# KOMP$^2$

*Knockout Mouse Production & Phenotyping:*

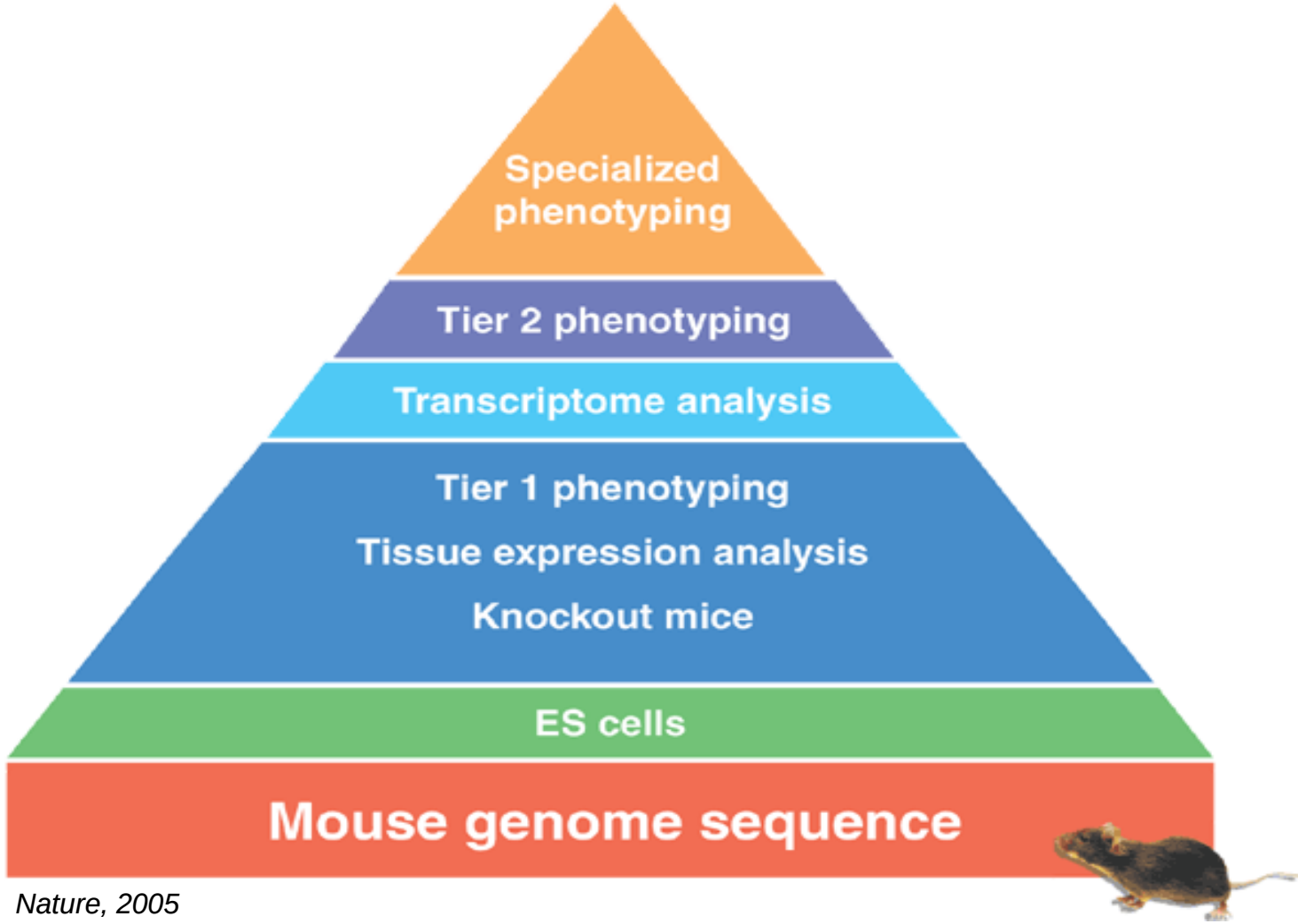
*a*  *project*


*What we've done…Where we're going*

**NIH Council of Councils**

**September 5, 2014**

**Bldg 31, NIH Campus, Bethesda, MD**


Specialized phenotyping
Tier 2 phenotyping
Transcriptome analysis
Tier 1 phenotyping
Tissue expression analysis
Knockout mice
ES cells
Mouse genome sequence

*Nature, 2005*

# KOMP[1]

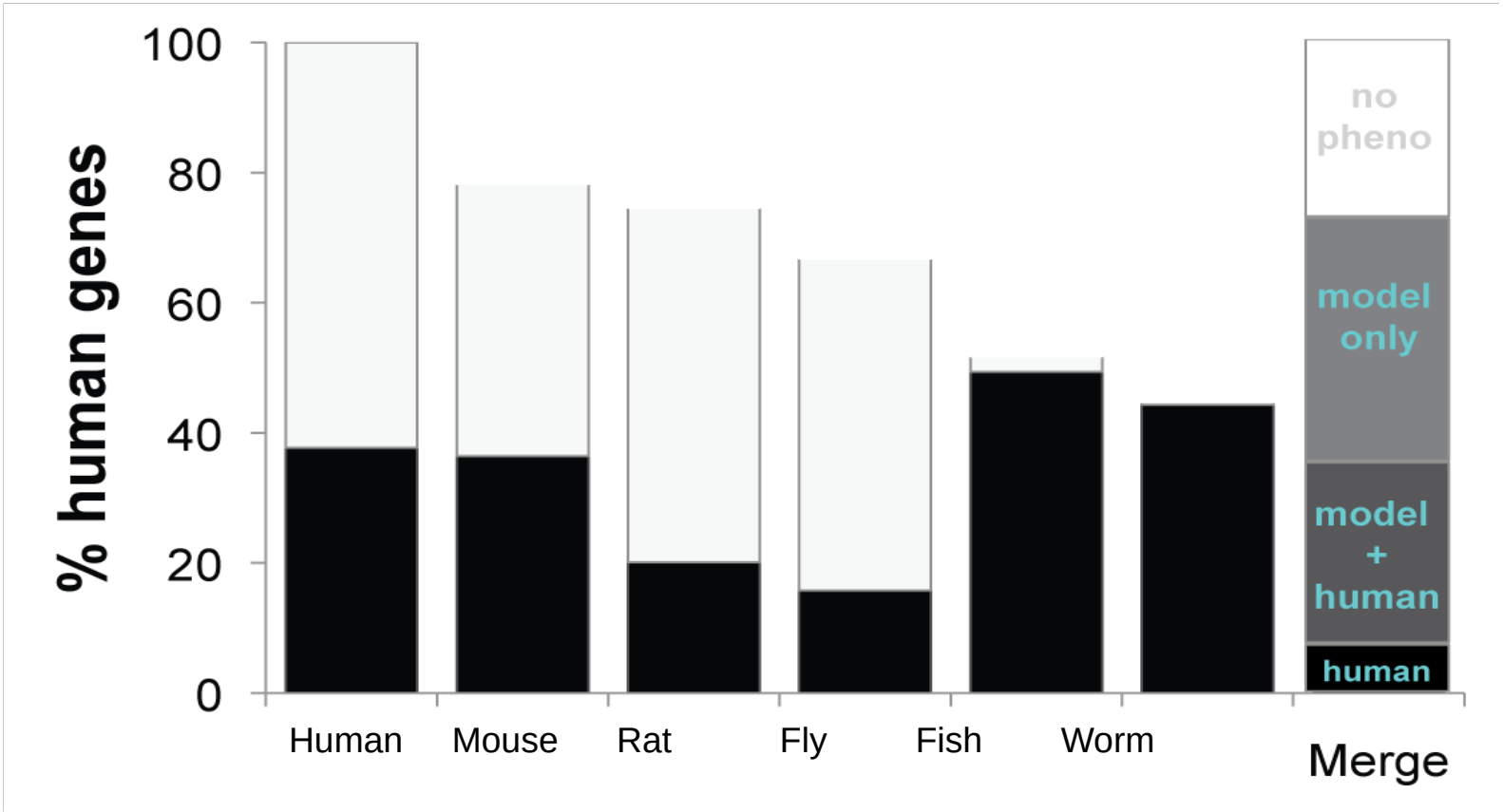
*"…a high-throughput effort to generate a comprehensive and public resource comprised of mouse embryonic stem (ES) cells containing a null mutation in 8500 mouse genes, and make them available and accessible to the entire research community..."*

*Impacts:*

- *near complete coverage of the mouse genome*
- *mostly conditional-ready alleles expressing lacZ*
- *founded International Knockout Mouse Consortium*

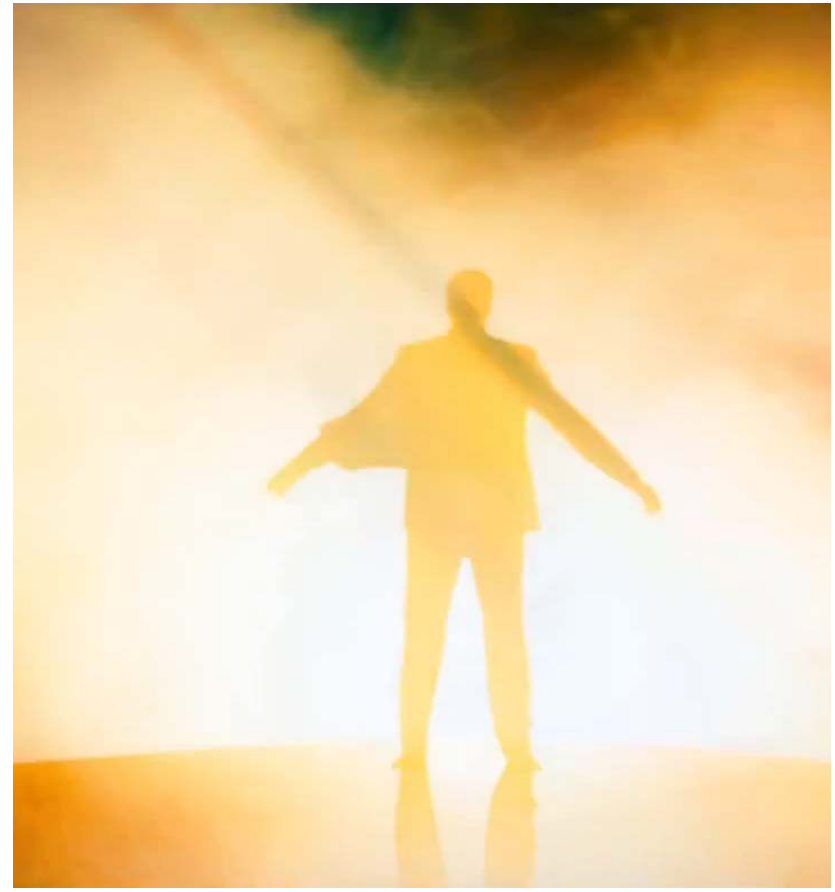
# How much phenotype data?

- Human genes have poor phenotype coverate (~35%)
- Mouse models available for ~35% of human genes
- All animal models and human phenotypes linked to >75% human genes.




Orthology via PANTHER v9

monarch INITIATIVE



National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# *Value-added features and benefits of KOMP²:*

- *Broad, genome-wide coverage*
- *Fully validated, "bench-ready" models, available at cost*
- *Harmonized and validated phenotyping protocols and procedures*
- *Facilities transparency, ensures reliability & emphasizes reproducibility*

# *Value-added features and benefits of KOMP²:*

- *Sex-balanced cohorts distinguishes male and female phenotypes*
- *Generates actionable findings of long-standing value for follow-up*
- *Creates infrastructure and processes for testing preclinical models*
- *Pushes real-time, public dissemination of products and data*

# KOMP$^2$

*"…a high-throughput, 5-year CF pilot project to produce and phenotype 2500 knockout mouse lines, and place all mice, data, and information into the public domain…"*

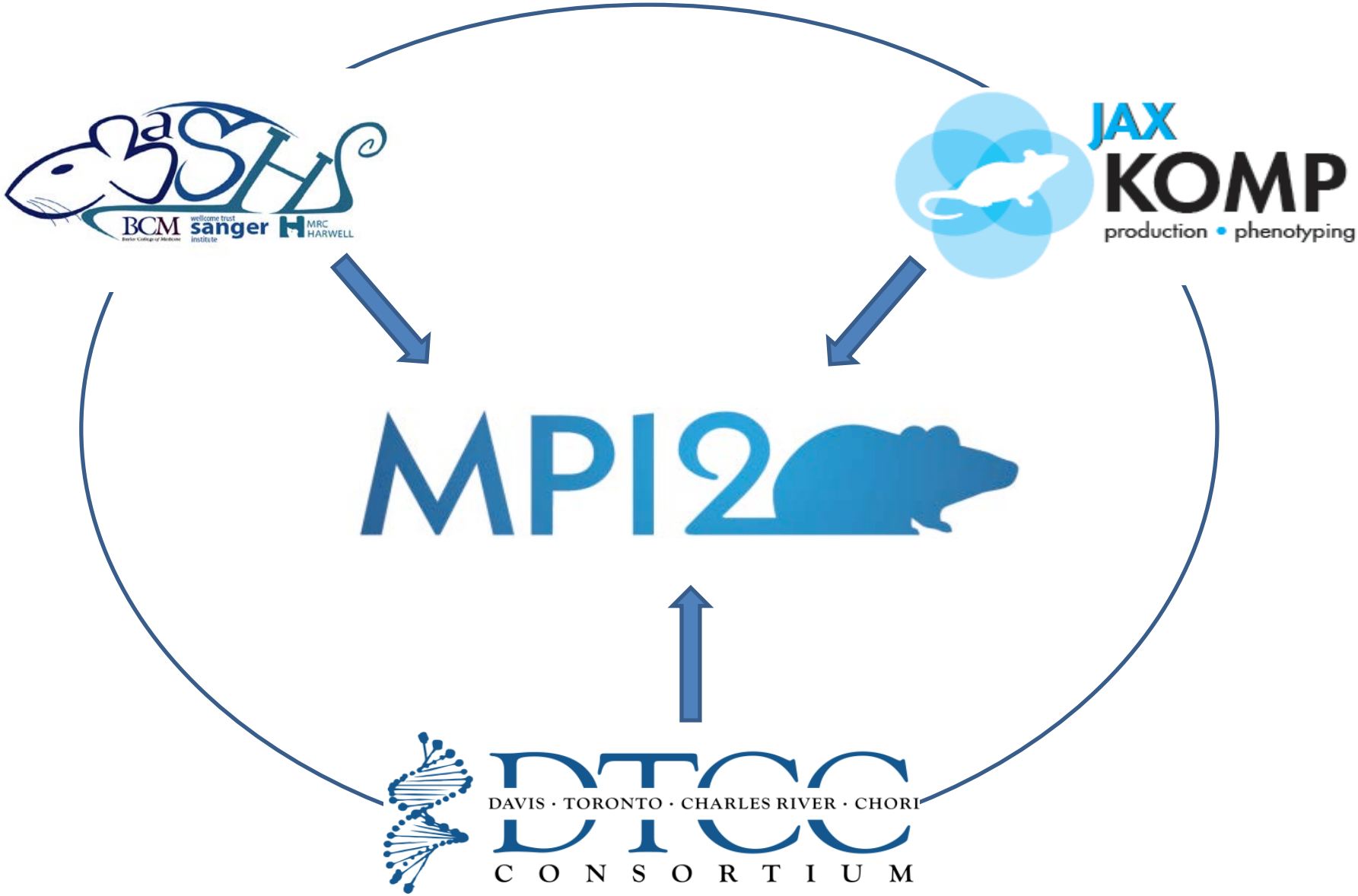
*Anticipated Impacts:*

- *functional annotation of the mouse genome*
- *pathophysiological consequences of single gene deletion*
- *associations with human disease, development, behavior*

