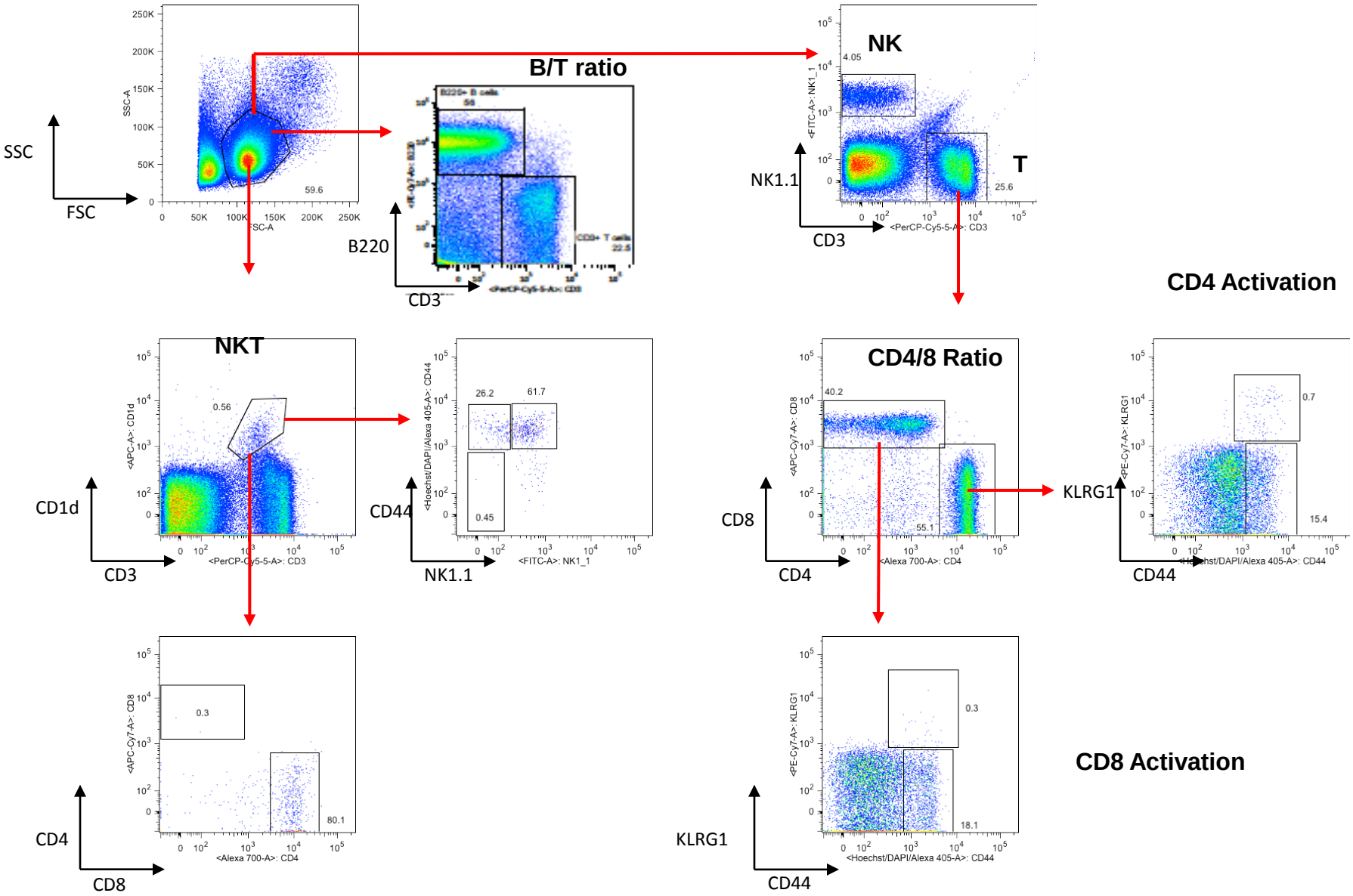
Immunisation screen of G3 mice from ENU pedigrees

