S2

The International Mouse Phenotyping Consortium (IMPC)

IMPC and its role in Precision Medicine

www.mousephenotype.org

IMPC

Delivering Mouse Genetics for Precision Medicine

- Comprehensive baseline (null allele) information on gene function and **pleiotropy**
- Sophisticated pipelines to deliver and analyse human genetic variation in the mouse
- Relevant pre-clinical models that will enable mechanistic and therapeutic insights

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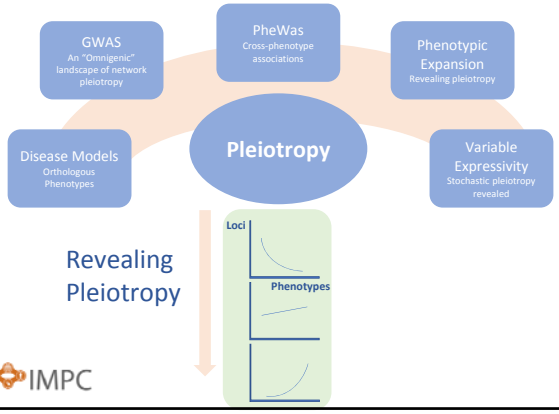
IMPC – revealing pleiotropy



IMPC

IMPC and Precision Medicine

- Providing a comprehensive catalogue of mammalian gene function
- Delivering insights into novel gene function and pleiotropy across diverse systems
- An extensive new fund of disease models
- Increasing integration of IMPC and human/clinical genetics initiatives
- Harnessing the infrastructure of mouse genetics centres worldwide to precision medicine initiatives

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IMPC Goals

- Generate a mouse mutant for every gene in the mouse genome
- Comprehensively phenotype each mouse mutant to determine developmental, physiological, and biochemical parameters
- Phenotype data uploaded from IMPC centres around the world to the MRC Harwell Data Coordination Centre
- Analysis of data to determine gene function, and identify disease models
- Mice available through the global network of mouse repositories

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IMPC Opportunities

- **Rare Disease and Mendelian Disorder programmes**
  - Capturing information on gene function (null allele) in synergy with analysis of targeted disease alleles
- **100,000 genomes project, the Precision Medicine Initiative and SV programmes**
  - Providing information on gene function, and the outcomes of additional alleles
  - Validating potential gene-phenotype relationships
- **Big data studies**
  - Provision in both mouse and human of multidimensional genetic and phenotype data underpins a new era of cross-species and synergistic analyses

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Folie 1

LS2 Updated map image
Luis Santos; 28.09.2017

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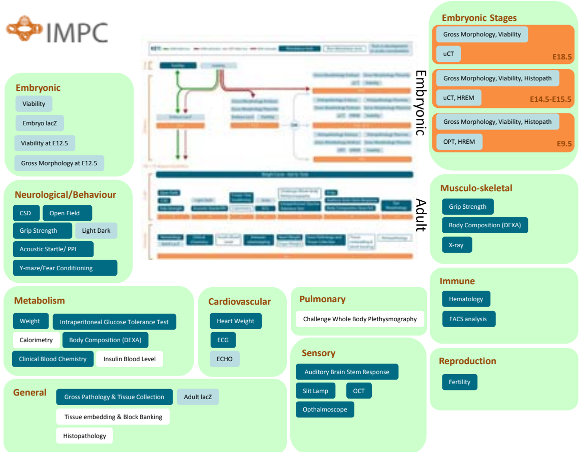
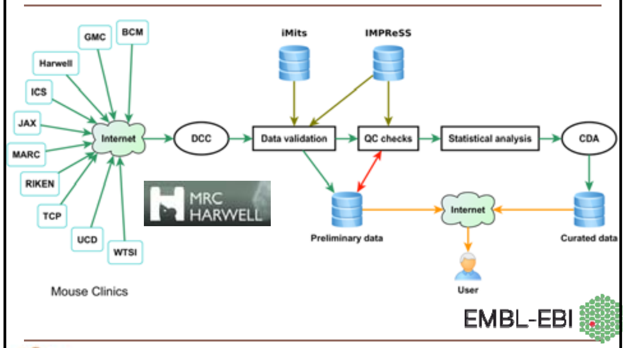


