IMPC
International Mouse Phenotyping Consortium

The International Mouse Phenotyping Consortium

An Encyclopedia of Mammalian Gene Function

Global Phenotyping - The Context

- The function of the majority of the genes in the mouse (and human) genomes is unknown
- We are remarkably poor at predicting the functions of genes – pleiotropy will be key to understanding systems
- KOs have been generated and analysed in only some 30% of mouse genes
- Data for these genes is patchy – and is dependent on the experience and interests of the investigator

2004 International KO Mouse Consortium (IKMC)

"...a high-throughput international effort to produce...knockouts for all mouse genes, and place these resources into the public domain."

COMMENTARY

*The Comprehensive Knockout Mouse Project Consortium**

NATURE GENETICS VOLUME 36 | NUMBER 9 | SEPTEMBER 2004

The Knockout Mouse Project

Mouse knockout technology provides a powerful means of elucidating gene function *in vivo*, and a publicly available genome-wide collection of mouse knockouts would be significantly enabling for biomedical discovery. To date, published knockouts exist for only about 10% of mouse genes. Furthermore, many of these are limited in utility because they have not been made or phenotyped in standardized ways, and many are not freely available to researchers. It is time to harness new technologies and efficiencies of production to mount a high-throughput international effort to produce and phenotype knockouts for all mouse genes, and place these resources into the public domain.

8,500 Targeted KOs

Nat Genet. 2004 Sep;36(9):925-7.

The European dimension for the mouse genome mutagenesis program.

Auwerx J, Avner P, Baldock R, Ballabio A, Balling R, Barbacid M, Berns A, Bradley A, Brown S, Carmeliet P, Chambon P, Cox R, Davidson D, Davies K, Duboule D, Forejt J,Granucci F, Hastie N, de Angelis MH, Jackson I, Kioussis D, Kollias G, Lathrop M, Lendahl U, Malumbres M, von Melchner H, Müller W, Partanen J, Ricciardi-Castagnoli P,Rigby P, Rosen B, Rosenthal N, Skarnes B, Stewart AF, Thornton J, Tocchini-Valentini G, Wagner E, Wahli W, Wurst W.

8,000 Targeted KOs

16,500 Total KOs

www.mousephenotype.org

IMPC

IKMC have produced >10,000 KO ES cell lines
(www.knockoutmouse.org)

Welcome to the IKMC

The International Knockout Mouse Consortium (IKMC) aims to mutate all protein-coding genes in the mouse using gene trapping and gene targeting in C57BL/6 ES cells. Read more...

Download the IKMC Gene List
View targeting strategies
View all allele types

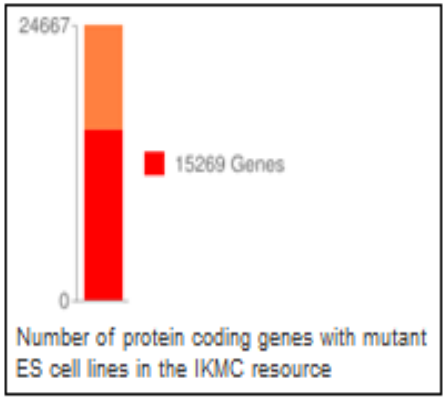
Search or Browse

Search IKMC database help
Enter gene symbols, gene IDs or genome location
Search
e.g., Adam19, Pax, ENSMUSG00000020681, Chr13:22210730-22311669
(coordinates from NCBI mouse genome assembly 37)
Advanced Search

Browse IKMC database help
Use the following links to browse genes
Browse by Gene Symbol
Browse by Chromosome

Status

ES Cell Lines Progress



Number of protein coding genes with mutant ES cell lines in the IKMC resource

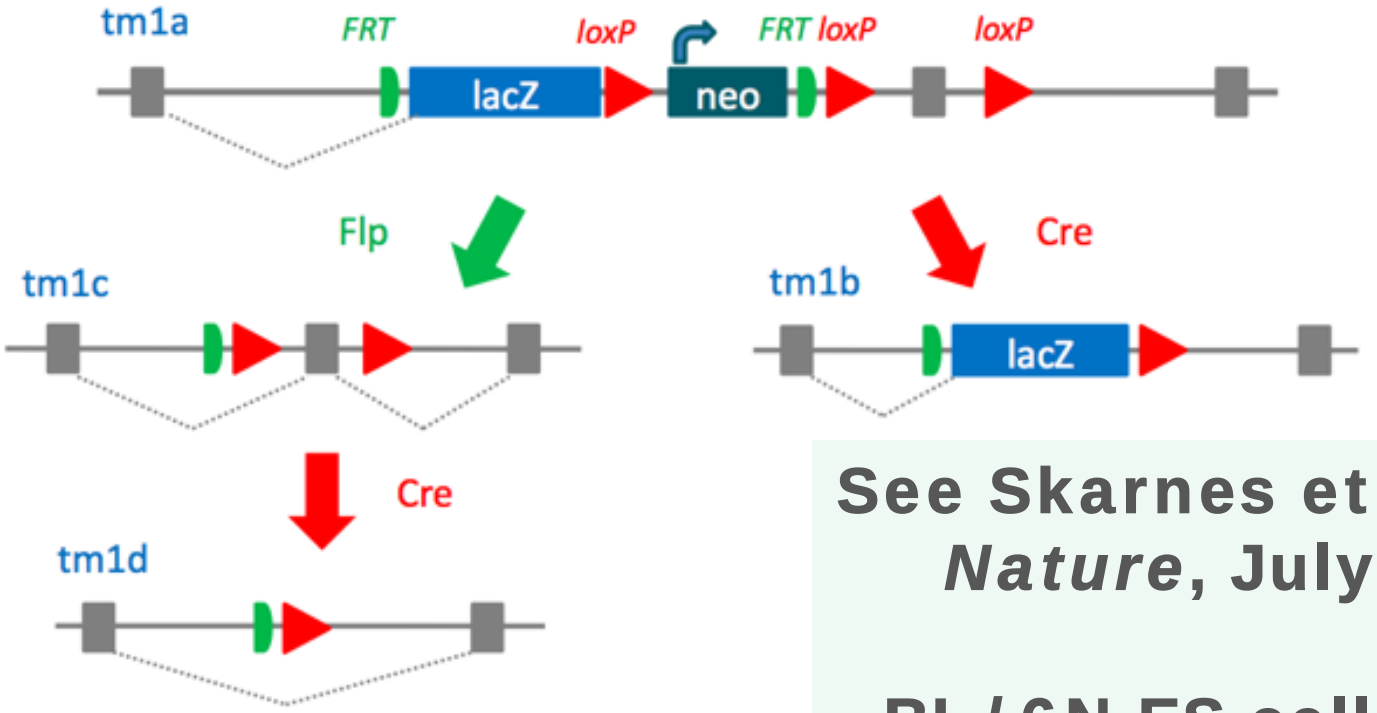
IKMC Gene Progress Summary

Total Genes	KOMP		EUCOMM	NorCOMM	TIGM
	CSD	Regeneron			
Project goal	5000	3500	8000	500	-
Vectors generated	6418	4867	6264	797	-
Vectors available	5867	3328	6264	797	-
ES cells generated	4012	2421	4583	397	-
ES cells available	3732	1755	4583	397	10689
Mutant mice generated	258	280	479	3	43
Mutant mice available	258	178	479	3	43