*Nature, 2005*

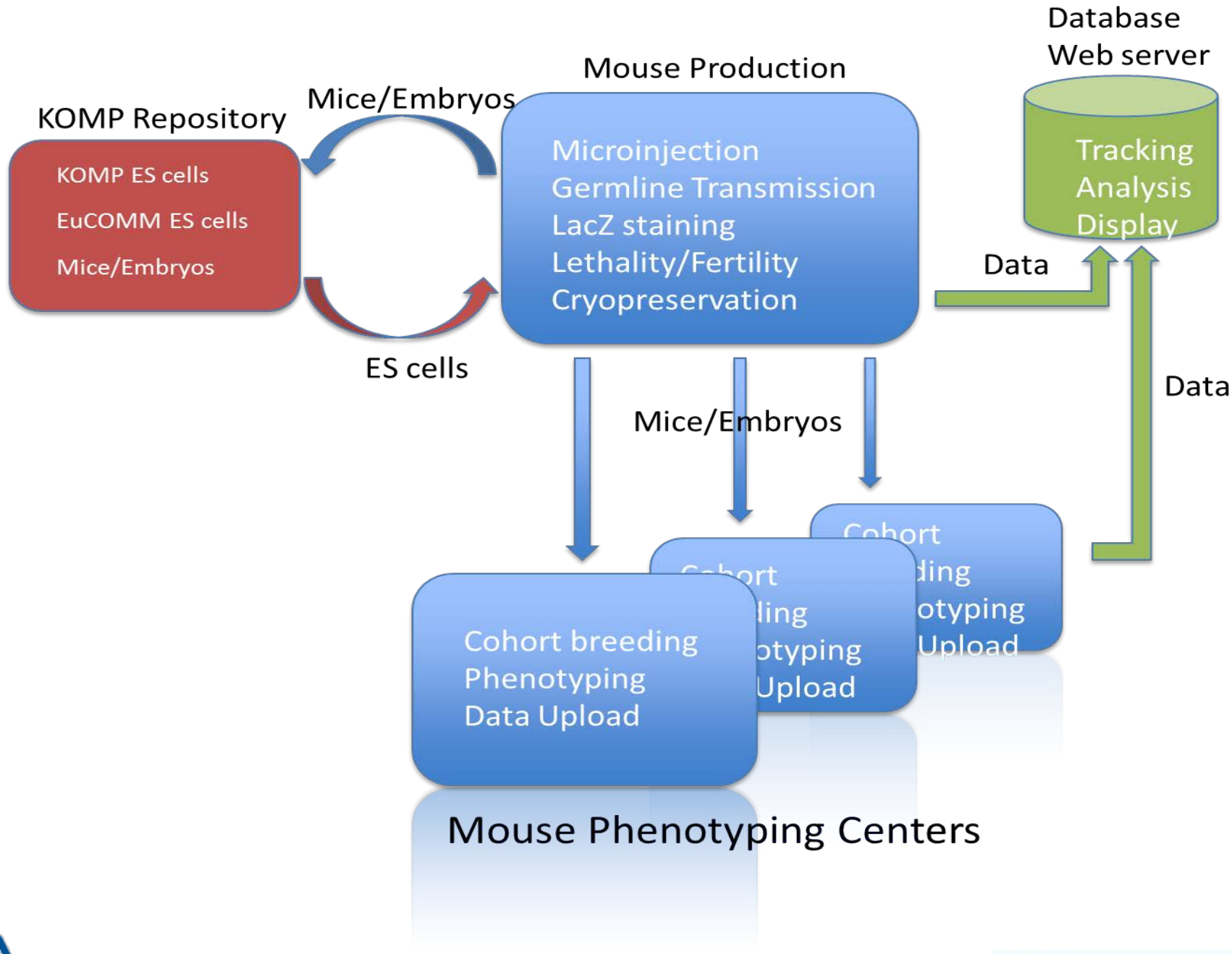
National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund




NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund


Database
Web server
Mouse Production
KOMP Repository
Mice/Embryos
KOMP ES cells
EuCOMM ES cells
Mice/Embryos
Microinjection
Germline Transmission
LacZ staining
Lethality/Fertility
Cryopreservation
Tracking
Analysis
Display
Data
ES cells
Mice/Embryos
Data
Cohort breeding
Phenotyping
Data Upload
Mouse Phenotyping Centers

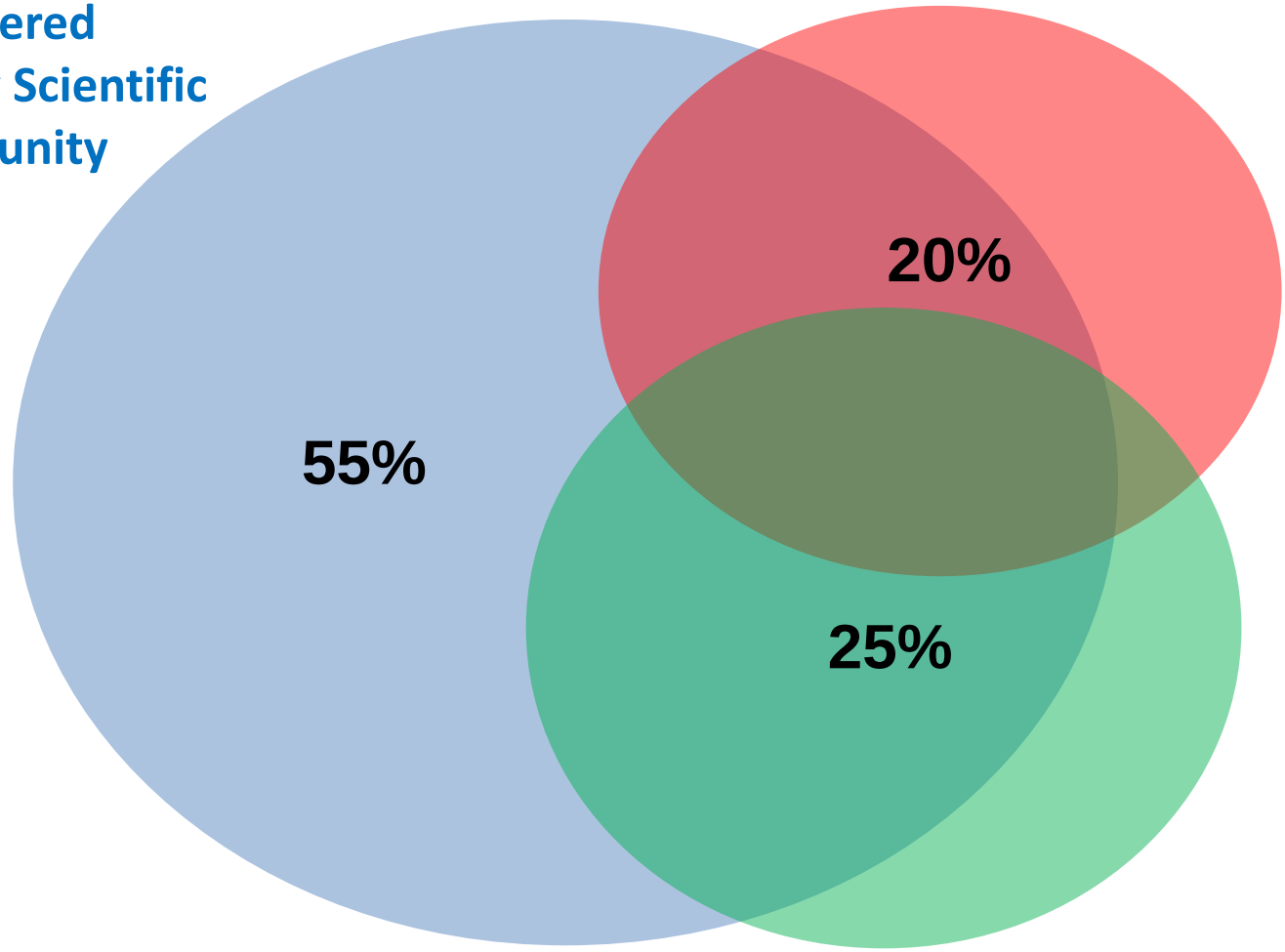
# IMPC

International Mouse Phenotyping Consortium

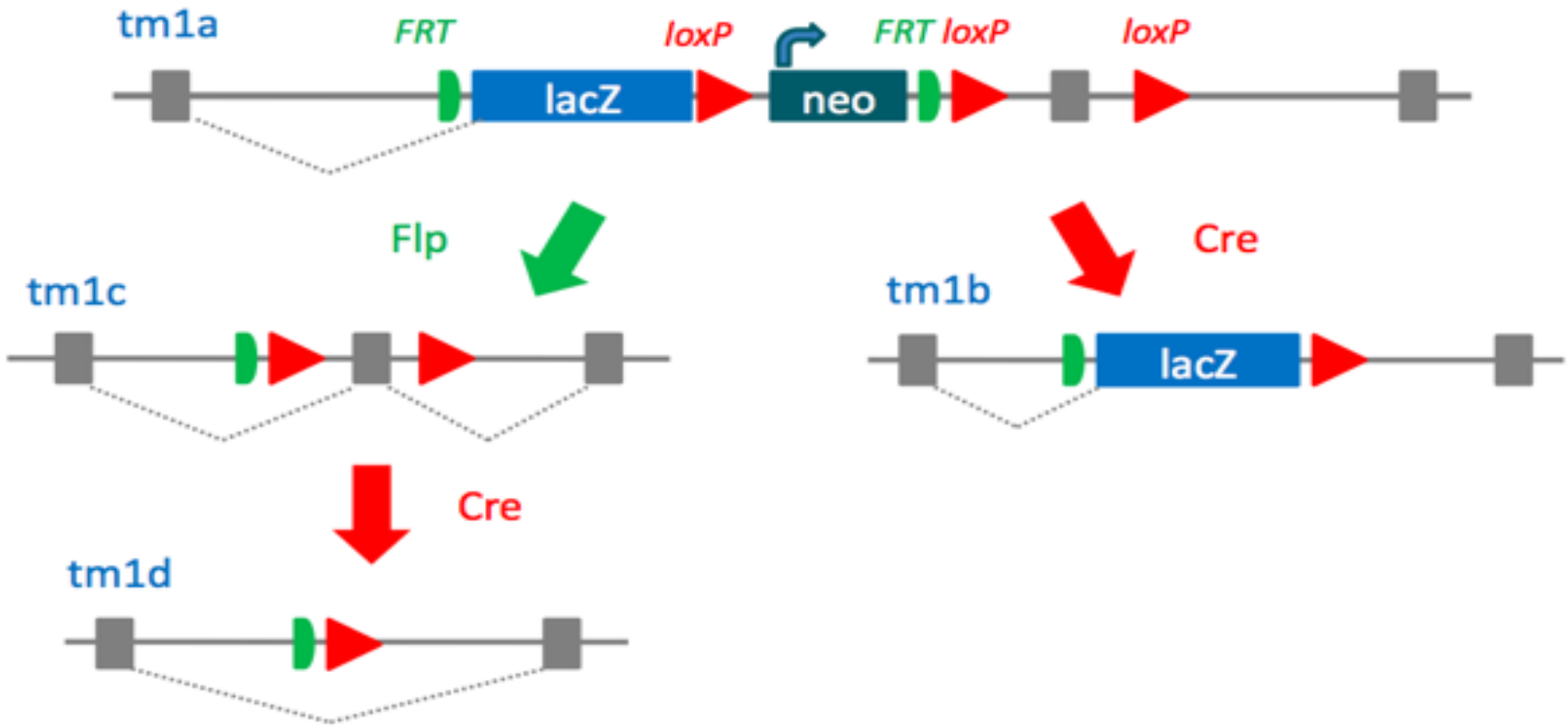

National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# *Gene selection…maximize "unknown" genes*