IMPC Informatics Team

MPI2



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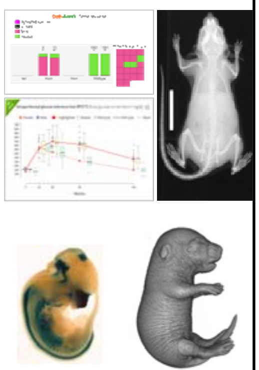
LS8

IMPC Programme Update

- 11773 microinjections
- 7016 genotype confirmed lines
- 5071 lines phenotyped
- Data Release (6.0) for 4745 lines
- 54.9 million data points
- Approx. 390k images



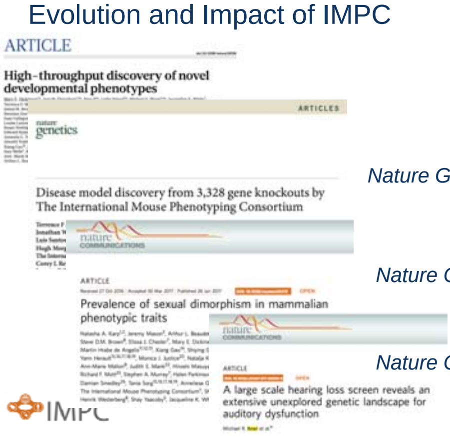
IMPC

Evolution and Impact of IMPC

- Revealing novel features of the mammalian genome landscape
  - Extensive new collection of disease models, new candidate disease genes and new functional knowledge
  - Novel insights into gene function e.g. metabolism, deafness
  - Pervasive sexual dimorphism revealed
  - Opportunities for the identification of new gene and phenotype relationships to elicit novel biological mechanisms
  - Insights into human disease from the analysis of mouse lethal (essential) genes

IMPC

Evolution and Impact of IMPC



Nature, 2016

Nature Genetics, 2017

Nature Comms, 2017

Nature Comms, 2017

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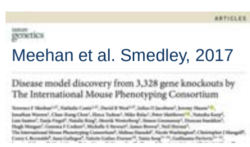
IMPC
Revealing novel features of the mammalian genome landscape

Disease Model Discovery and New Functional Knowledge



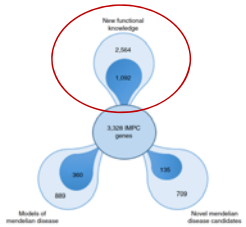
Meehan et al. Smedley, 2017

IMPC

Folie 9

LS8 updated numbers; visual tweaks and combined the 2 previous slides
Luis Santos; 28.09.2017

Disease Model Discovery
IMPC v5.0 – analysis of 3,328 genes



New functional knowledge

- 90% of gene-phenotype annotations not reported before
- 1,830 of the 3,328 genes phenotyped in this release have not had a mouse mutant produced
- New functional knowledge for 1,092 genes


Meehan et al. Smedley, 2017

Disease model discovery from 3,328 gene knockouts by The International Mouse Phenotyping Consortium

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Disease Model Discovery
IMPC v5.0 – analysis of 3,328 genes

Models of Mendelian Disease

- 889 known disease gene associations within OMIM/ORPHANET with an orthologous IMPC strain with at least one phenotype
- 360/889 had phenotypic overlap
- 78% (279) represent the first report of a mouse model for these diseases

Novel Mendelian Disease Candidates

- New candidate genes for mendelian diseases for which broad genetic localisation is available
- 135 potential candidates

IMPC MPI2

IMPC
Revealing novel features of the mammalian genome landscape

Insights into novel gene function


Bowl et al., 2017

A large scale hearing loss screen reveals an extensive unexplored genetic landscape for auditory dysfunction

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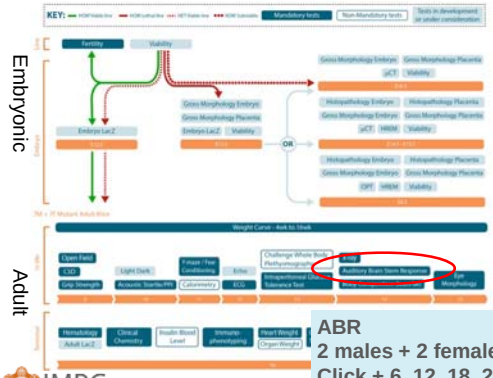
LS17