View details about this table View details about the acronyms used

IMPC Alleles
IKMC - EUCOMM/KOMP

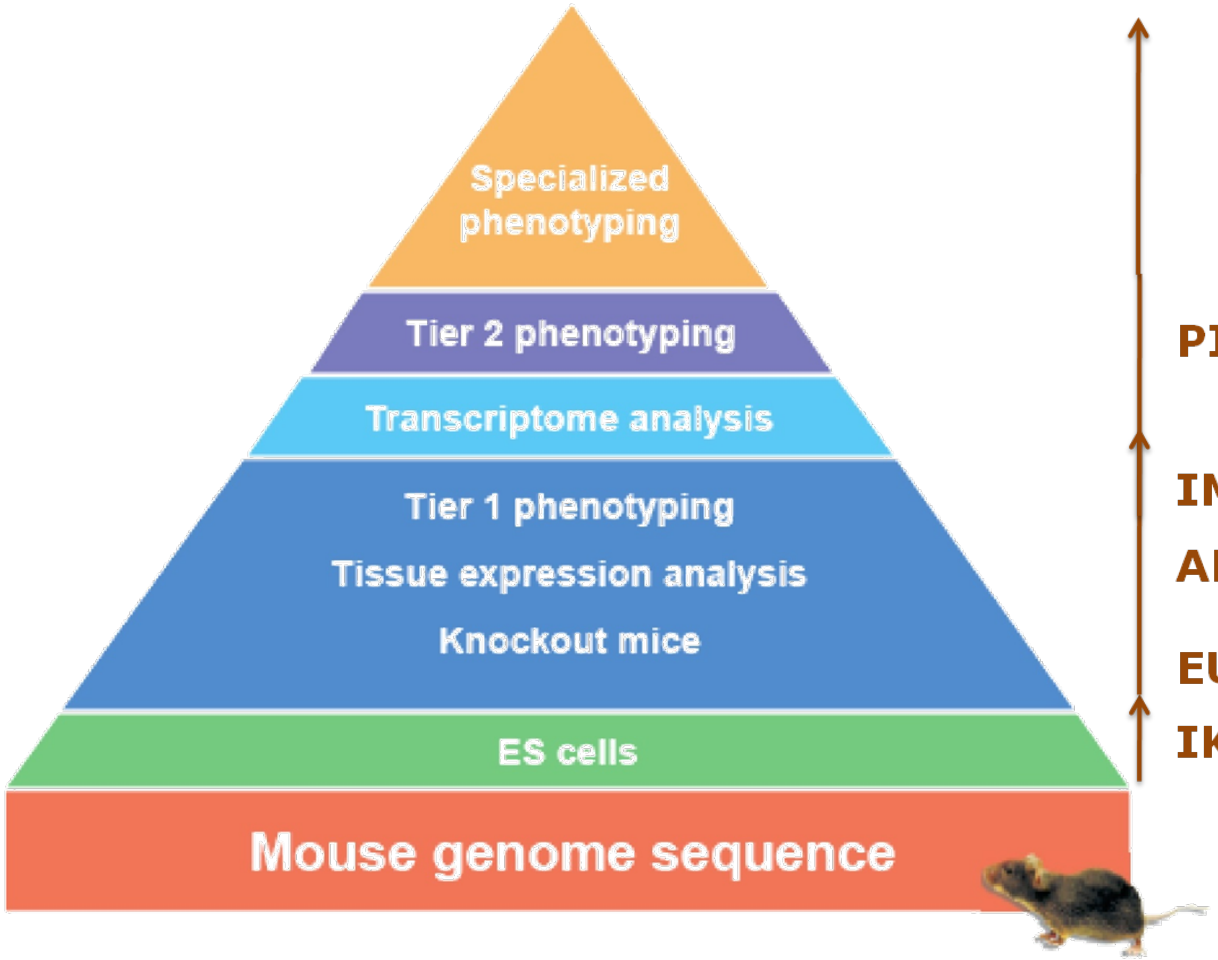
Knockout-first, conditional-ready allele:



See Skarnes et al. *Nature*, July

BL/6N ES cells

Post IKMC: Tier 1 Phenotyping



PI Driven

IMPC (2011-21)

ARRA (2010-11)

EUMODIC (2008-11)

IKMC (2006-11)

F.S. Collins, 2007, Cell 128: 9-13.

IMPC History

- **Community workshops: Rome in 2007, Bar Harbor and Toronto in 2008**
  - to establish vision for an IMPC & discuss international, coordinated phenotyping efforts
- **Medical Research Council / Wellcome Trust workshops in Nov 2008 and Oct 2009**
  - to engage UK scientific community
- **NIH Phenotyping meeting, Bethesda October 2009 (survey)**

- **Pilot projects**
  - EC–funded EUMODIC (Helmholtz, Munich; ICS, Strasbourg, MRC Harwell, WTSI) project
  - MGP Project (WTSI)

EUMODIC (www.eumodic.org)

Undertake a major pilot programme

- ❑ Utilise standardised phenotyping pipeline - EMPReSSslim
- ❑ Analysis of 500 IKMC (EUCOMM) mutants

EU Framework Funded

- ❑ 4 Major Mouse Infrastructures

Assess the utility and efficiency of broad-based primary phenotyping of KO mice

- ❑ Logistics of mouse production and phenotyping
- ❑ Utility of assays (identifying disease models)
- ❑ Sensitivity of assays (number of mice)
- ❑ Capture, disseminate and build on rich phenotypic information