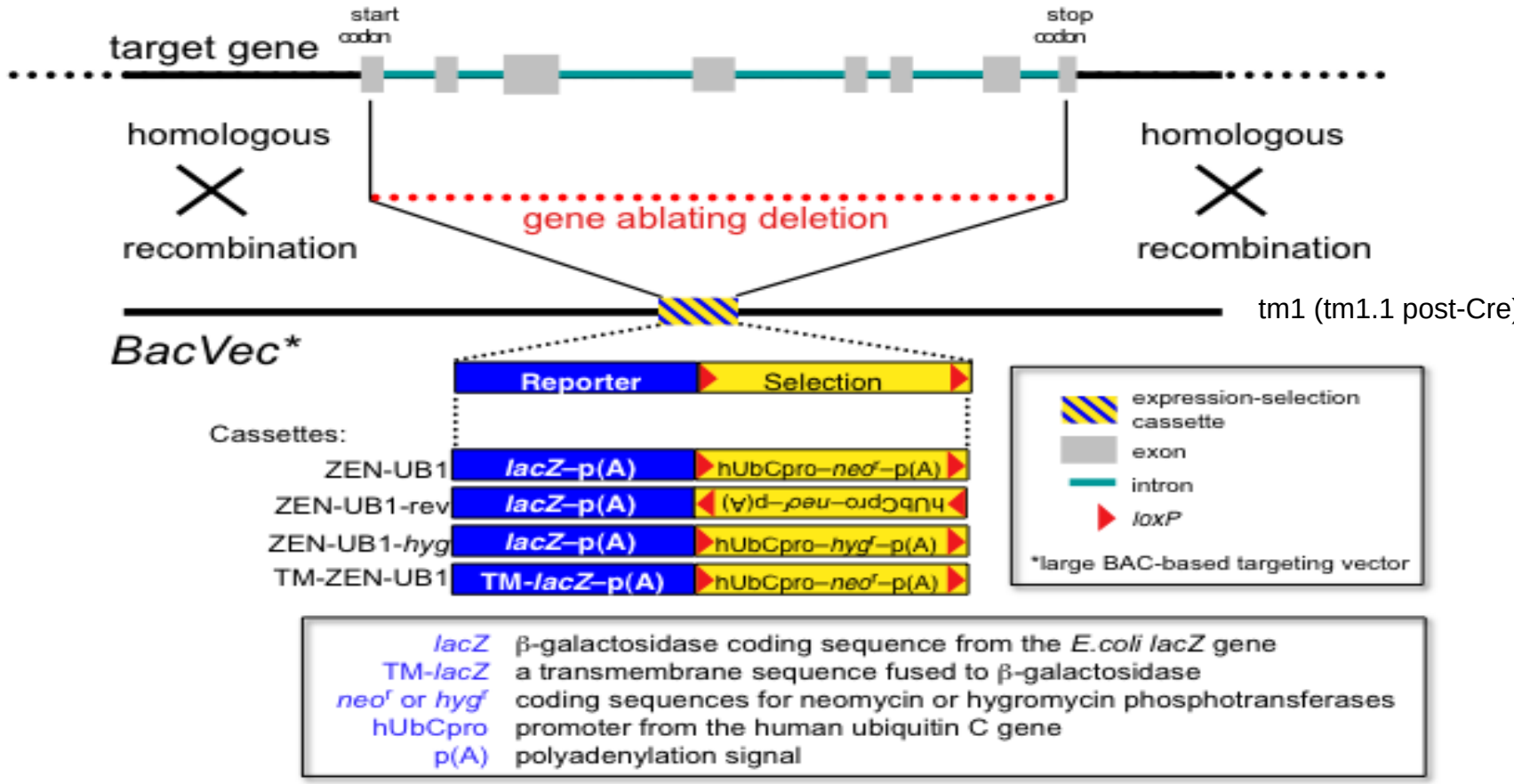


# CSD knockout-first, conditional-ready allele



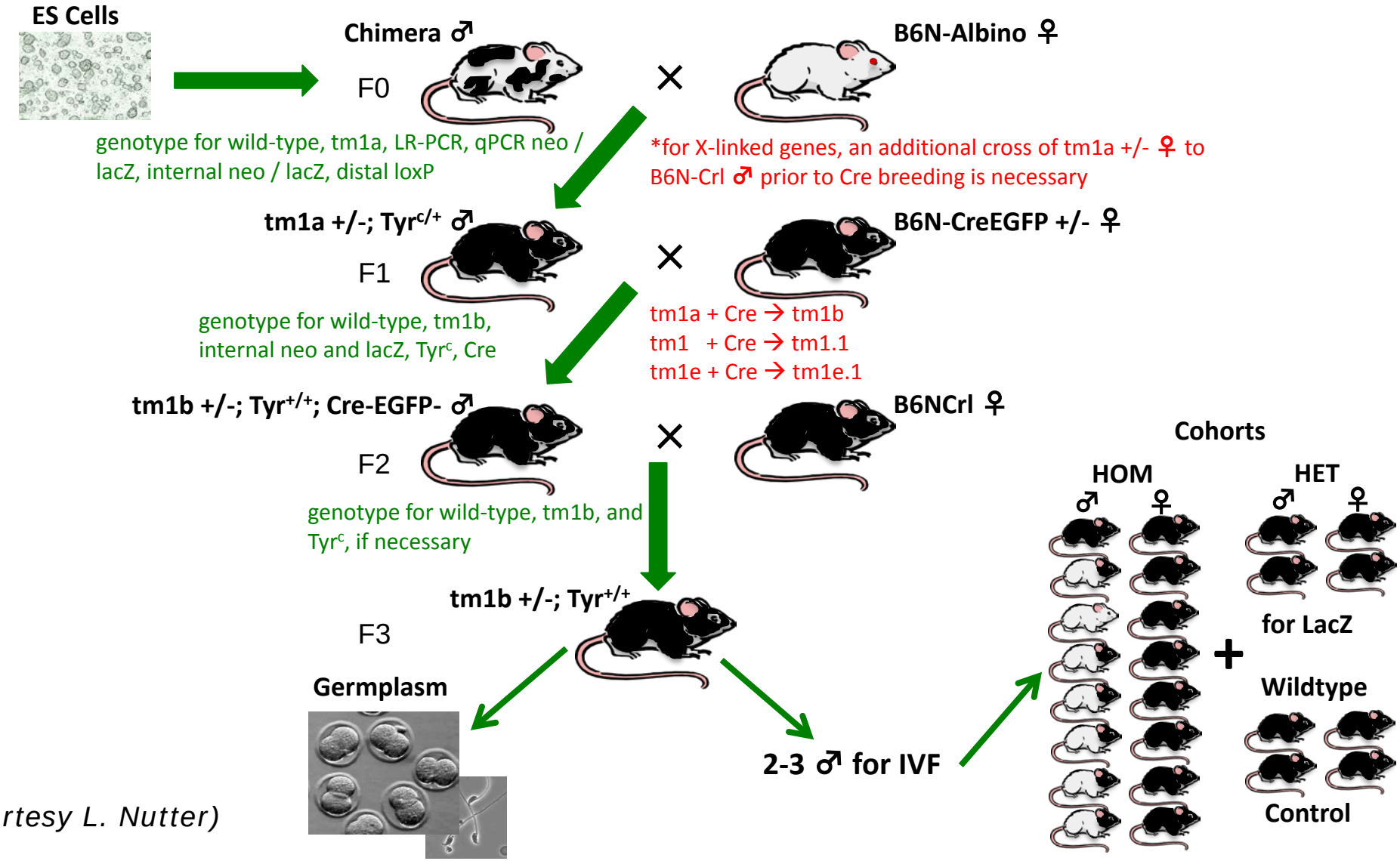

Skarnes et al., *Nature* 2011

# Regeneron VelociGene® definitive null allele




Valenzuela et al., *Nat. Biotechnol. 2013*

# Production pipeline

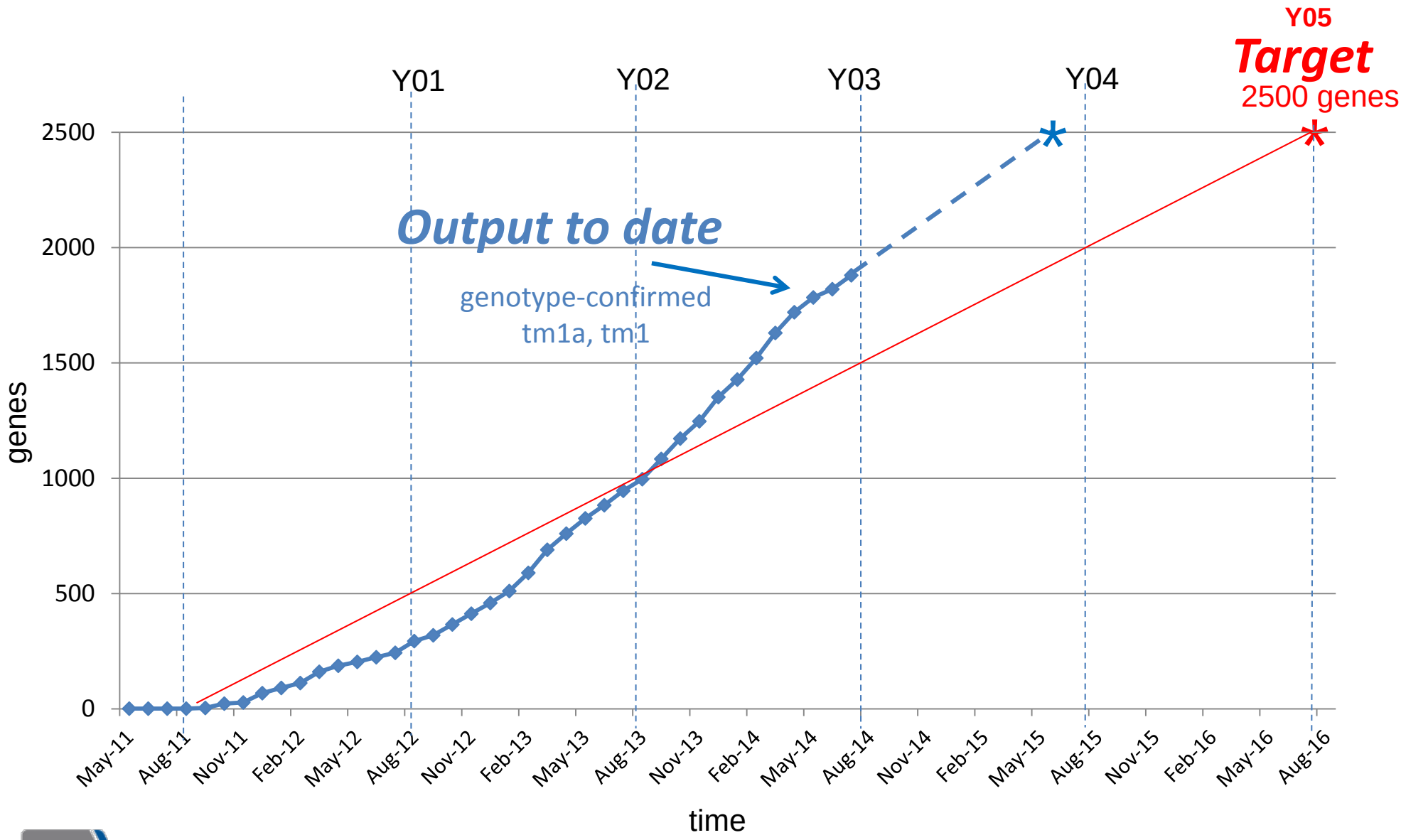



*(slide courtesy L. Nutter)*

National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# Production pipeline





NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# Gene expression by LacZ (Adult)

- tm1b or tm1.1 (post-Cre)
- Whole mount & frozen section
- Adult HETs
  - 1 M and 1 F

## Example: Mcam (Melanoma cell adhesion molecule)

- Angiogenenesis, tissue lymphocytosis, organogenesis, cell-signaling

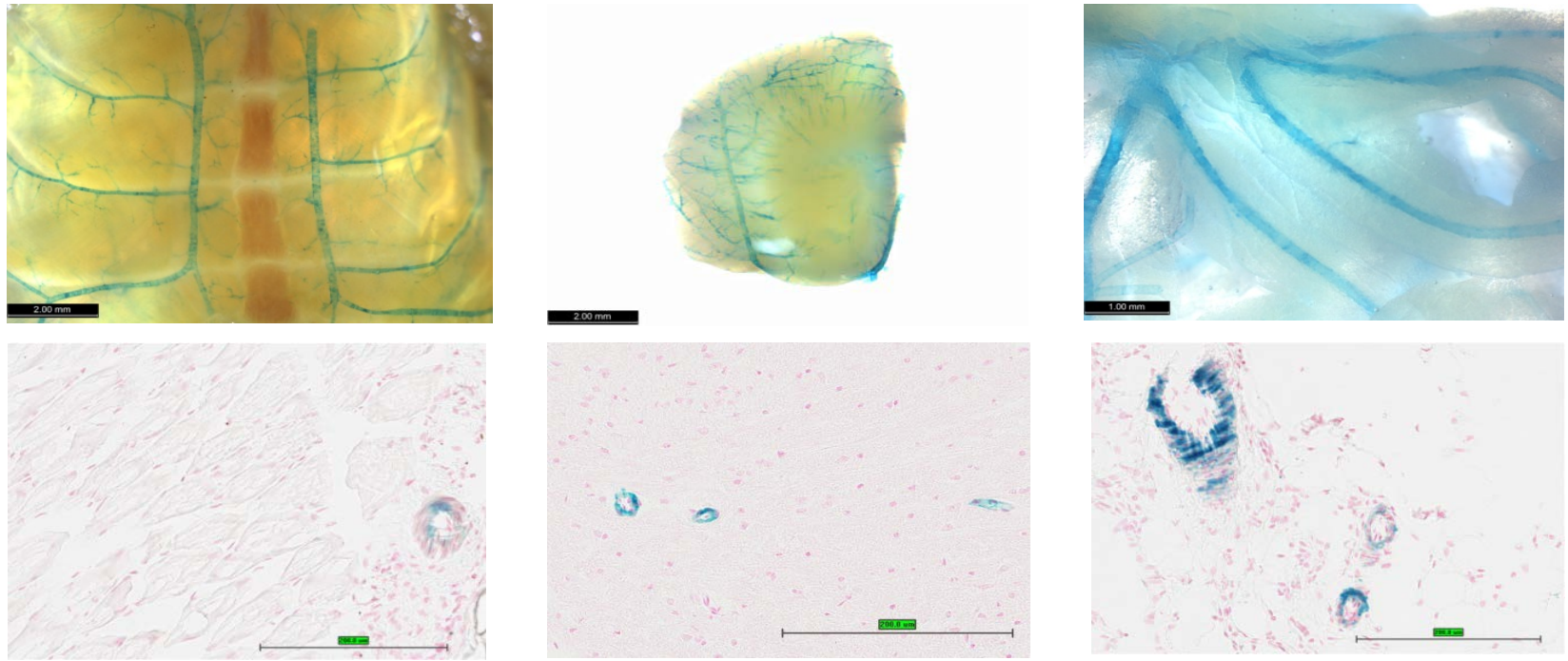
KOMP2 PHENOTYPING FINDINGS:

- No adult HOM phenotypes at $p < 0.0001$
- Ubiquitous vascular endothelium, smooth muscle (GI/GU, gall bladder)

Interpretation:

- Role beyond angiogenesis and development

Muscle | Brain | Adipose



*(data, slide courtesy KOMP2-DTCC)*

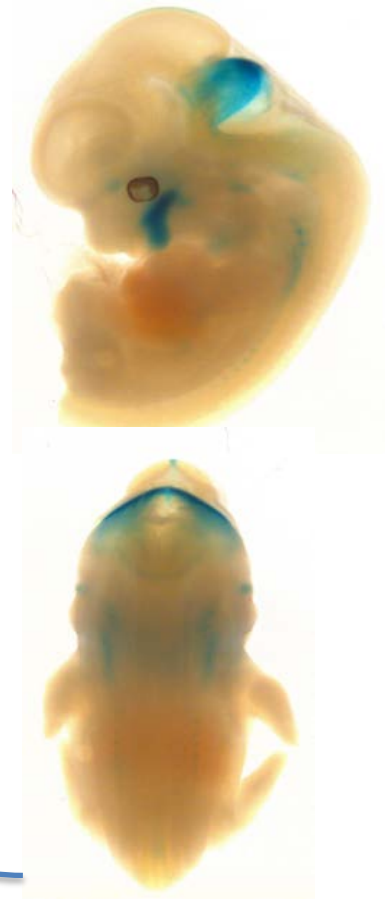
NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

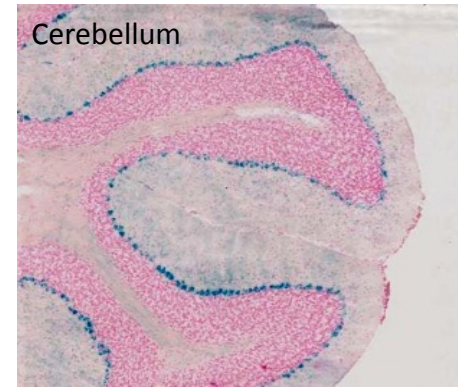
# Gene expression by LacZ (Embryo)

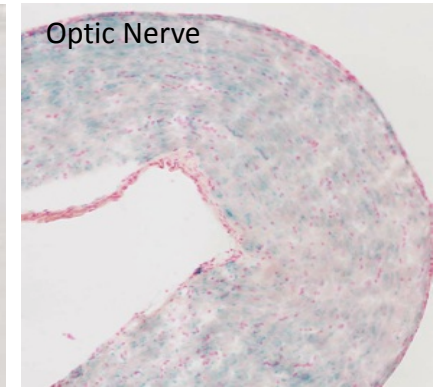
18634 B6N(Cg)-Htr1b$^{tm1.1(KOMP)Vlcg}$/J

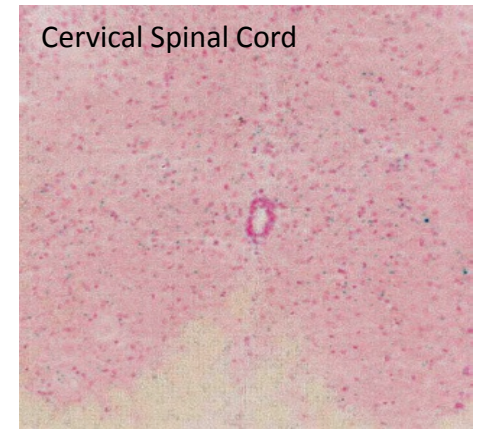
e12.5 embryo
Heterozygous

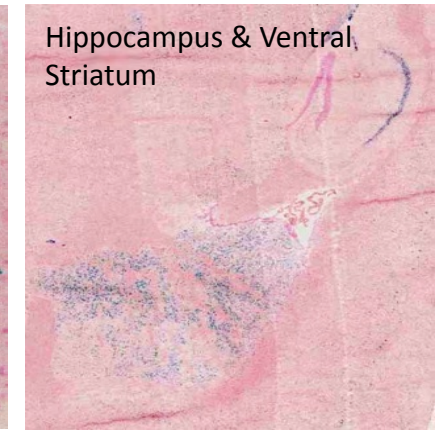


p56 Adult
Heterozygous




*(data, slide courtesy KOMP2-JAX)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

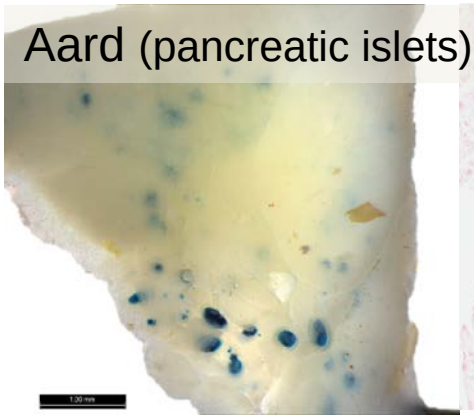
The NIH Common Fund

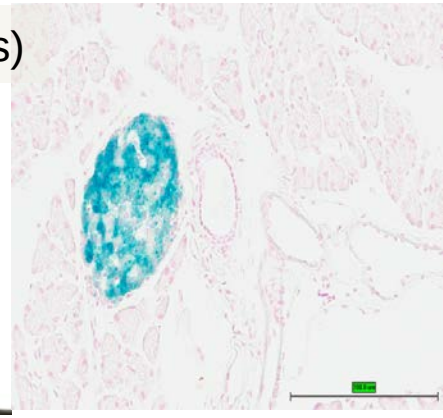
# Gene expression by LacZ

## ~80% of mutant lines show specific LacZ expression

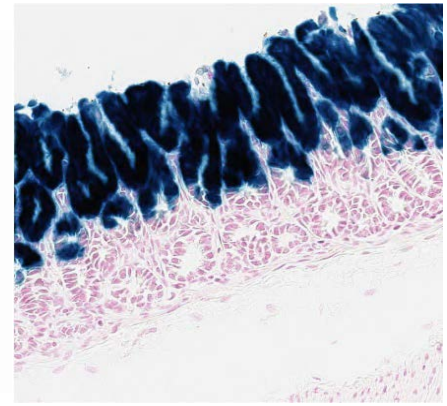
## Unique expression patterns in >20% of lines

Aard (pancreatic islets)

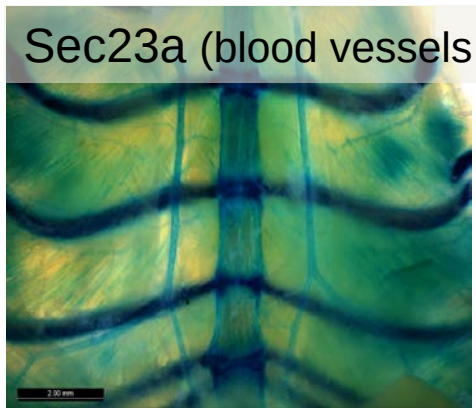


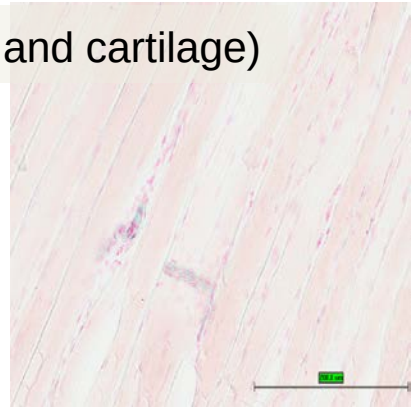


Gkn2 (gastric antrum)

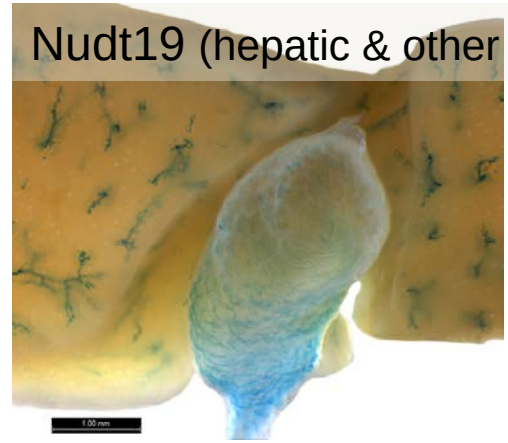


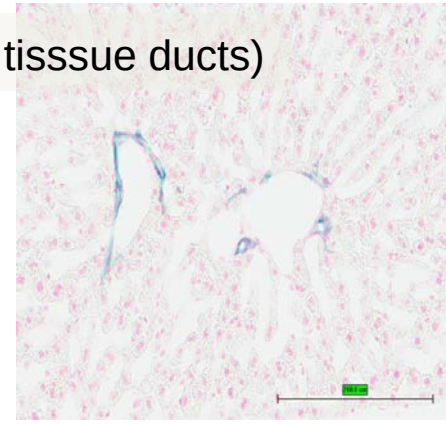
Sec23a (blood vessels and cartilage)





Nudt19 (hepatic & other tisssue ducts)





*(data, slide courtesy KOMP2-DTCC)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

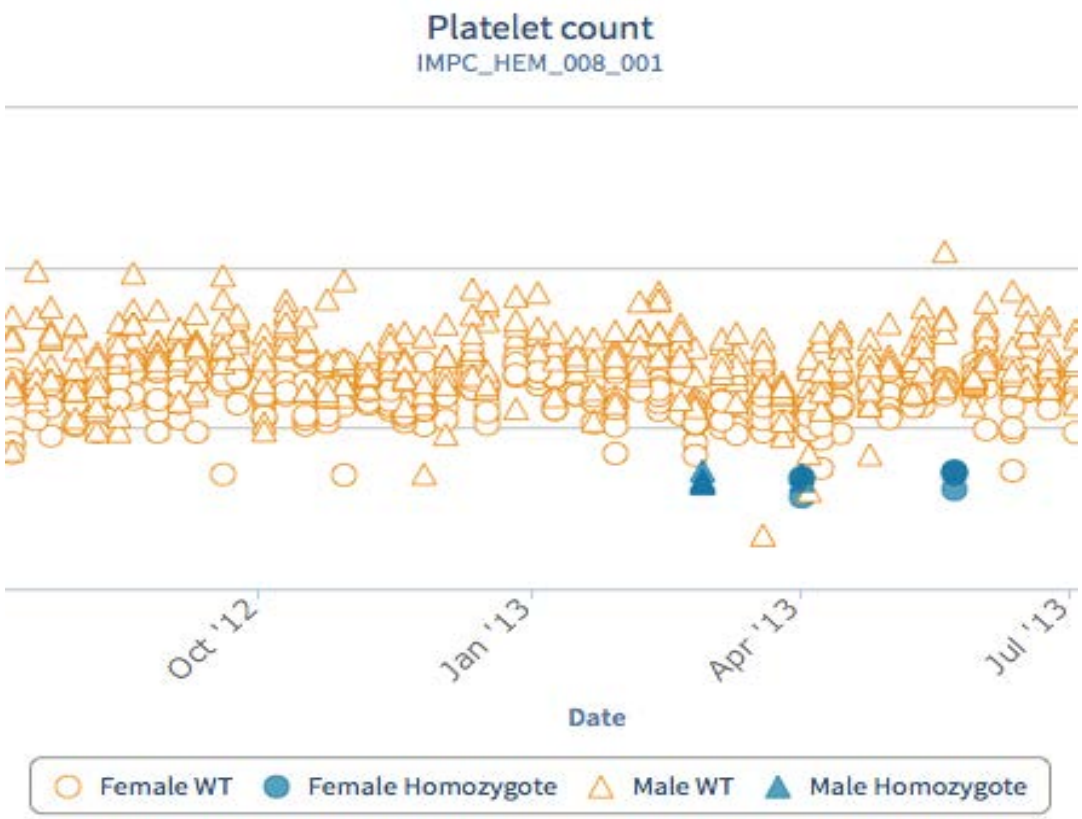
# Adult phenotyping pipeline

## Output to date

- *IMPC adult core pipelines established and operational at IMPC centers*
- *Baseline control data uploaded to Data Coordination Center (DCC)*
- *Preliminary QC'd phenotyping data on ~1200 mutant lines (IMPC)*
- *All KOMP$^2$ Centers processing ~15-16/week to complete by August 2016*

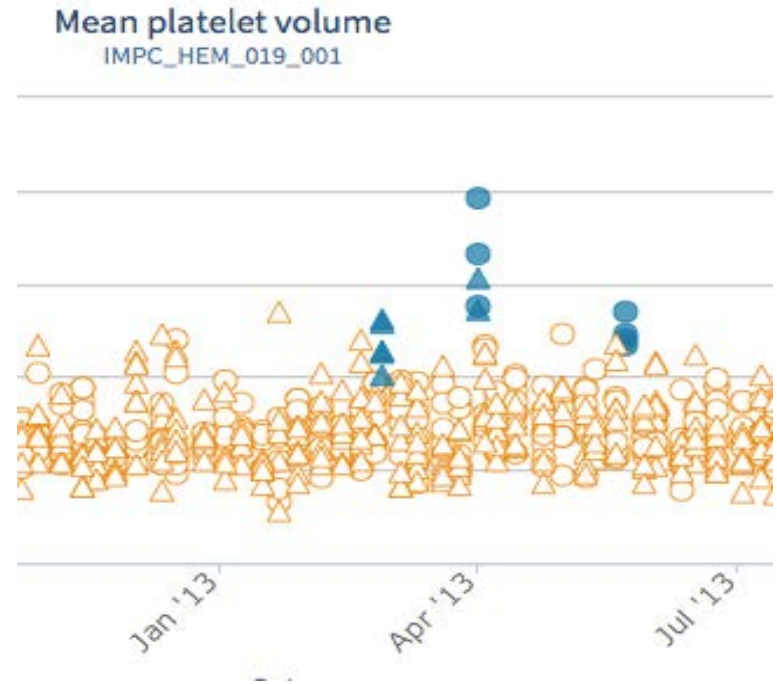
# Case Study: Gene with known disease

Nbeal2 (Neurobeachin-like 2): “Grey Platelet Syndrome”