IMPC phenotyping pipeline



ABR
2 males + 2 females
Click + 6, 12, 18, 24, 30kHz

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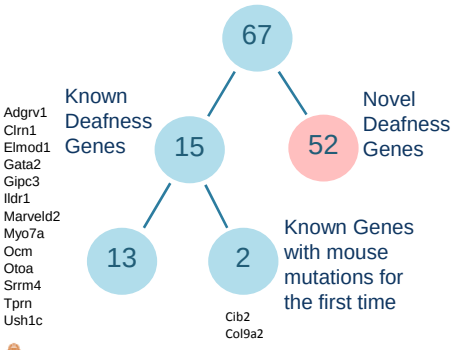
Summary – novel deafness genes
- from 3006 lines analysed by ABR



A730017C20Rik
Aak1
Acsl4
Acvr2a
Adgrb1
Ahsg
Ankrd11
Ap3m2
Ap3s1
Ap4e1
Atg4b
Atp2b1
B020004J07Rik
Baiap2l2
Ccdc88c
Ccdc92
Cyb5r2
Dnase1
Duoax2
Emb
Eps8l1
Ewsr1
Gga1
Gpr152
Gpr50
Ikzf5
Il1r2
Klc2
Klhl18
Med28
Mpdz
Myh1
Nedd4l
Nfatc3
Nin
Nisch
Nptn
Odf3l2
Phf6
Ppm1a
Sema3f
Slc4a10
Slc5a5
Spsn2
Tmem30b
Tmtc4
Tox
Tram2
Ube2b
Ube2g1
Vti1a
Wdtc1
Zcchc14
Zfp719

IMPC MPI2

IMPC
Revealing novel features of the mammalian genome landscape

Pervasive sexual dimorphism revealed


Karp et al., 2017

Prevalence of sexual dimorphism in mammalian phenotypic traits

Natasha Karp
Jeremy Mason
Terry Meehan
Jacqui White

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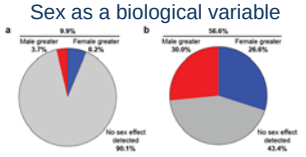
Folie 16

LS17 updated impress pipeline image
Luis Santos; 28.09.2017

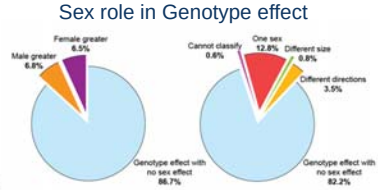
Sexual Dimorphism

Sex as a biological variable



Categorical variables *Continuous variables*

Sex role in Genotype effect



MPI2[1]

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IMPC Interactions

IMPC's key role in mammalian functional genomics

MGI
MARRVEL
MONARCH
PhenoDigm
G2F

Drosophila
Zebrafish
Rat
Worm

IMPC

- Gold-standard mutants
- Robust, reproducible phenotyping platforms
- Sophisticated QC and analysis tools
- Integration with human phenotype data

UDN
UDNI
CMG
RDDM
IRDiRC
IRUD
TUDP
UDP
Genomics England

IMPC

IMPC and Precision Medicine

IMPC underpins future developments

GEMM
GENOME EDITING MICE FOR MEDICINE

IMPC
International Mouse Phenotyping Consortium

Genomics england

biobank

BIG DATA INSTITUTE

Validation of specific candidate pathogenic variants

Sara Wells
Annie Mallon
Damian Smedley

Underpinning information on gene function and pleiotropy

IMPC

IMPC and Precision Medicine

- IMPC has delivered nearly 7,000 mouse lines, a third of the coding genome
- Phenotype data from over 5,000 phenotyped lines
- Substantive step towards a comprehensive catalogue of mammalian gene function
- Transforming the opportunities for rare disease and precision medicine initiatives
- Establishing the context and data for a new era of cross-species analysis via mouse and human multidimensional genetic and phenotype datasets

Twitter @impc www.mousephenotype.org IMPC

LS1
LS19

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International Mouse Phenotyping Consortium

National Institutes of Health (USA)
The Centre for Phenogenomics (Canada)
Medical Research Council & MRC Harwell (UK)
The Wellcome Trust Sanger Institute (UK)
Wellcome Trust
Helmholtz Zentrum Munich (Germany)
Phenomin
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
National Laboratory Animal Center (Taiwan)
Model Animal Research Center (Nanjing)
Baylor College of Medicine
Charles River Laboratories
Korea Mouse Phenotyping Center
Universitat Autònoma de Barcelona
Cambridge-SUDA Genomic Resource Centre (Soochow)

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Folie 23

LS1 updated
Luis Santos; 28.09.2017

LS19 updated collaborators image
Luis Santos; 28.09.2017