EUMODIC Workflow

EUCOMM → GLTs → Heterozygotes → Homozygotes

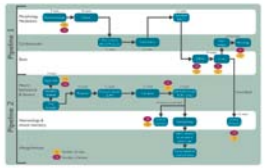
Non-viable homozygotes

viable homozygotes

Mouse clinics
Helmholtz, Munich
ICS, Strasbourg
MRC, Harwell
Sanger, Hinxton

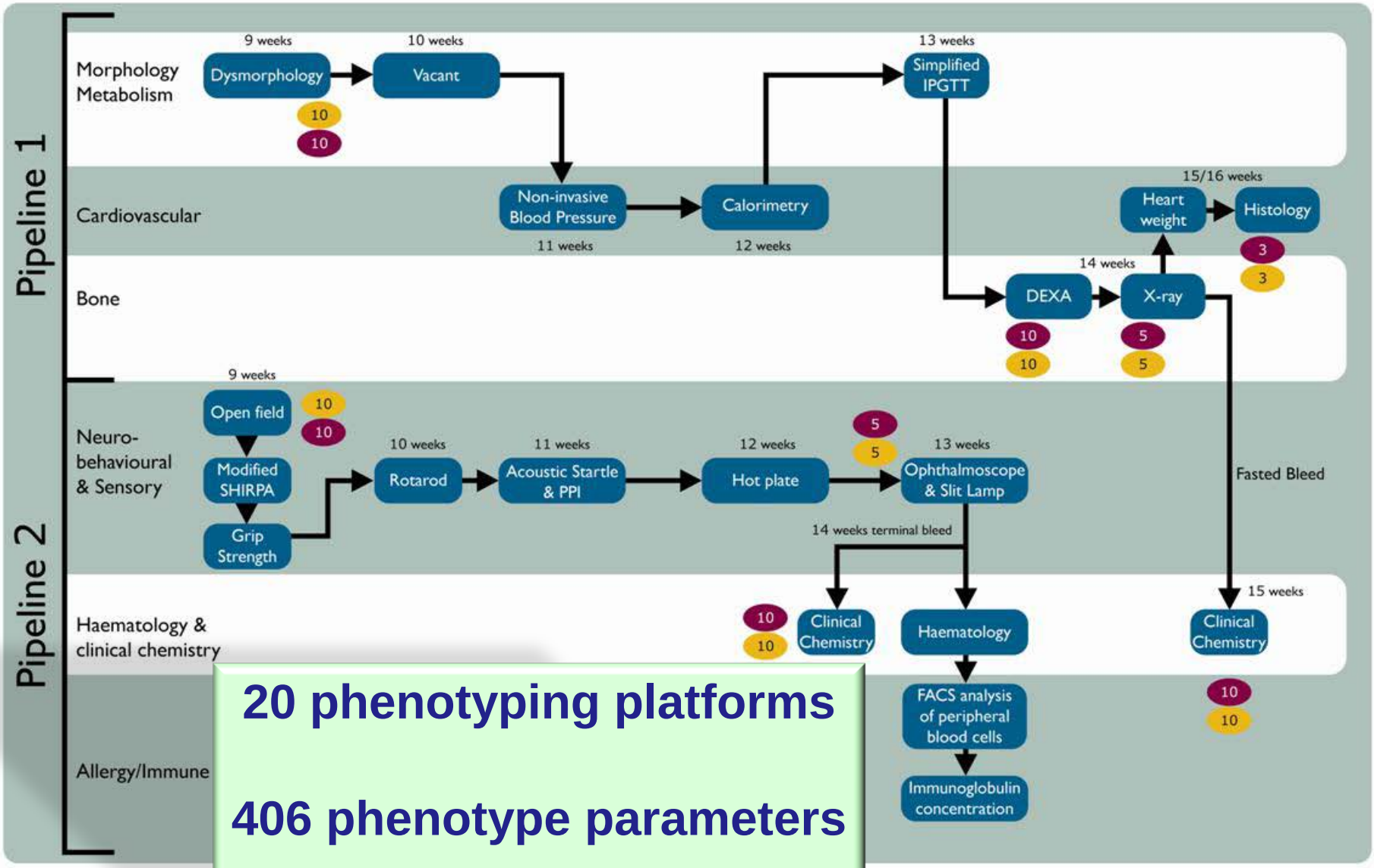
7 males
7 females

Primary Phenotyping
EMPReSSslim



europhenome

EMPReSSslim Primary Phenotyping Pipelines



20 phenotyping platforms

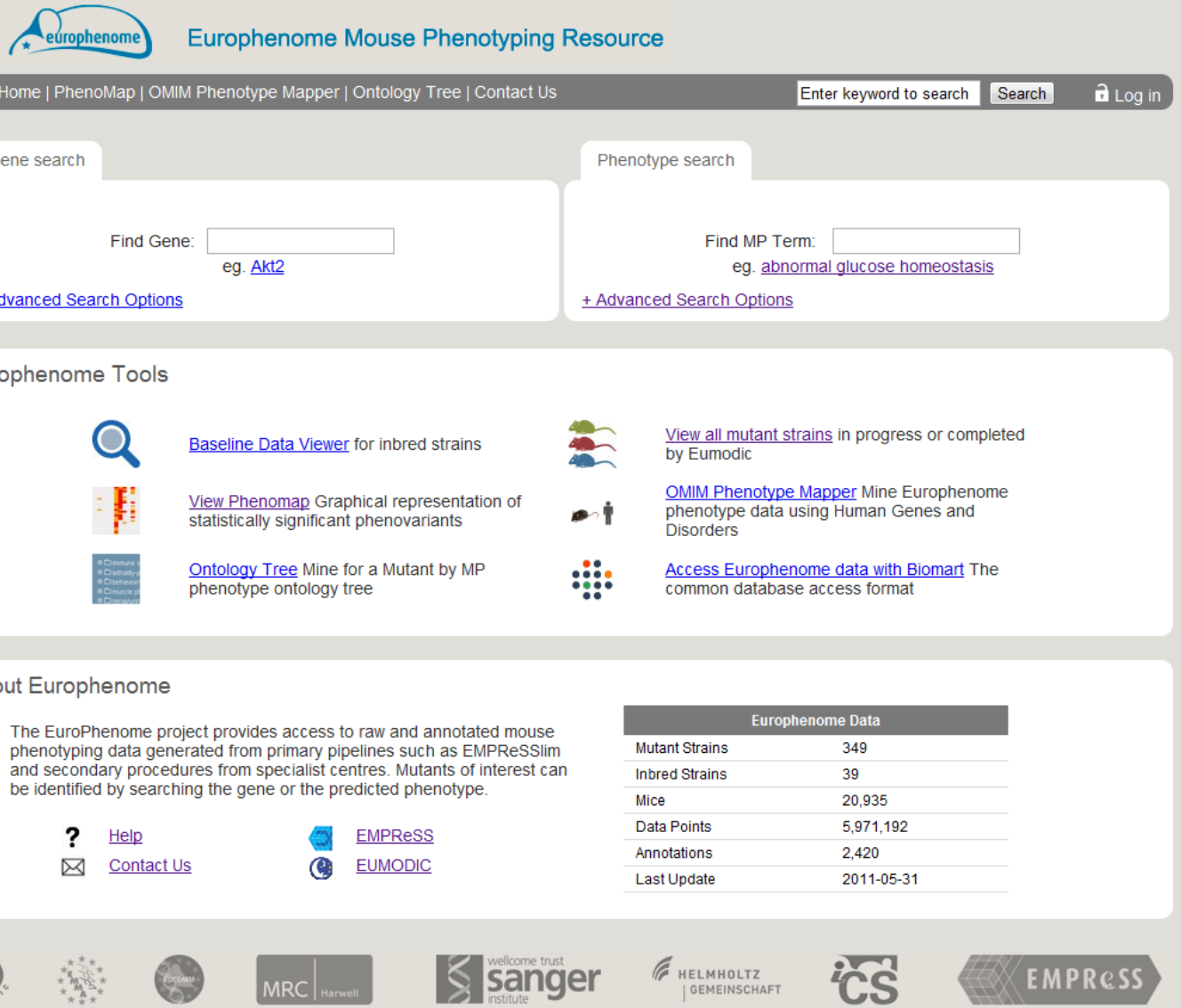
406 phenotype parameters

155 metadata parameters

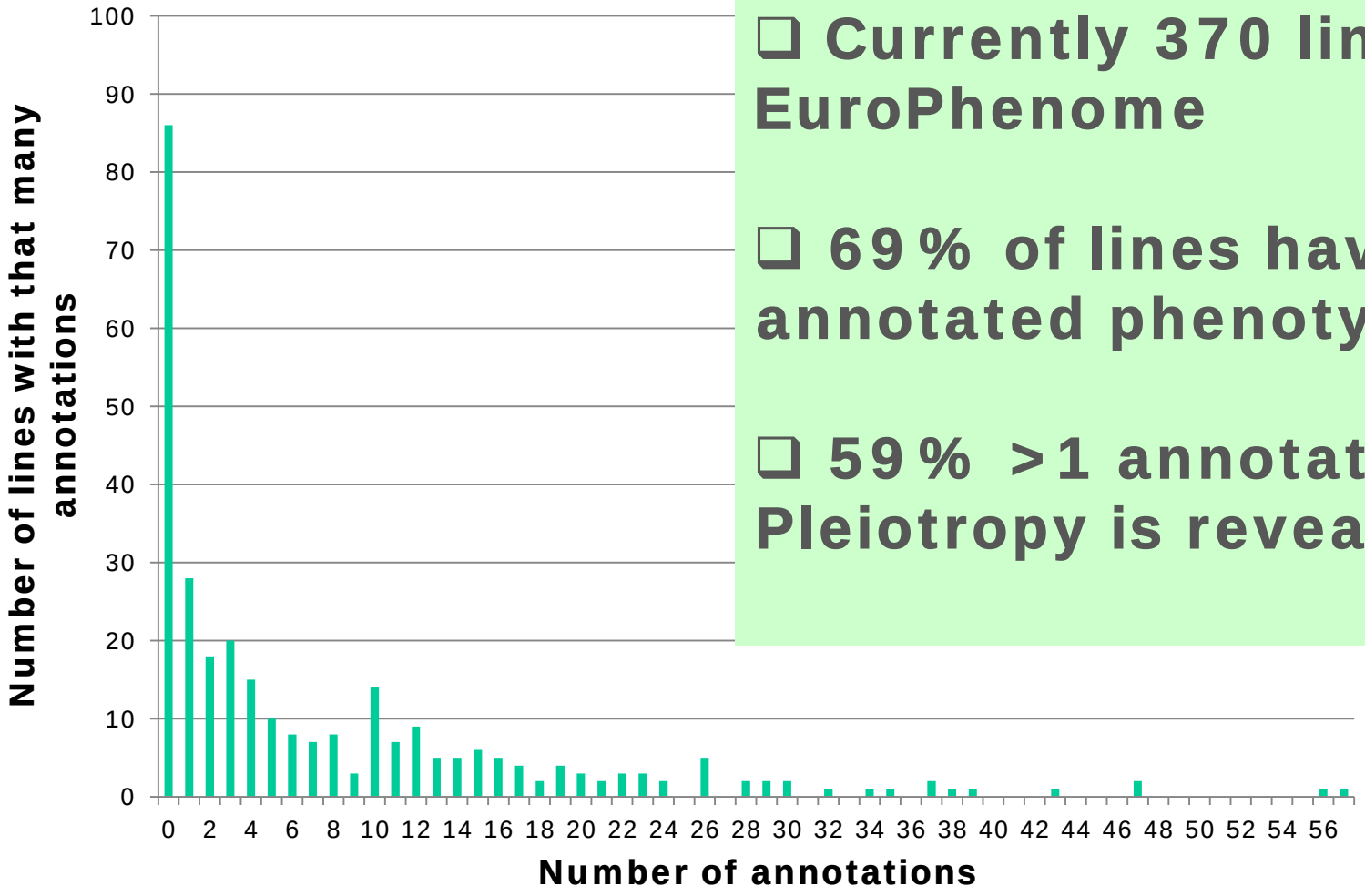
EUMODIC Summary:

- 500 lines committed to the pipeline => GLT or beyond
- Data for 370 lines entered into EuroPhenome
- All lines available through EMMA
- Phenotyping finishes January 2012

EuroPhenome
(www.europhenome.org)



Distribution of Phenotype Annotations ($P<10^{-4}$) in EuroPhenome



- ❑ Currently 370 lines in EuroPhenome
- ❑ 69% of lines have an annotated phenotype
- ❑ 59% >1 annotation Pleiotropy is revealed

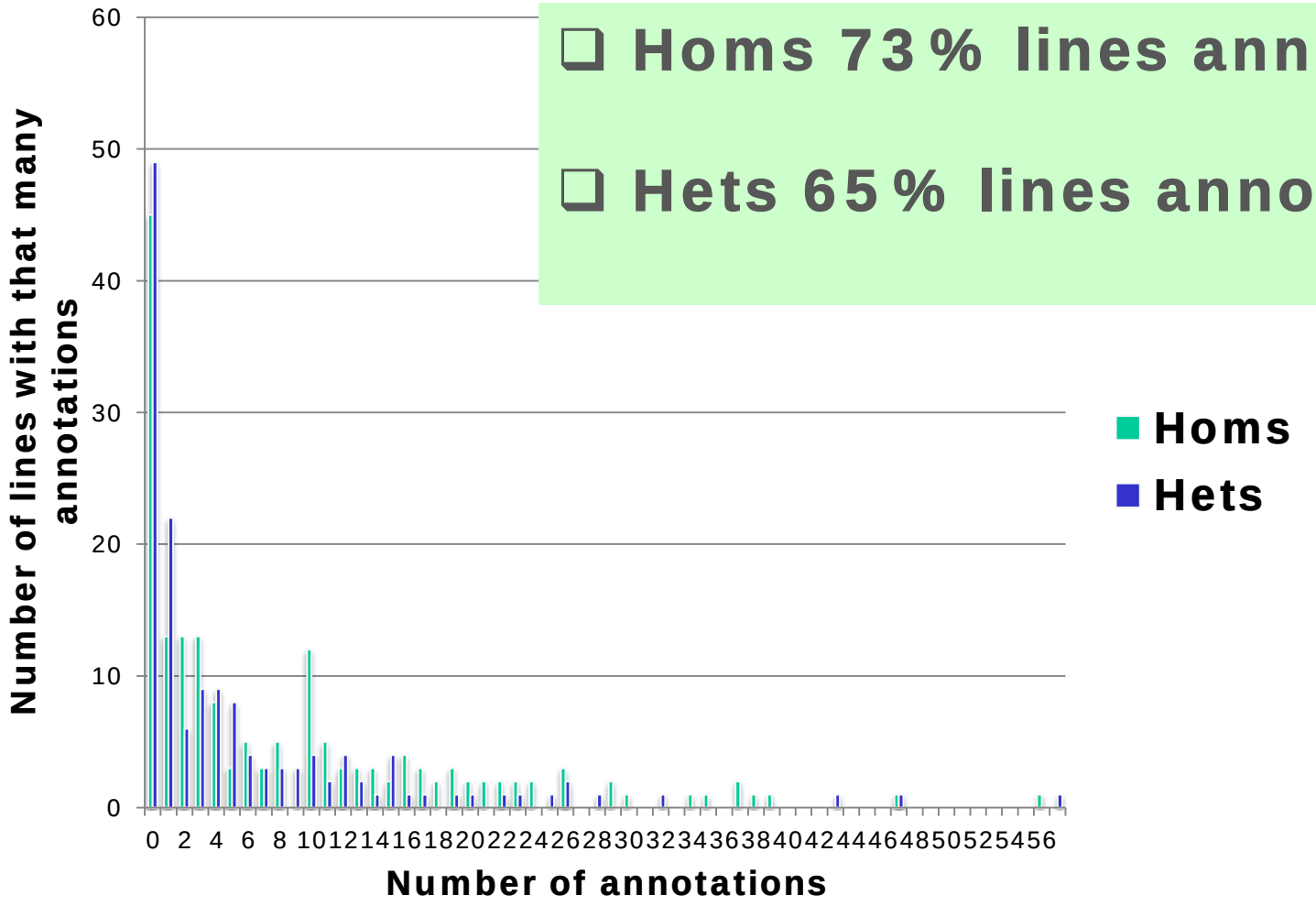
Distribution of Phenotype Annotations Viability

- 80% of lines have an annotation including viability and fertility

Viability	%
Lethal	34
Sub-viable	12
Viable	54

Distribution of Phenotype Annotations by Zygosity

- Homs 73% lines annotated
- Hets 65% lines annotated



Distribution of Phenotype Annotations Homs vs Hets

- 38 lines analysed for both hets and homs

Zygosity	Number of annotations	Number of lines
Hets	53	38
Homs	173	38
Overlap	11	5

- Limited overlaps of hom and het phenotypes

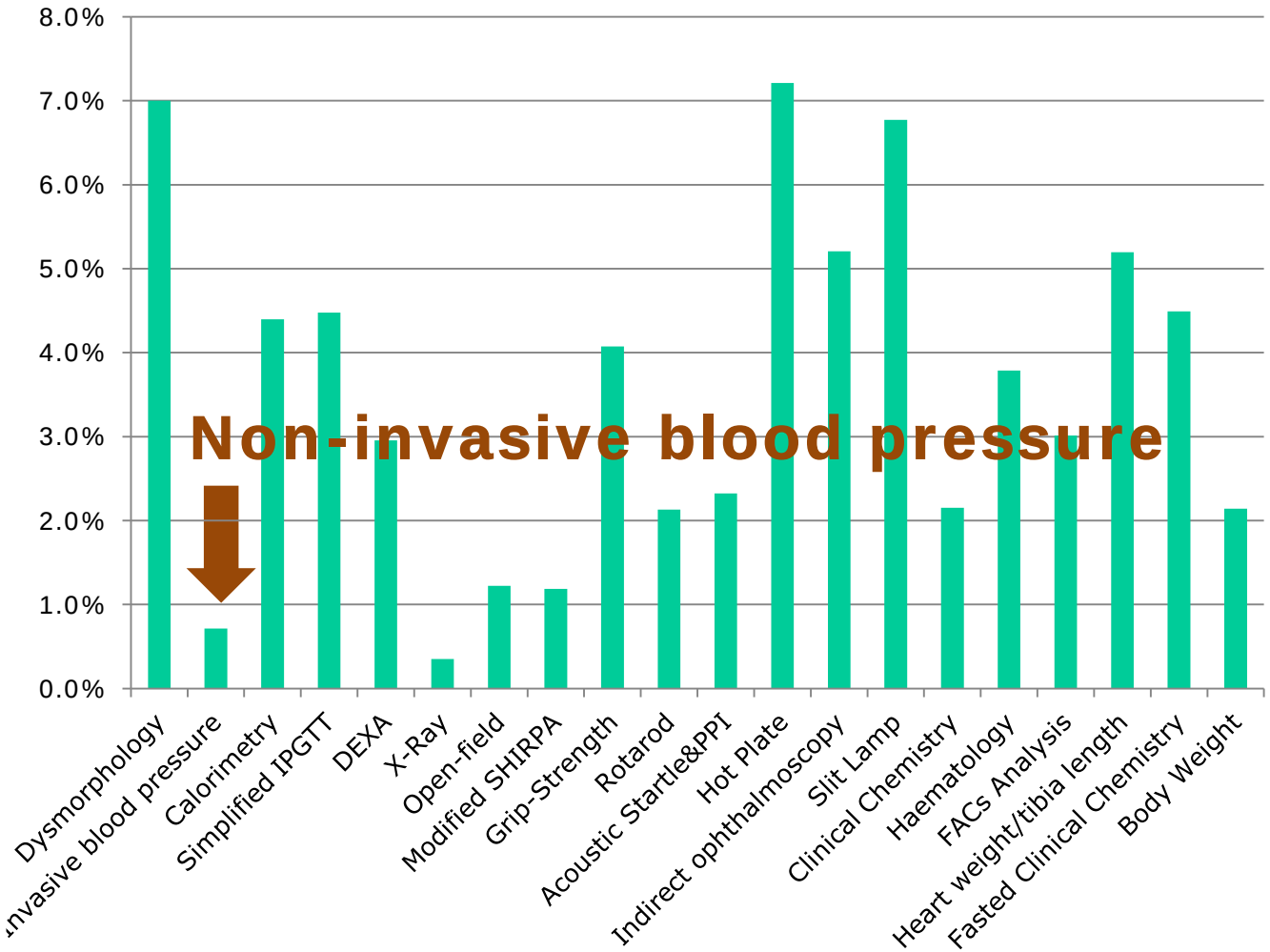
Example line with multiple annotations and no available annotations