## KOMP2 Phenotyping:

- Reduced platelet count
- Enlarged platelets



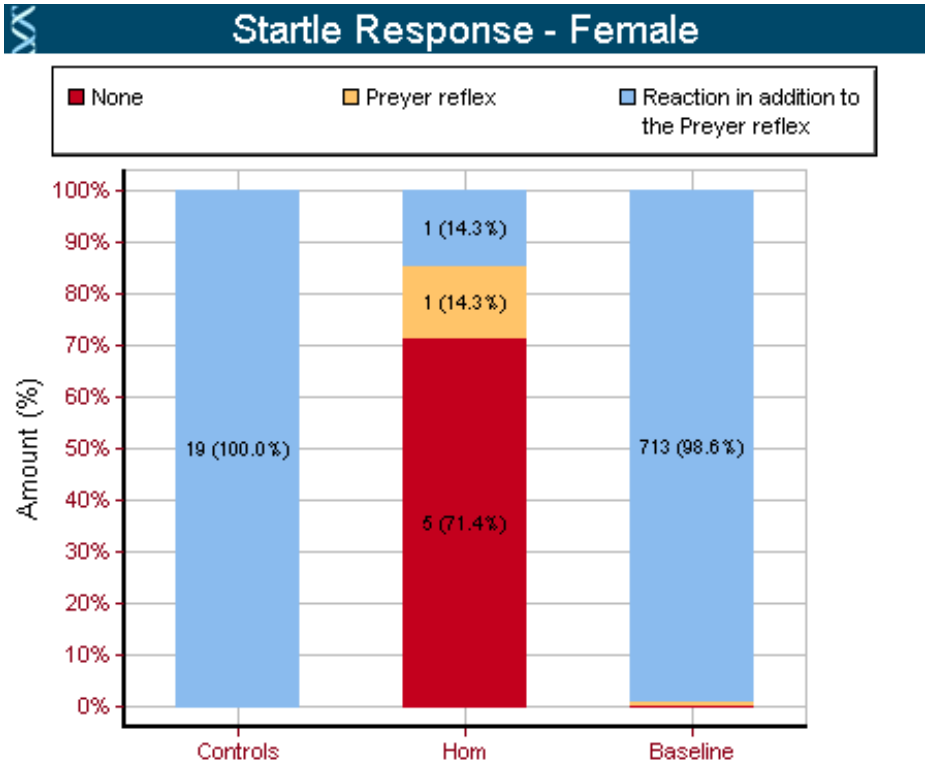

*(slide courtesy MPI2)*

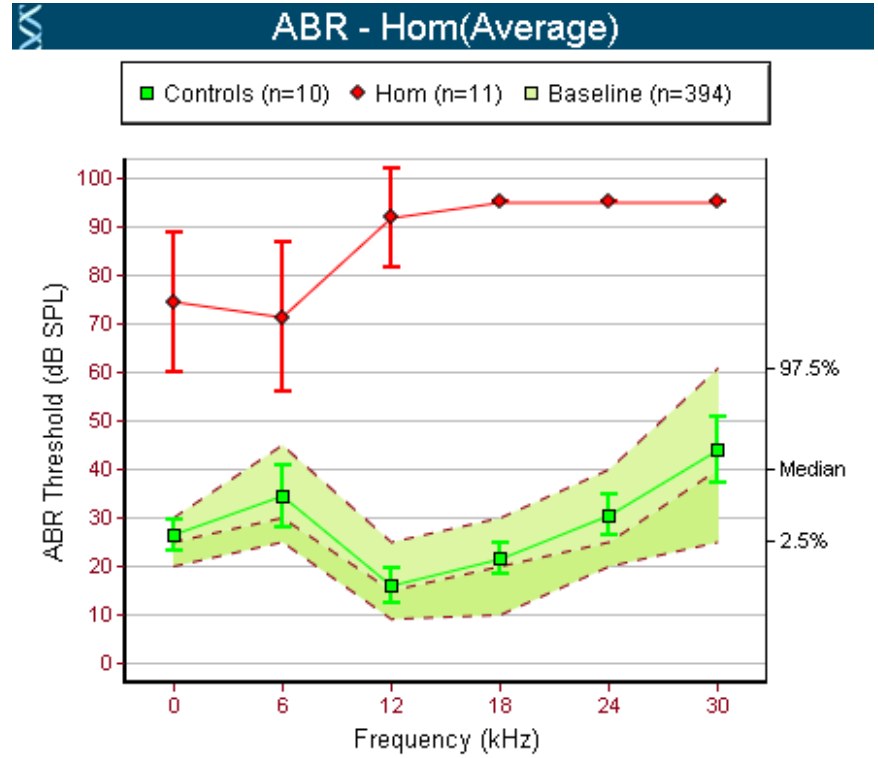
# *Case Study: Gene with no known disease*

Zfp719 (Zinc finger protein 719): no phenotypic associations in mouse or human

KOMP2 Phenotyping:

- Abnormal acoustic startle
- Elevated ABR response
- Significant hearing loss




*(data courtesy KOMP2-BaSH; Ramiro Ramirez-Solis PhD)*

National Institutes of Health
Office of Research Infrastructure Programs

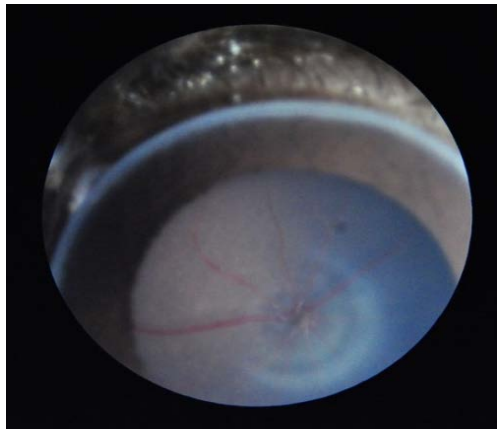
The NIH Common Fund

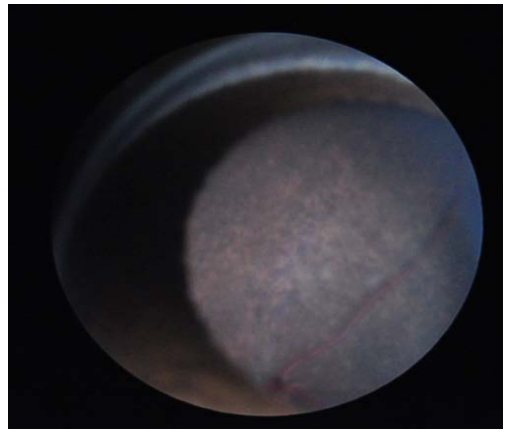
# *Case Study: Gene with unknown function*

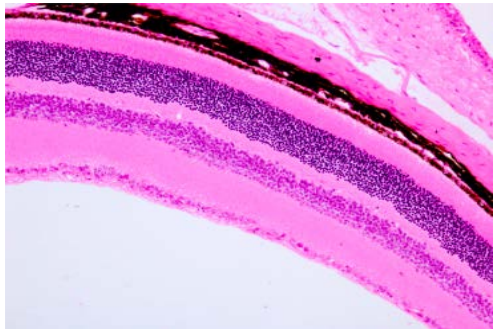
Fam151b (family with sequence similarity 151, member “B”): “uncharacterized”

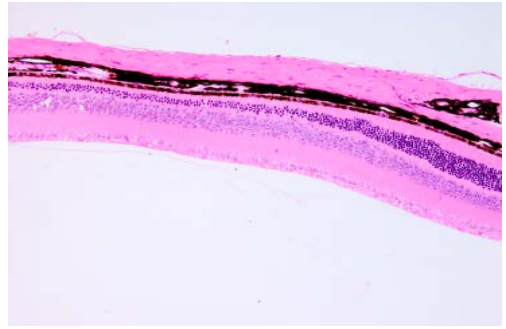
Wildtype

Fam151b$^{-/-}$









## KOMP2 Phenotyping:

- Retinal atrophy
- Reduced outer nuclear layer

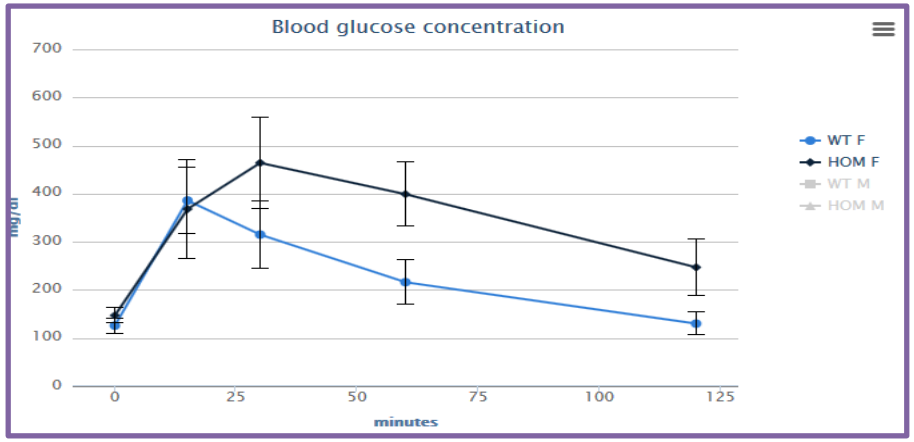
↓

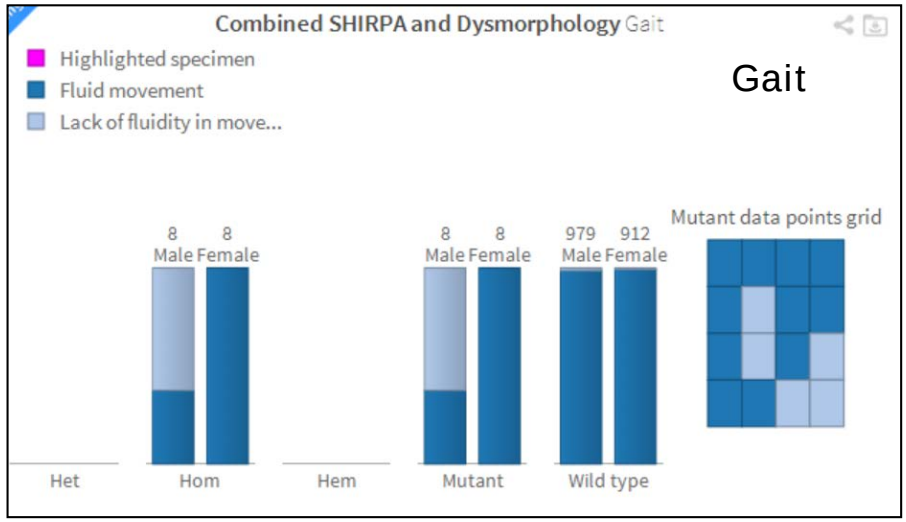
photoreceptor deficit

*(data, slide courtesy Harwell)*

# Case Study: Known gene/first mouse model

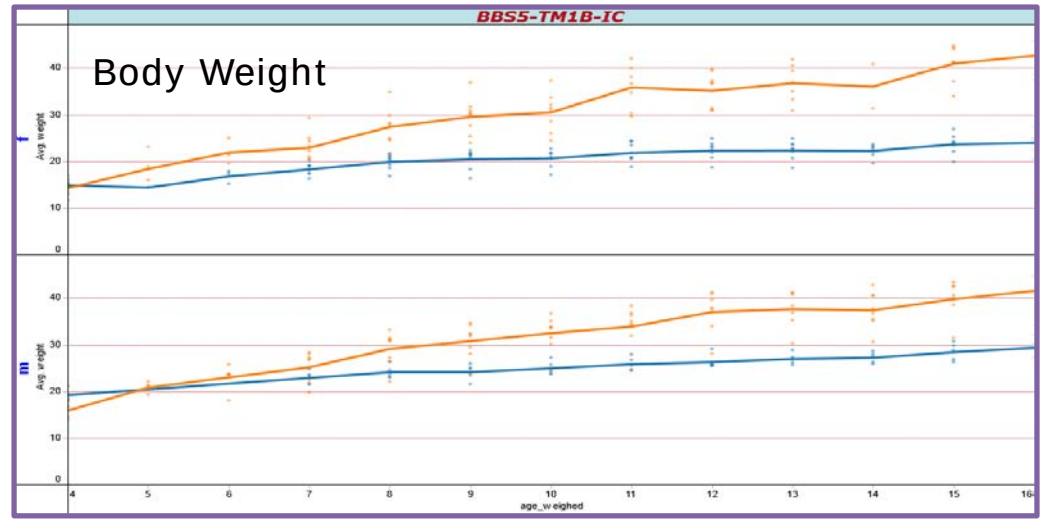
Bbs5 (Bardet-Biedl Syndrome): No previous KO model




## KOMP2 Phenotyping:

- Abnormal gait
- Obesity
- Glucose metabolism




*(data, slide courtesy Harwell)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

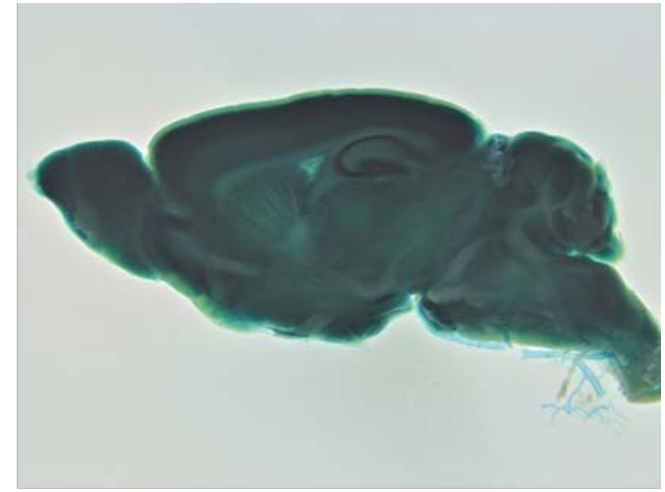
The NIH Common Fund

# *Case Study: Known gene, revised mouse model*

Atn1 (atrophin 1): Dentatorubral-pallidoluysian atrophy


## KOMP2 Phenotyping:

- Abnormal gait
- Limb grasping
- CNS expression E12.5; ubiquitous adult



*(data, slide courtesy Harwell)*

NIH National Institutes of Health
*Office of Research Infrastructure Programs*

The NIH Common Fund

# Case Study: Known gene/new phenotype

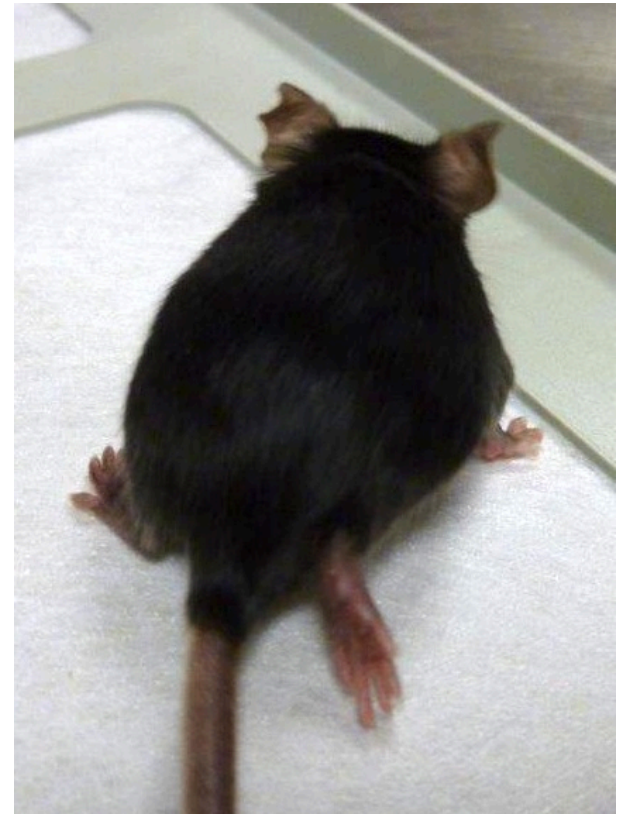
Cast (calpastatin): calpain/calpastatin system; inhibits myoblast fusion, gene expression