Day 0
Influenza A HKx31, ABA-CGG and *B. Pertussis*

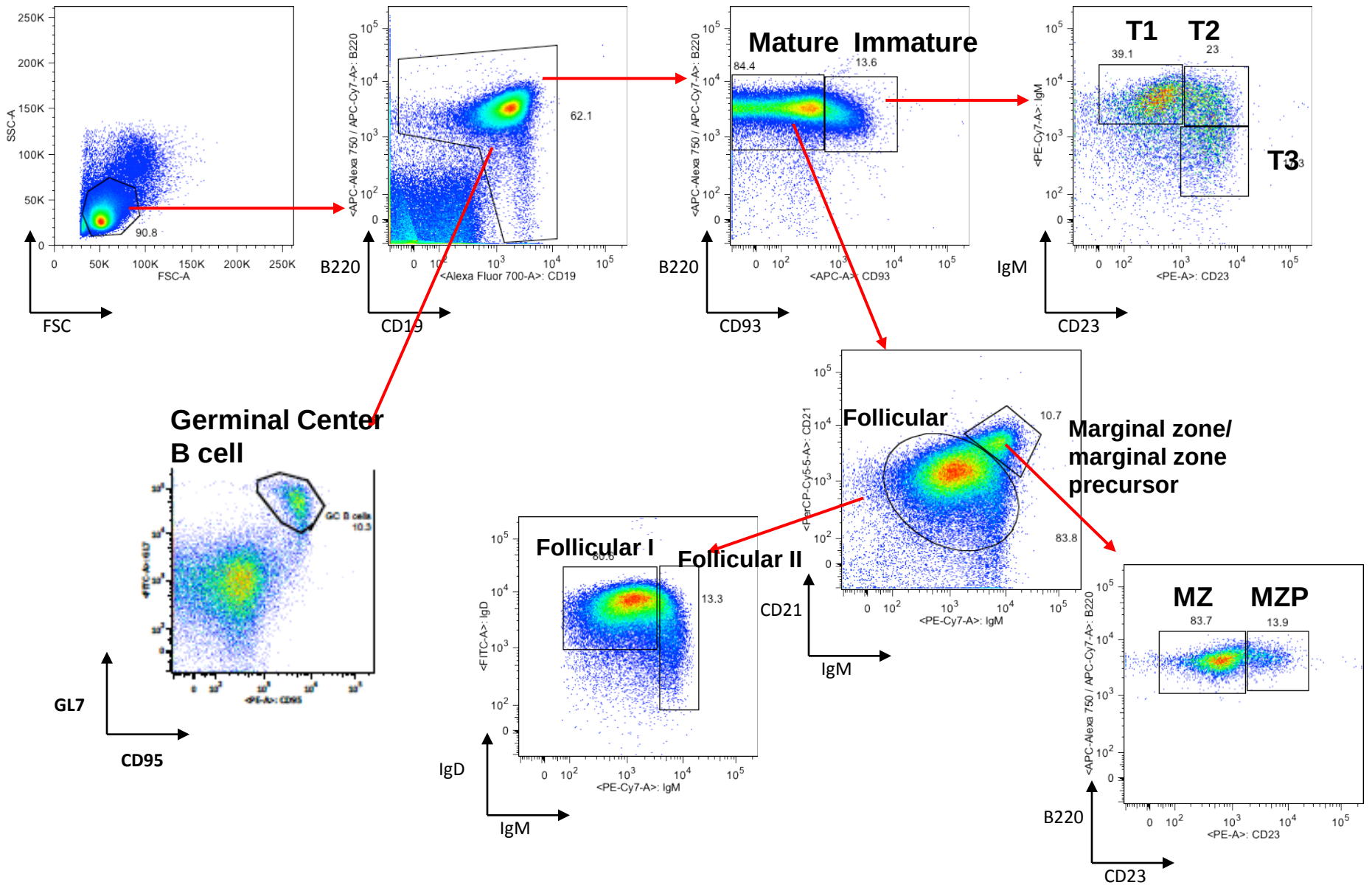
Day 14: Screen
Peripheral blood FACS screen and serum collection