- ***Srsf4*** **(serine / arginine-rich splicing factor 4)**
- **Not annotated in MGI**
- **Uncertain gene function, a probable role in alternative splice site selection during pre-mRNA splicing**
- **Annotated to a number of body systems:**
  - Reduced RBC count, haemoglobin concentration, haematocrit across sexes and zygosities
  - Much lower Grip Strength in both sexes
  - More subtle changes in Calorimetry and Opthalmoscope

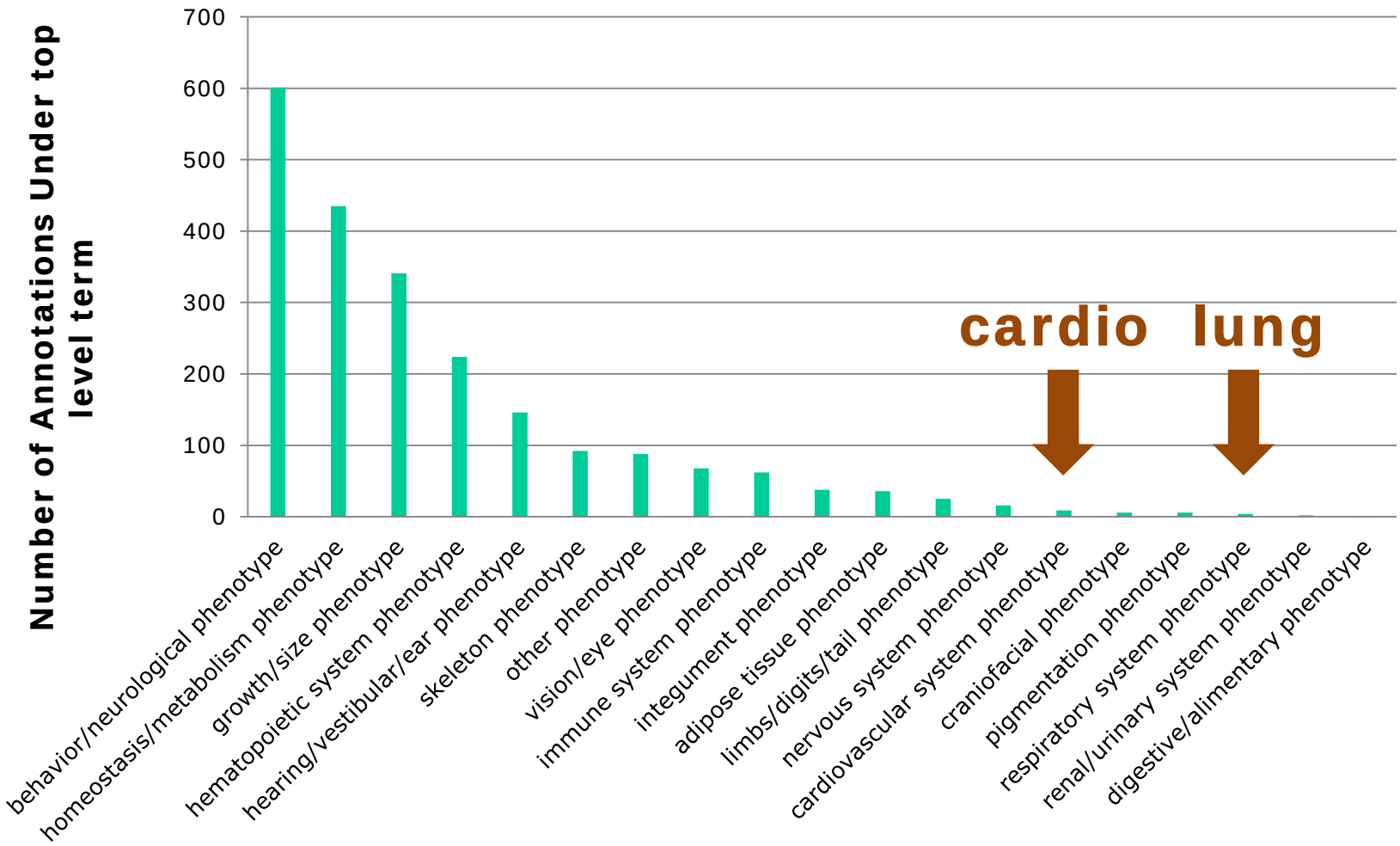
Body weight analysis

- ¼ of all lines have a body weight phenotype
- 91.7% of these lines are also annotated to another parameter
- 61.9% of all lines in EuroPhenome are annotated to a non-body weight parameter
- Body weight is potentially an indicator of additional phenotypes rather than a specific body weight phenotype

Normalised Percentage Hit Rate for EMPReSSslim Procedures



Number of Annotations per top level ontology term



Rationale
An Encyclopaedia of Mammalian Gene Function

Supporting a broad phenotyping effort would provide the following advantages:

- A single cohort of mice would go through multiple phenotyping assays, so the cost of producing multiple cohorts in different laboratories for phenotyping would be eliminated.
- Each mutant mouse strain would be characterized for a broad set of phenotypes in a way that will allow direct comparisons and result in a more thorough description of gene function.
- Quality standards will be established and maintained, so the data will be of the highest reliability.
- The risk of not finding a phenotype will be greatly reduced.
- Important, but unpublishable, negative results will be captured.