## KOMP2 Phenotyping:

- Longbone (tibia) malformation defect

14 wks

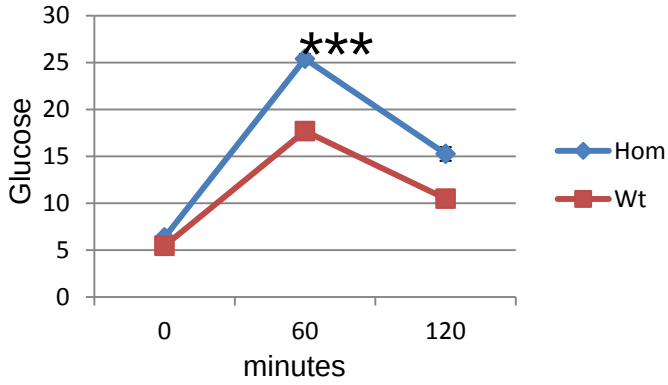
8 wk

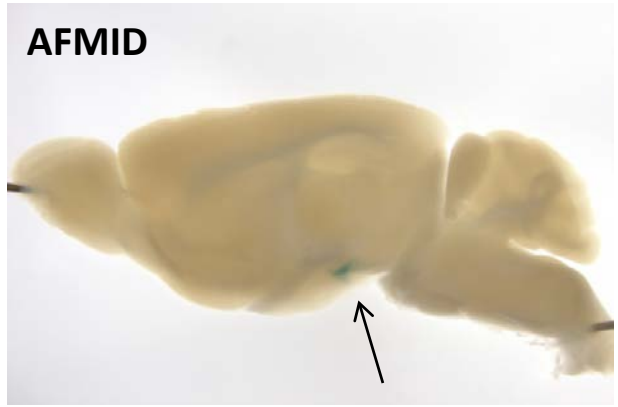


*(data, slide courtesy KOMP2-JAX)*

# Case Study: Known gene/new male phenotype

Afmid (arylformamidase): liver and kidney expression, glomerulosclerosis




## KOMP2 Phenotyping:

- Male-specific hyperglycemia
- Hypothalamic LacZ expression suggests endocrine function

↓

Secondary & tertiary phenotyping by scientific interest group who confirmed a progressive diabetic phenotype not previously described in other mouse KO models of this gene.

*(data, slide courtesy Harwell)*

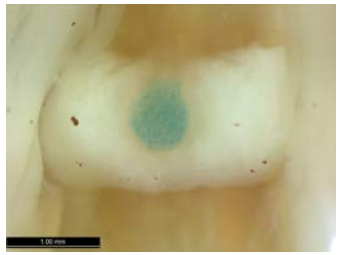
# *Case Study: Known gene/new female phenotype*

Ccdc33 (coiled-coil domain containing 33): testis, spermatogenesis, peroxisomal protein

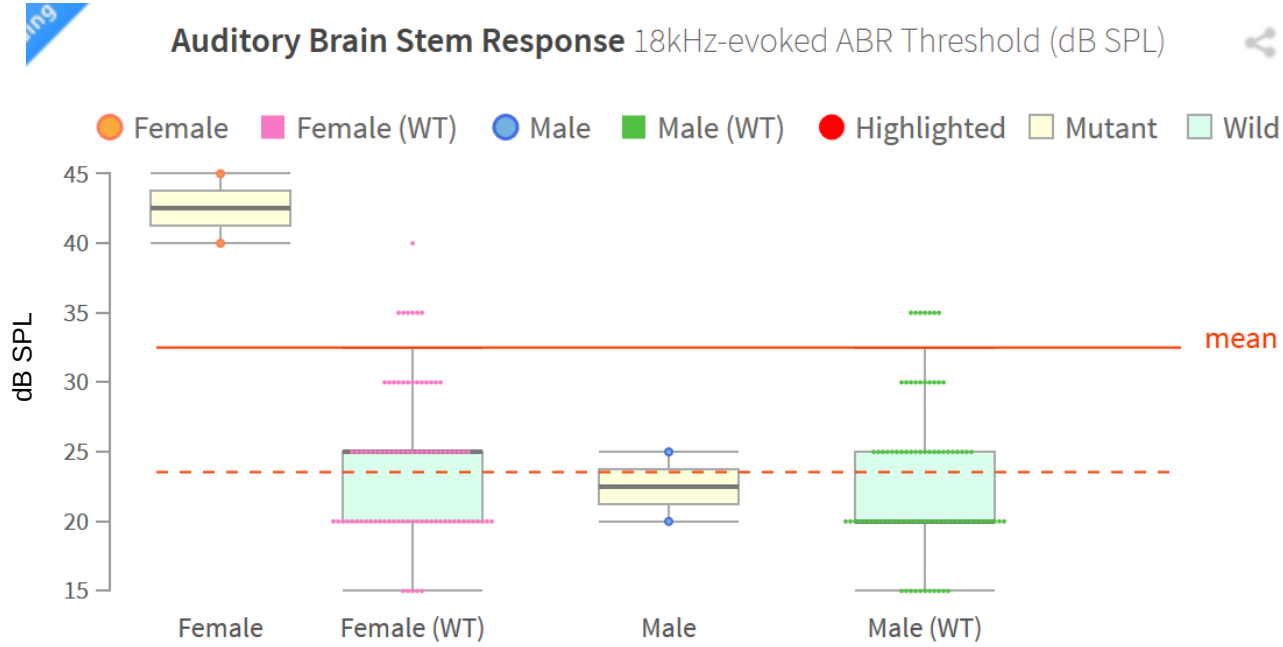
KOMP2 Phenotyping:

- Increased auditory brain stem response
- Female-specific hearing loss

Testis (male)



Pituitary (both sexes)




*(data, slide courtesy KOMP2-DTCC)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

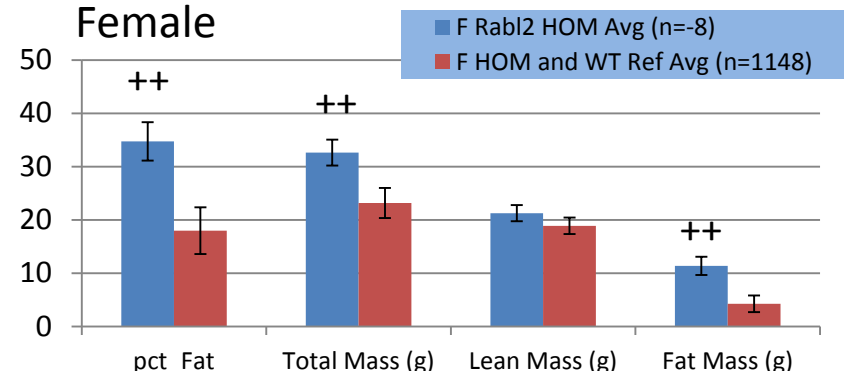
# Case Study: Known gene, pleiotropic effects

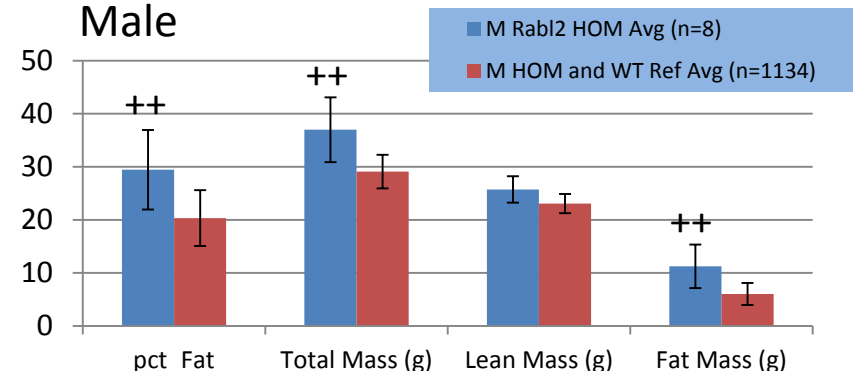
Rabl2 (RAS oncogene family-like 2): male infertility

KOMP2 Phenotyping:

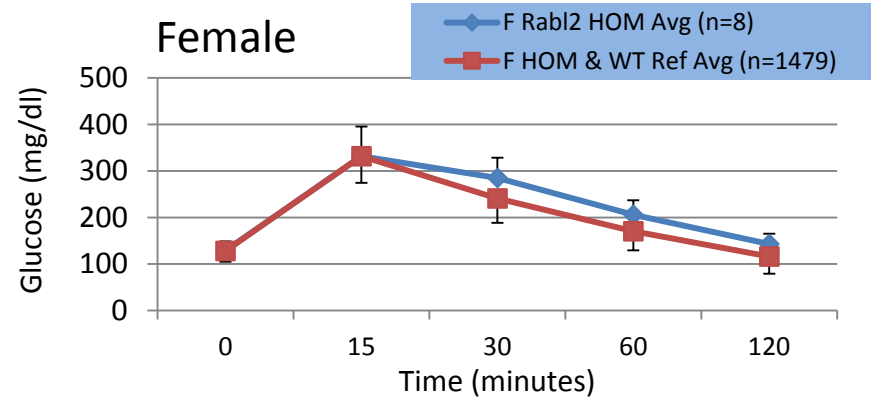
- Polydactyly
- Increased body fat
- Impaired GTT (male)

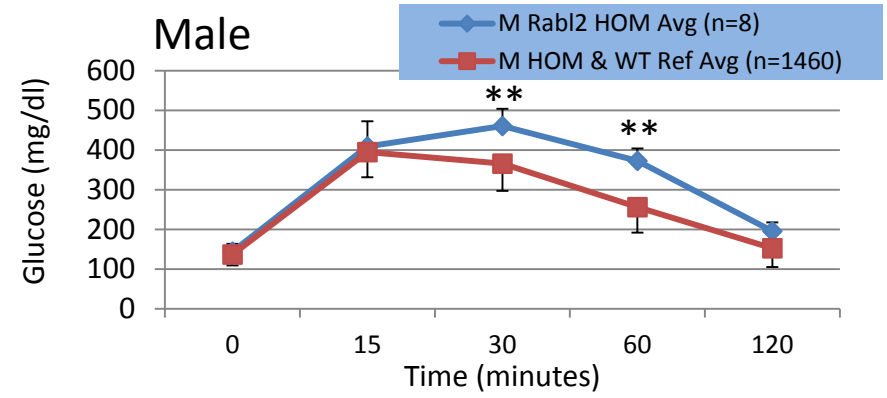
DEXA




IPGTT (blood glucose)



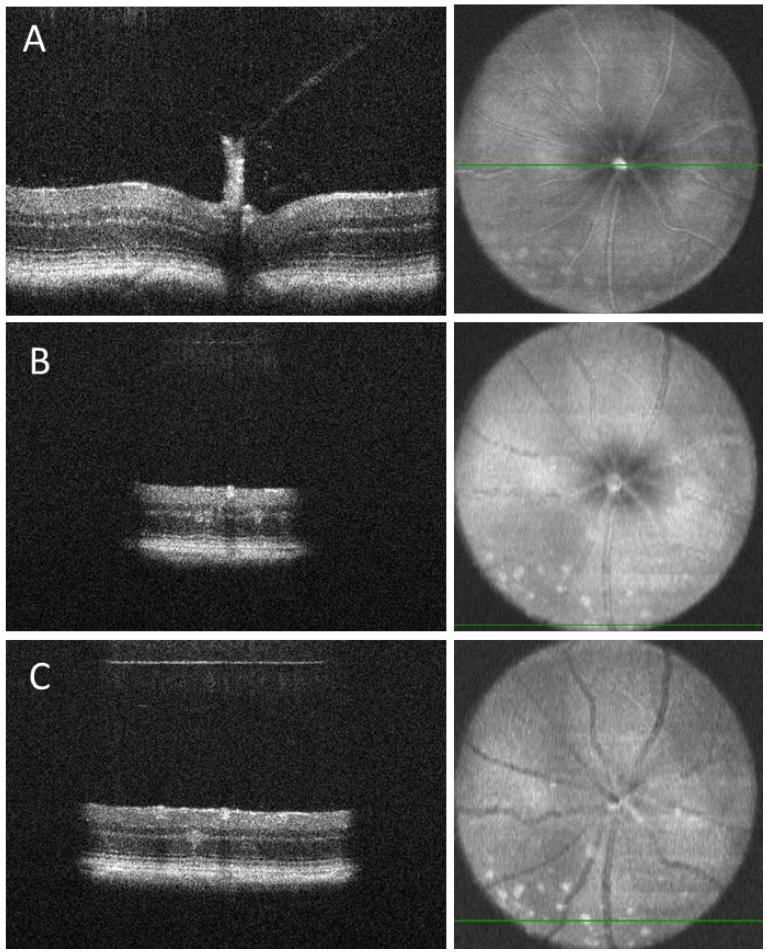

*(data, slide courtesy KOMP2-DTCC)*


NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# *Case Study: Known gene/new pleiotropic effects*

Tead1 (TEA domain family member 1): notochord development, cell proliferation, survival, Sveinsson's chorioretinal atrophy/helicoid peripapillary chorioretinal degeneration




## KOMP2 Phenotyping:

A. Retinal B-scan and corresponding fundus volume intensity projection (VIP) of left eye. Faint spotting visible in fundus
B. Frame 3 of sample in A, showing early rosettes/dysplasia on B-scan and spotting of fundus on VIP
C. Frame 10 of sample in A showing increased rosettes/dysplasia and increased spotting