Day 21:Screen
Mice sacrificed for spleen FACS screen

Spleen Screen NK/ T cell Gating Strategy



Spleen Screen B cell Gating Strategy



Adapted from Allman and Patel 2008, Curr Op Immunol 20:149

Other Activities - The Missense Mutation Project

Objectives

Utilise the additional information coming from this sequencing by making available to researchers, a list of all SNVs identified in each pedigree, not just the causative variation

Sequence at G1 stage and make SNV list available early so mice can be ordered whilst still breeding

Sequence of 15-20 ENU variant pedigrees per month

Result

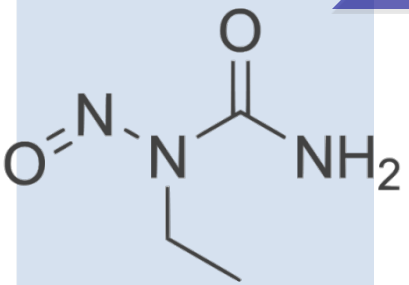
By the end of 2012, the APF will have a holding catalogue of 15,000 missense SNVs actively breeding

Australian National University

The Australian Phenomics Facility and Immunogenomics Laboratory at The John Curtin School of Medical Research

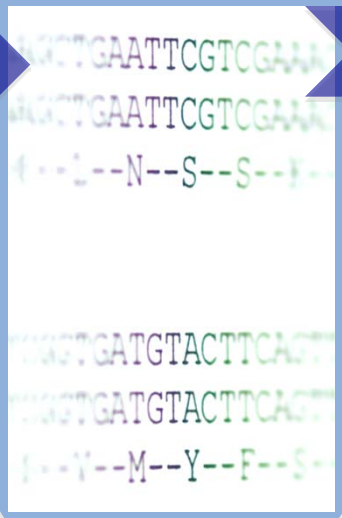
Other Activities - The Missense Mutation Project

Induce germ-line single nucleotide variants with ENU



Exome capture and high-throughput sequencing

Mutation detection and custom variant filtering



Public access to annotated missense variant database

Other Activities – Data Management

Objectives

•Develop systems to collect, store, analyse, annotate and share data generated by the APN/APF activities

•Ensure systems meet requirements set out by Australian government and funding agencies

•Access data from and provide data to other relevant databases

•Ensure APN systems are compatible with others in place or in development

•Work with IMPC and other international projects to minimise duplication and maximise efficiency through sharing and re-use of systems already developed and adopting, where possible, standards and protocols already in place

Future Interactions with IMPC

Continue to support the promotion of IMPC (and IKMC) to Australian Researchers

Secondary/Specialised Phenotyping

- Of mice generated by ES cell to mouse service for researchers (would require further funding and some changes to current MOU and MTAs)

- Of mice generated by the APN based on IMPC gene list (would require further funding)

Collaboration on Data Management

- To allow linkage of APN data sets, eg flow cytometry and histopathology images, with IMPC data sets (at the appropriate time)

The People of the APN

ENU Variant Collections
Chris Goodnow
Doug Hilton
Ben Kile
Simon Foote
Warwick Britton
Emma Whitelaw
Geoff Sjollema
Ed Bertram

RNAi
Ricky Johnstone
Louise Winteringham
Ross Dickins
Rohan Teasedale
Michael Hanzal-Bayer
Kaylene Simpson

ES Cell to Mouse
Moira O'Brien
Leanne Cotton
Debbie Bianco

Phenome Bank
Chris Goodnow
Moira O'Brien
Gabriel Garcia-Marquez
Stuart Read

Management
Chris Goodnow
Steve Winslade
Adrienne McKenzie
Linda Hewitt
Michael Dobbie

Pathology
John Furness
Tina Cardamone
Tim Kuchel
Dorota Garcensz

Genomics
Chris Goodnow
Ben Kile
Belinda Whittle
Dan Andrews

Immune Phenotyping
Chris Goodnow
Ed Bertram
Geoff Sjollema

Data Management
Philip Wu

www.australianphenomics.org