Future Vision

An Encyclopaedia of Mammalian Gene Function

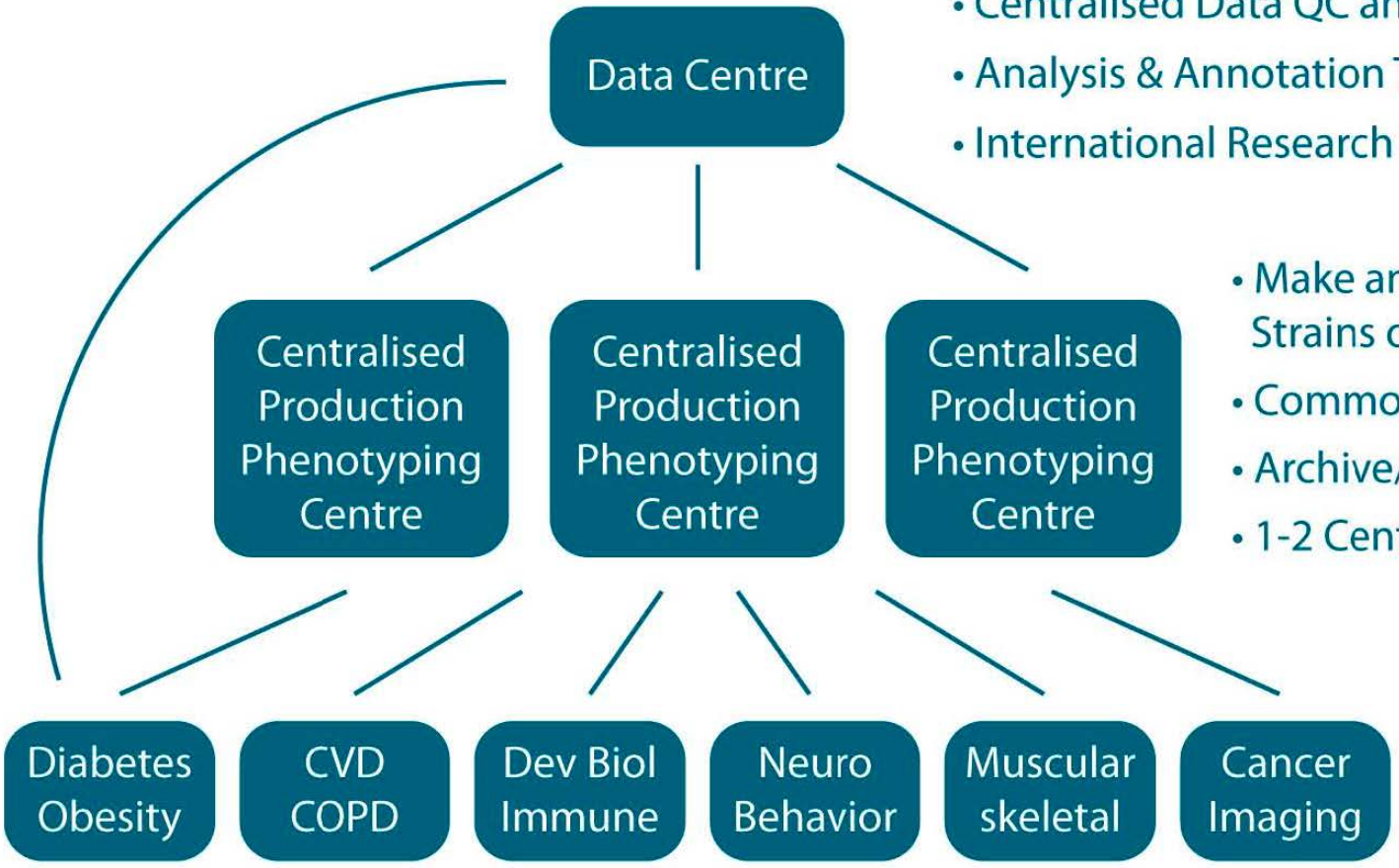
- Build a resource of KO mice and associated encyclopedia of gene function, in a cost efficient and robust manner
- Free thousands of researchers from tool generation
- Uncover unforeseen novelty in mammalian gene function
- A rich seam for future hypothesis driven research, with the potential for breakthrough discoveries
- A transformative project that will underpin the future of biomedical science and the biology of disease systems

IMPC Activities

- **Undertake broad based primary phenotyping of 20,000 mutants from the IKMC resource**
  - A coordinated effort of mouse clinics worldwide
- **Phase I (2011-2016): phenotype up to 5,000 lines**
  - Pipeline development, logistics
  - Phenotyping technology developments e.g. imaging
  - Ramp up
- **Phase II (2016-2021): Phenotype 15,000 mutants**
- **Data freely available through a Data Coordination Centre, supported by R&D groups at clinics**

International Mouse Phenotyping Consortium (IMPC)

- EU, North America, Asia
- Co-ordinated Funding & Operations
- Industry Access



- Centralised Data QC and Standards
- Analysis & Annotation Tools
- International Research Scientists

- Make and Breed 20,000 KO Strains of Mice
- Common Phenotyping Pipeline
- Archive/Distribute Strains
- 1-2 Centres/Country

- Network of Specialist Labs
- High Content Phenotyping
- Sensitized Screens

IMPC

International Mouse Phenotyping Consortium

www.mousephenotype.org

IMPC
22 Academic, Government Institutes

- **MRC Harwell** (Steve Brown, current Chair Steering Comm.; Tom Weaver)
- **Sanger Institute** (Allan Bradley, Dave Adams, Karen Kennedy)
- **NIH KOMP2**
  - **BASH, Baylor** (Monica Justice)
  - **DTCC (UC Davis** (Kent Lloyd)**, TCP, Charles River, Children's Hospital Oakland RI)**
  - **Jackson Lab** (Karen Svenson)
- **Toronto Centre for Phenogenomics** (Colin McKerlie)
- **Helmholtz Zentrum Munich** (Martin Hrabe de Angelis)
- **Institut Clinique de la Souris** (Yann Herault)
- **Australian Phenomics Network** (Adrienne McKenzie)
- **RIKEN BioResource Center** (Yuichi Obata)
- **MARC** (Xiang Gao)
- **CNR** (Glauco Toccinni Valentini)
- **EBI** (Paul Plicek)

- **Secretariat** (Mark Moore, Executive Director; Joerg Rossbacher)

- ***FUNDERS***
- **MRC** (Nathan Richardson, Clare Newland)
- **NIH** (Jane Peterson, Eric Green, Jim Battey, Colin Fletcher, Martin Guyer)
- **Wellcome Trust** (Michael Dunn, Clare McVicker)
- **Infrafrontier** (Martin Hrabe de Angelis)
- **Genome Canada** (Cindy Bell)
- **European Commission** (Observer status)
- **Canadian Institutes of Health Research, CIHR** (Jane Aubin)

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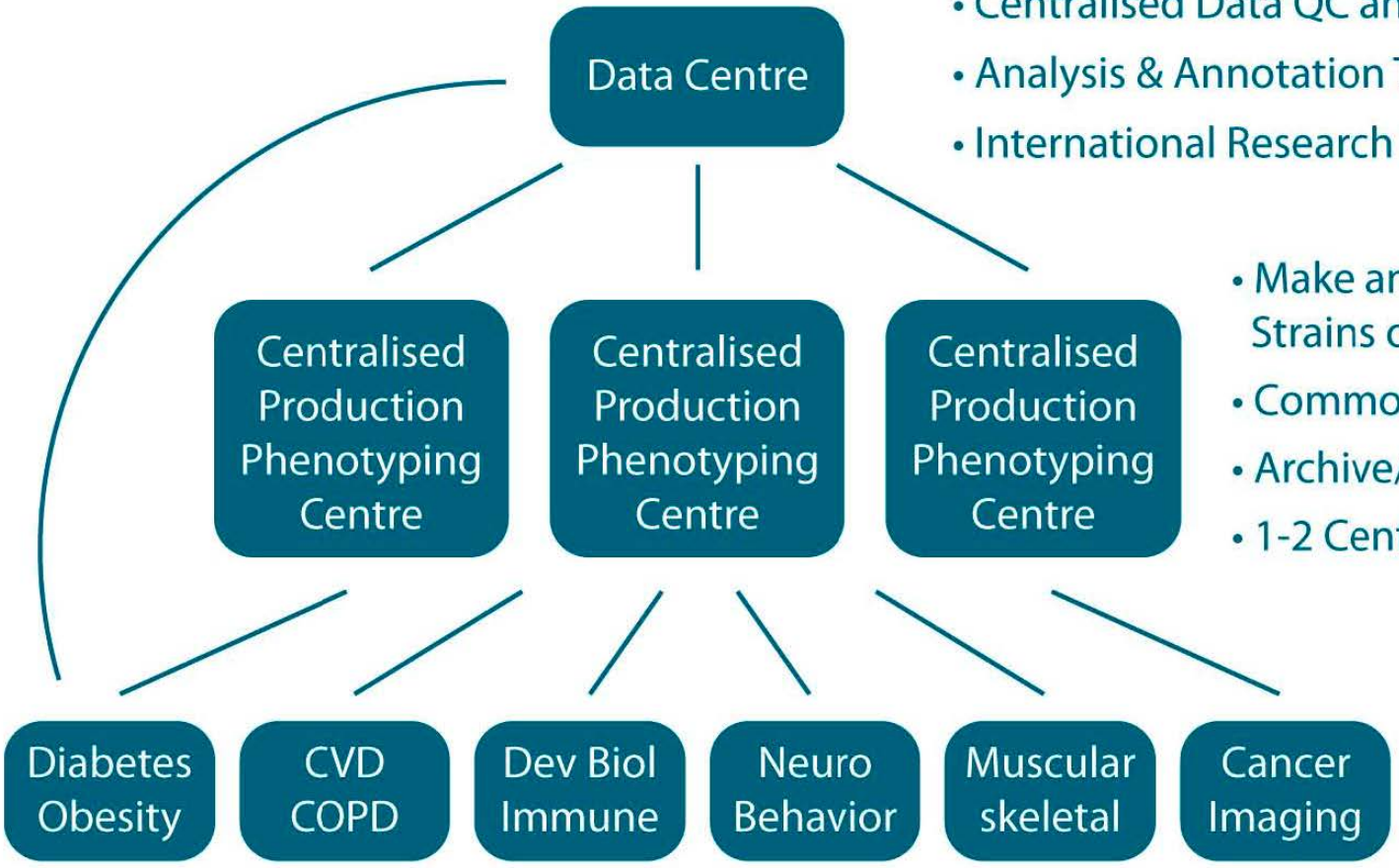