*(data, slide courtesy KOMP2-BaSH; Mary Dickinson, PhD)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# Case Study: Known gene/complex phenotype

Galc (galactosylceramidase):

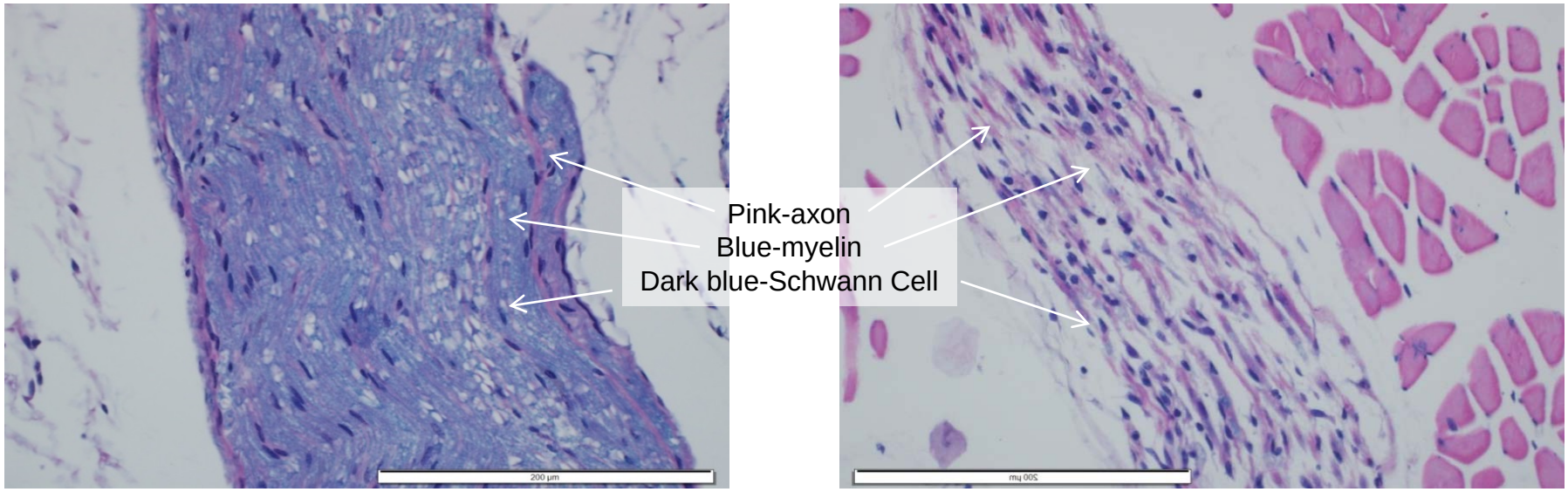
knockout mice: tremors, twitching, paralysis, death @ 7 wks

humans: “Krabbe Disease”, Globoid Cell Leukodystrophy

*KOMP2 conditional allele enable refined study of disease mechanism*

Wildtype

Galc$^{-/-}$

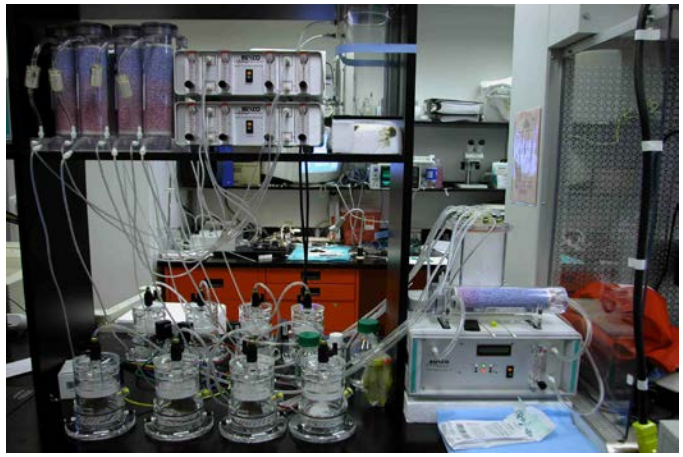



*Peripheral nerve of skeletal muscle stained with Luxol fast blue*

*(data, slide courtesy KOMP2-DTCC)*

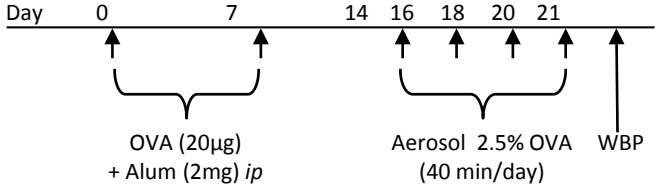
# Challenge Pipeline

Unsensitized and MCh-challenge screen:



**Mutants (6F + 6M)**

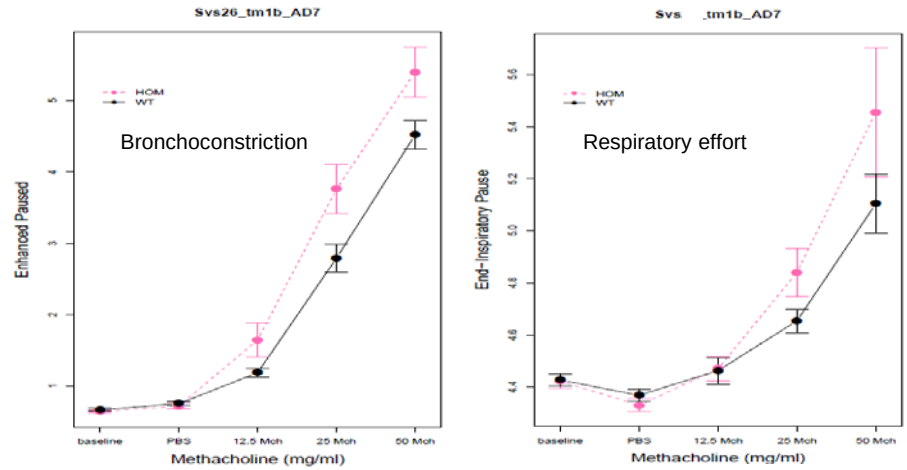
**WT Controls (2F + 2M)**



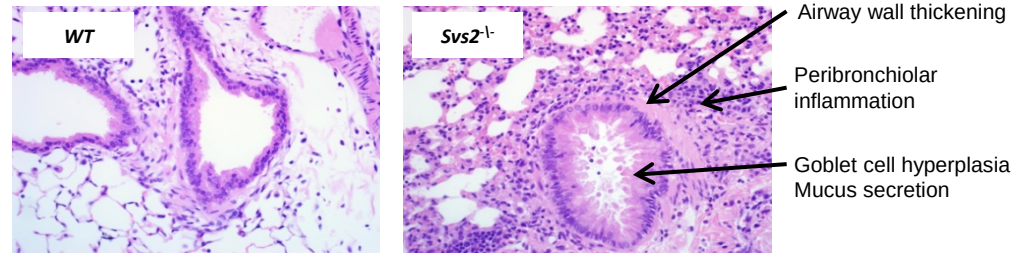

## Svs2

- Seminal vesicle secretory protein 2
- GO: fertilization, sperm capacitation

**Respiratory Function, Lung Development, and Airway Hyper-reactivity**




**Histopathology (allergic airway disease)**




**BAL (Inflammatory Cells, Cytokines)**
**Serum Ig (OVA-specific IgE & OVA-specific $IgG_1$)**
**Sample analysis in progress**

*(data, slide courtesy KOMP2-DTCC)*


NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

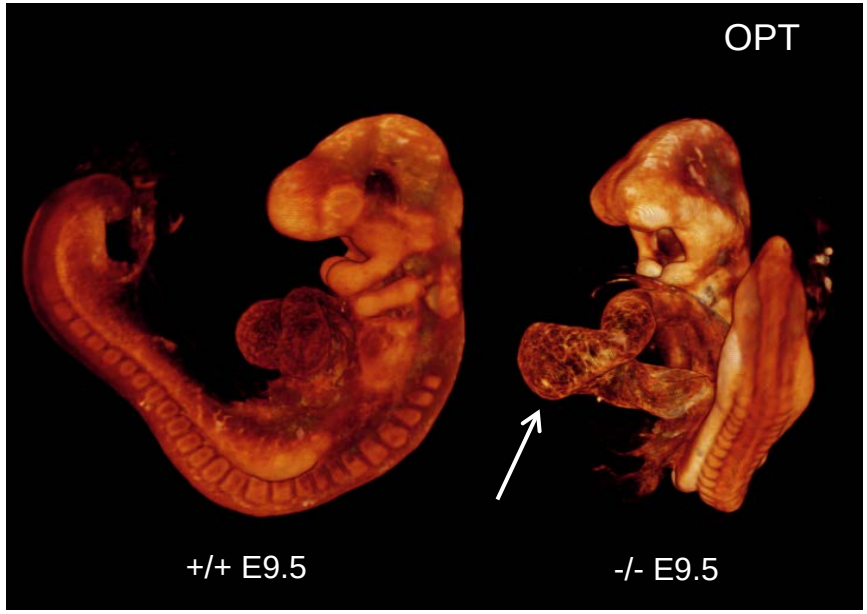
# *Embryo/Subviable phenotyping pipeline*

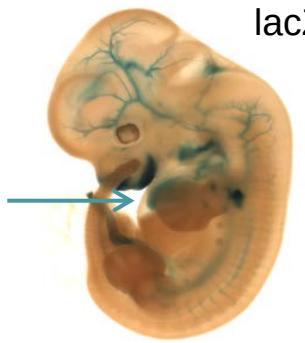
## *Output to date*

- *IMPC pilots suggest ~30% rate of homozygous lethal knockouts*
- *KOMP2 Centers all established embryo/subviable pipeline*
- *Triage pipeline according to Bloomsbury Report, 2012:*
  *Viability, Gross Morphology, Histopathology, 3D Imaging*
- *Data and image capture procedures per stage established*
- *Data collection and validation underway*

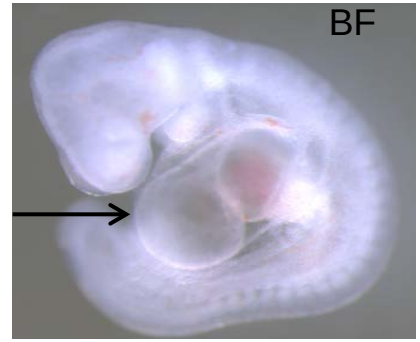
# Embryo phenotyping pipeline

Tmem100$^{tm1e.1(KOMP)Wtsi}$




+/- E12.5




-/- E9.5

**<u>Transmembrane Protein 100</u>** – BMP/ALK1 signaling pathway

## <u>KOMP2 Phenotyping</u>:

HOM lethal at E12.5 – lacZ in arterial endothelium, heart (arrow)

HOM viable at E9.5 – large pericardial effusion (arrow) and cardiac dsymorphology, enlargement (brightfield) and OPT (arrow)

*(data, slide courtesy KOMP2-DTCC)*

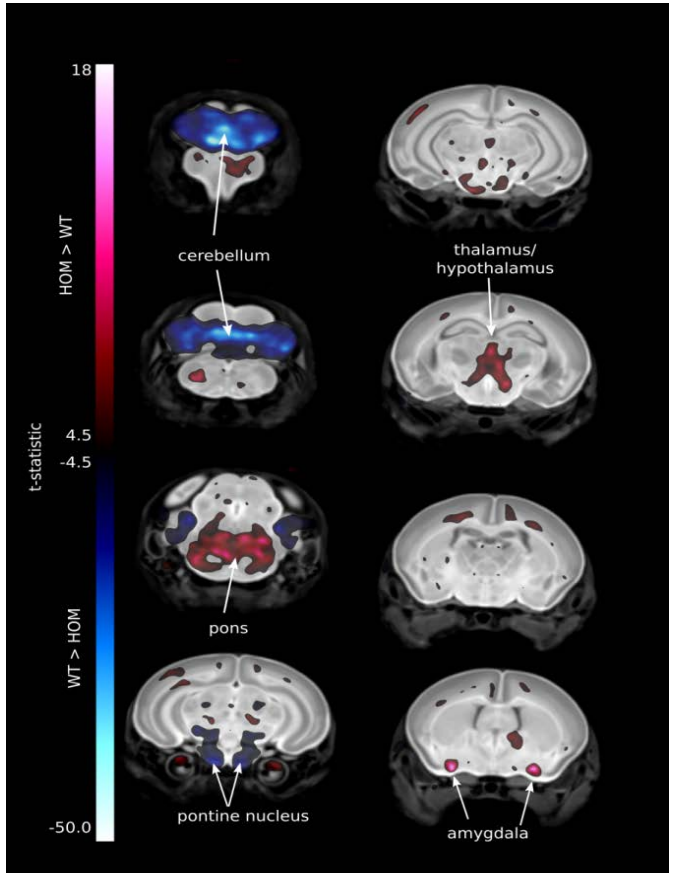
NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# *Subviable phenotyping pipeline*

## Tox3: HOM neonatal (P7) subviable

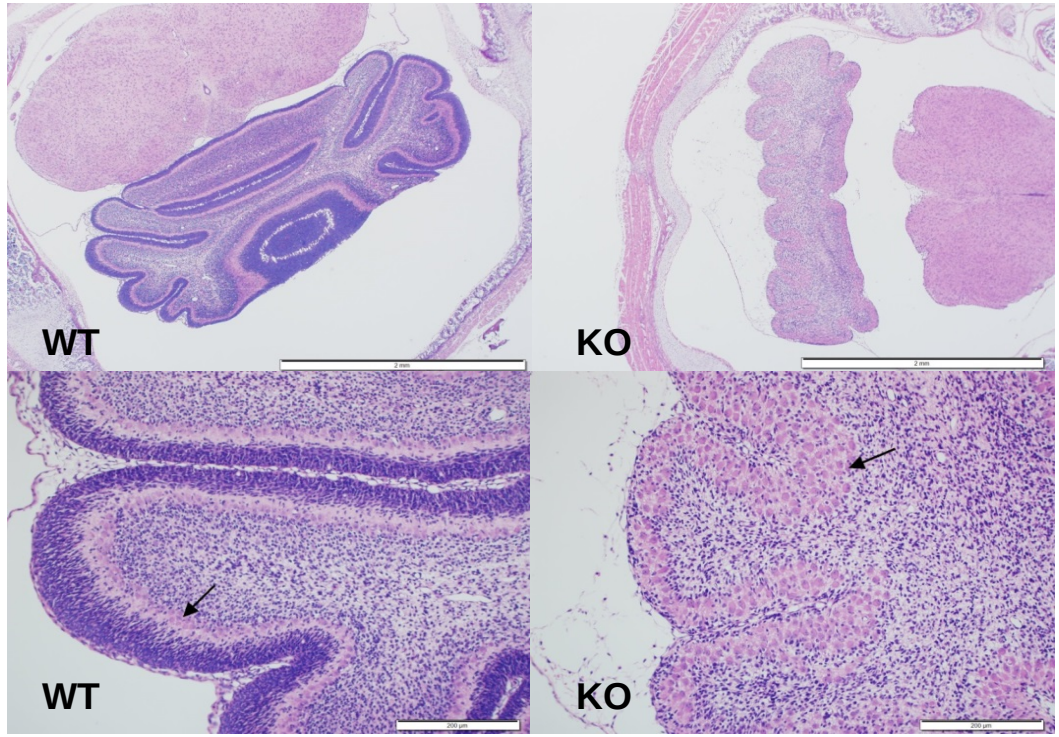
MRI (whole brain, P7)