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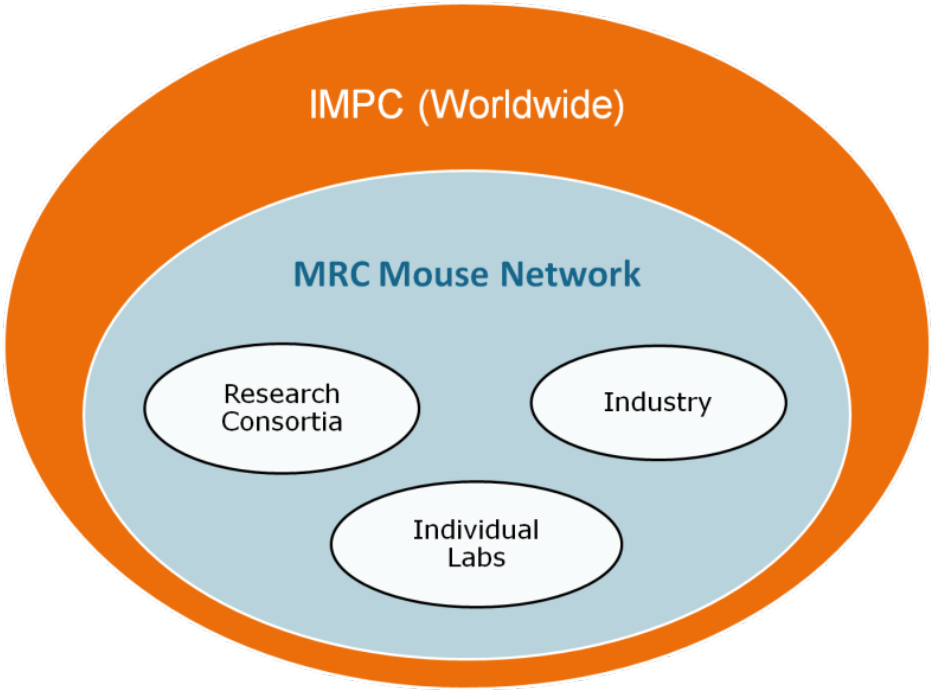
IMPC Engagement
MRC Mouse Networks

MRC Mouse Networks incorporate :

- ❑ Neuro
- ❑ Obesity and Diabetes
- ❑ Ubiquitination
- ❑ Bone
- ❑ Liver
- ❑ Haematopoiesis
- ❑ Fibrosis
- ❑ Vision
- ❑ Respiratory
- ❑ Renal
- ❑ Macrophages
- ❑ Cardiovascular
- ❑ Development



IMPC

Phenotyping Working Group

Barca Meeting

- ❑ March 2011
- ❑ Representatives from Clinics
- ❑ External Experts
- ❑ Secondary Screeners
- ❑ Industry

Disease Categories

- ❑ Cardio
- ❑ Respiratory
- ❑ Metabolism
- ❑ Immune and Blood
- ❑ Neuro/Behaviour
- ❑ Sensory
- ❑ Skin
- ❑ Musculoskeletal
- ❑ Imaging
- ❑ Cancer
- ❑ Development

7 M + 7 F Mutant Adult Mice

Proposed IMPC adult phenotyping pipeline

Weight Curve – 4wk to 16wk

In life

- **9**: Open Field, Modified SHIRPA, Dysmorphology, Grip Strength
- **10**: Acoustic Starte/PPI
- **11**: ECG / Echo
- **12**: Calorimetry
- **13**: Intraperitoneal Glucose Tolerance Test
- **14**: Challenge Whole Body Plethsmography, Auditory Brain Stem Response, Body Composition (lean/fat), Pain Test
- **15**: X-ray (5 + 5), Slit Lamp, Opthalmoscope

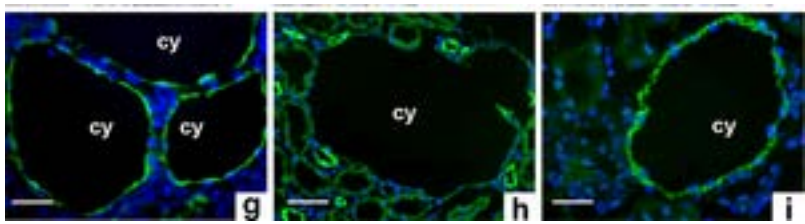
Terminal

- **16**: Hematology, Clinical Blood Chemistry, Insulin Blood Level, FACS spleen/BM, Heart Weight, Gross Pathology (2+2), Block Banking, Histopathology (2+2) - from blocks where required

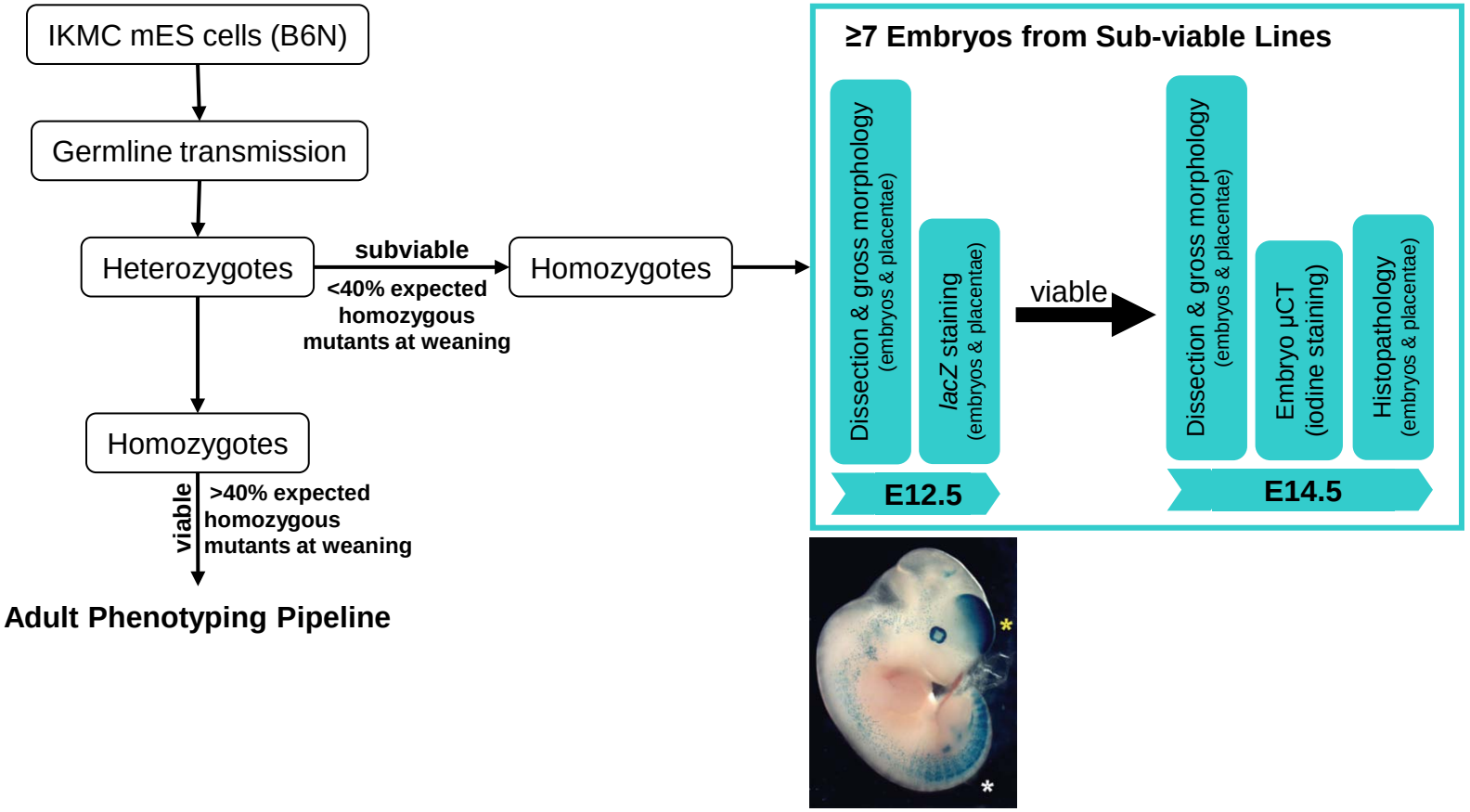
Mandatory tests

Non-mandatory tests

Tests in development or under consideration



Proposed IMPC Embryonic Phenotyping Pipeline

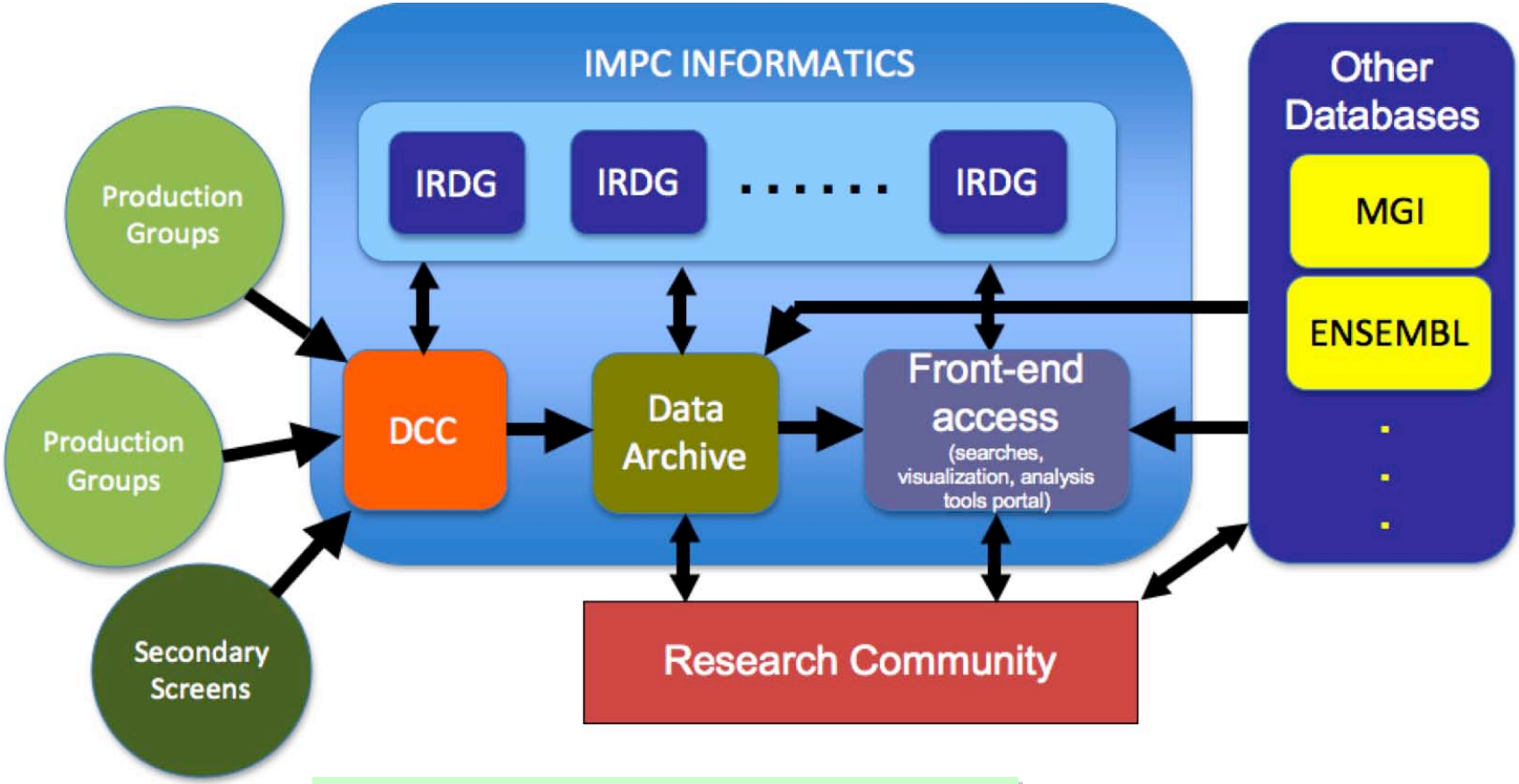


Draft Pipeline – Under Consultation, Report Available (www.mousephenotype.org)

Status:
Launch – Sept 28th 2011

Centre		Total for Phase 1
MRC Harwell		330
Sanger Institute		1000
NIH - BASH	Baylor	830
NIH - DTCC	UC Davis	830
NIH - JAX	Jackson Lab	830
TCP, Toronto		150
Helmholtz, Munich		250
ICS, Strasbourg		250
Riken BRC		250
MARC, Nanjing		250
CNR, Monterotondo		250
TOTAL		**5220**

IMPC Informatics



MPI2

EBI, Harwell, Sanger

Challenges Ahead 1

- **Delivering a rich, robust phenotype pipeline that meets the needs of the community**
  - Learning from each other
  - New assays/new disease areas
  - Development pipeline
- **Addressing the challenge of aging phenotypes – from cancer to neurodegeneration**
- **Delivering to the consortium an effective data acquisition, data analysis and data dissemination pipeline**
  - Statistical approaches to annotation
- **Development of approaches to describe and map phenotypes to human disease states**
  - Working with the ontology community

Challenges Ahead 2

- **Networking with the community**
  - Ensuring utilisation of data and uptake of resources
  - Fostering networks of activity that add value and understanding
  - Capturing secondary and tertiary phenotyping information
  - Measuring and reporting that activity
  - Bringing the community into the fold
    - Incorporation of specialist centres into IMPC e.g. aging
    - Implementation of niche, challenge and sensitised screens

- **Integration with phenotyping of other genetic reference populations**
  - Link-up with planning for phenotyping in the CC community, outbred studies

IMPC Critical Steps

- **Phenotyping Workgroup**
  - Agreement and implementation at DCC of SOPs and parameter sets for adult pipeline
  - Test development, validation – cross-talk between clinics
  - New tests – new disease/biology areas
  - Development pipeline
  - Imaging modalities

- **IT workgroup – and associated activities**
  - Controls and statistical approaches to annotation
  - Continuing development of analytical tools
  - Ontologies and mapping to disease states

IMPC

International Mouse Phenotyping Consortium

- National Institutes of Health (USA)
- Toronto Centre for Phenogenomics (Canada)
- Medical Research Council & MRC Harwell (UK)
- The Wellcome Trust Sanger Institute (UK)
- Wellcome Trust
- Helmholtz Zentrum Munich (Germany)
- Institute Clinique de la Souris (France)
- UC Davis
- European Bioinformatics Institute
- The Jackson Laboratory
- Children's Hospital Oakland Research Institute
- Consiglio Nazionale delle Ricerche (Italy)
- European Commission (EU)
- Infrafrontier (EU)
- Australian Phenomics Network (Australia)
- RIKEN BioResource Center (Japan)
- Genome Canada
- Model Animal Research Center (Nanjing)
- Baylor College of Medicine
- Charles River Laboratories

www.mousephenotype.org

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