Coronal sections: pink – tissue volume HOM > WT for amygdala, thalamus, pons; blue – tissue volume WT > HOM for pontine nucleus, cerebellum

KOMP2 Phenotyping:

Histopathology (cerebellum, P7)




DX: Marked diffuse cerebellar hypoplasia and dysplasia with vermis aplasia

*(data, slide courtesy KOMP2-DTCC)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# KOMP2 Informatics:


## Goals

- *Provide high quality data that is freely available, in "real time"*
- *Promote availability of KOMP2 generated mice, tools, SOPs*
- *Transparent, versioned statistical analysis, fully reproducible*
- *Intuitive web portals and API for data discovery*

# MPI2 Informatics: Data Flow

IMPC Mouse Production

wellcome trust sanger institute

JAX

BaSH

DTCC

KOMP2

other IMPC partners

Data

QC

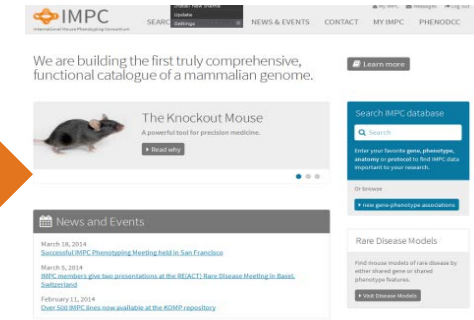
phenodcc

MRC HARWELL

Data Version

Stats Version

EMBL-EBI




Display

www.mousephenotype.org

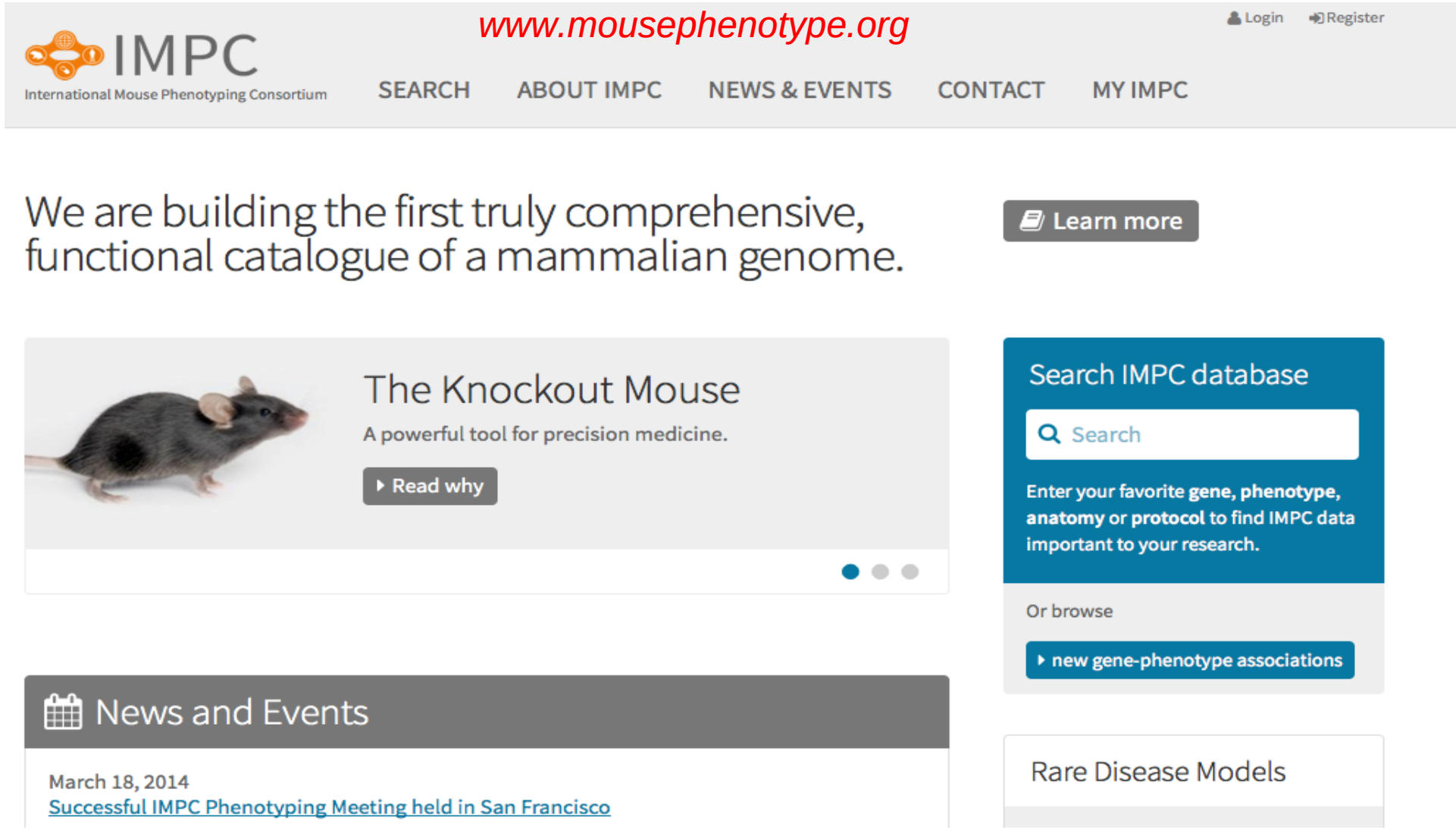
*(slide courtesy MPI2)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# Data Dissemination: IMPC portal

www.mousephenotype.org




*(slide courtesy MPI2)*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# Materials Dissemination

*(since September 2012)*

| KOMP2 Center | Orders | |
|---|---|---|
| | Placed | Fulfilled |
| BaSH | 385 | 99 |
| JAX | 288 | 189 |
| DTCC* | 575 | 414 |
| Totals: | 1248 | 702 |

* UCDAVIS KOMP Repository KNOCKOUT MOUSE PROJECT

# Responses to 2014 KOMP2 Survey

*Details of Survey:*

*4 question "Survey Monkey" instrument*

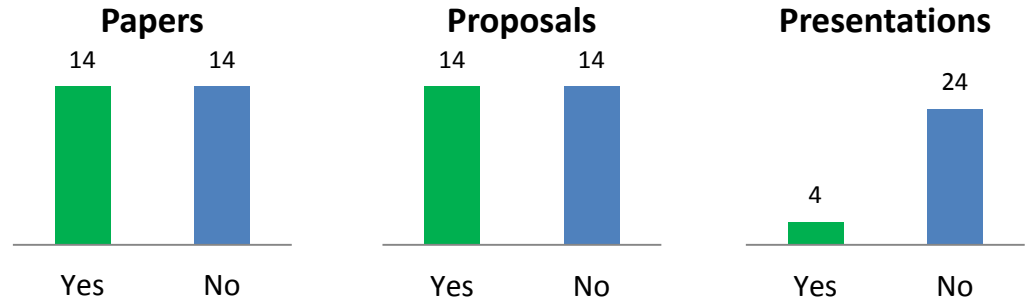
*"publications, presentations, proposals, & opinions"*

*571 recipients of KOMP2 mice and/or germplasm*

*opened August 18 (closes September 15)*

*Results thus far:*

*28 responses first 24 h*




**Opinions**

*"…great program…"*

*"…KOMP mice…instrumental to our research given (my) small budget…"*

*"…without the ready-made mouse, we would not have generated the line on our own and would not be pursuing our current research line…"*

*"…greatly facilitated discovery…will hopefully lead to a publication and grant…"*

# Research Use

Science
AAAS

**The Cells and Circuitry for Itch Responses in Mice**
Santosh K. Mishra and Mark A. Hoon
*Science* **340**, 968 (2013);
DOI: 10.1126/science.1233765

OPEN ACCESS Freely available online

PLOS | GENETICS

## Genetic Disruption of the Copulatory Plug in Mice Leads to Severely Reduced Fertility

**Matthew D. Dean***
Department of Molecular and Computational Biology, University of Southern California, Los Angeles, California, United States of America


Immunology:
**TBK1-associated Protein in Endolysosomes (TAPE)/CC2D1A Is a Key Regulator Linking RIG-I-like Receptors to Antiviral Immunity**


Kuan-Ru Chen, Chun-Hung Chang, Ching-Yu Huang, Chun-Yang Lin, Wan-Ying Lin, Yin-Chiu Lo, Chia-Yu Yang, En-Wei Hsing, Lin-Fang Chen, Shin-Ru Shih, Ai-Li Shiau, Huan-Yao Lei, Tse-Hua Tan and Pin Ling
*J. Biol. Chem.* 2012, 287:32216-32221.
*doi: 10.1074/jbc.C112.394346 originally published online July 25, 2012*

THE JOURNAL OF IMMUNOLOGY



## The Role of Sphingosine-1-Phosphate Transporter *Spns2* in Immune System Function

Anastasia Nijnik, Simon Clare, Christine Hale, Jing Chen, Claire Raisen, Lynda Mottram, Mark Lucas, Jeanne Estabel, Edward Ryder, Hibret Adissu, Sanger Mouse Genetics Project, Niels C. Adams, Ramiro Ramirez-Solis, Jacqueline K. White, Karen P. Steel, Gordon Dougan and Robert E. W. Hancock

ELSEVIER

FEBS Letters

journal homepage: www.FEBSLetters.org

FEBS

## Two non-vesicular ATP release pathways in the mouse erythrocyte membrane

Feng Qiu [a], Junjie Wang [a], David C. Spray [b], Eliana Scemes [b], Gerhard Dahl [a,*]

genesis
The Journal of Genetics and Development

TECHNOLOGY REPORT

## Troponin T3 Expression in Skeletal and Smooth Muscle Is Required for Growth and Postnatal Survival: Characterization of *Tnnt3*$^{tm2a(KOMP)Wtsi}$ Mice

Yawen Ju,[1,2] Jie Li,[1] Chao Xie,[1,2] Christopher T. Ritchlin,[1,3] Lianping Xing,[1,2] Matthew J. Hilton,[1] and Edward M. Schwarz[1,2]*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# Launchpads

- *Technology development*
  - *2i media, Permeable Cre, "Prefect Host" blastocyst*

Transgenic Res (2014) 23:177–185
DOI 10.1007/s11248-013-9764-x

TECHNICAL REPORT

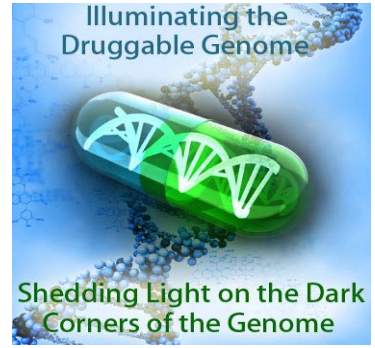
**Rapid conversion of EUCOMM/KOMP-CSD alleles in mouse embryos using a cell-permeable Cre recombinase**

Edward Ryder · Brendan Doe · Diane Gleeson · Richard Houghton · Priya Dalvi · Evelyn Grau · Bishoy Habib · Evelina Miklejewska · Stuart Newman · Debarati Sethi · Caroline Sinclair · Sapna Vyas · Hannah Wardle-Jones · Sanger Mouse Genetics Project · Joanna Bottomley · James Bussell · Antonella Galli · Jennifer Salisbury · Ramiro Ramirez-Solis

- *Leveraging NIH programs*

  Phenotyping Embryonic Lethal Knockout Mice (R01)
  (PAR-13-231)
  *Eunice Kennedy Shriver* National Institute of Child Health and Human Development

- *Rare, Undiagnosed Disease Models*




- *Coordinating with other CF Projects*

MRC

| Consortium | Nominated Genes | Mutant lines made | Assay development | Data enquiry | Mouse line sent | Outstandi |
|---|---|---|---|---|---|---|
| Accelerated Drug Discovery | ■ | ■ | | | 1 | |
| Disorders of Bone and Cartilage | ■ | ■ | ■ | ■ | 1 | |
| Cardiovascular Trait Consortium | ■ | ■ | ■ | ■ | 1 | 5 |
| Developmental Disorders | ■ | ■ | ■ | ■ | 5 | 5 |
| Diabetes and Obesity | ■ | ■ | ■ | ■ | 3 | 3 |
| Vision Research Consortium | ■ | ■ | ■ | ■ | 2 | |
| Tissue Remodelling and Fibrosis | ■ | ■ | | ■ | | |
| Haematopoiesis | ■ | ■ | | | | |
| Ion Channels | ■ | ■ | | ■ | 2 | 1 |
| Liver Disease Consortium | ■ | ■ | | ■ | | |
| Processes of Ageing | ■ | ■ | ■ | ■ | 1 | 2 |
| Neuromouse | ■ | ■ | ■ | ■ | 5 | 13 |
| Kidney and Urogenital System | ■ | ■ | ■ | ■ | 2 | |
| Respiratory | ■ | ■ | ■ | ■ | 1 | 3 |
| Macrophages | ■ | ■ | | | 2 | |
| immune system | ■ | ■ | | | 1 | 1 |
| Total for MMN | | | | | 27 | 33 |
| Rest if the community | | | | | 80 | 41 |

- *Mouse "Networks" for follow-up phenotyping*

- *"Innovation at the edge"…annotating unannotated genes*

NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# *Where do we go from here?*

- *"Phase 2" (2016-2021)…'kompleting' the mouse genome*
  - *~6000 new mutant mouse lines over 5 years*
  - *Less costly per mutant than Phase 1*

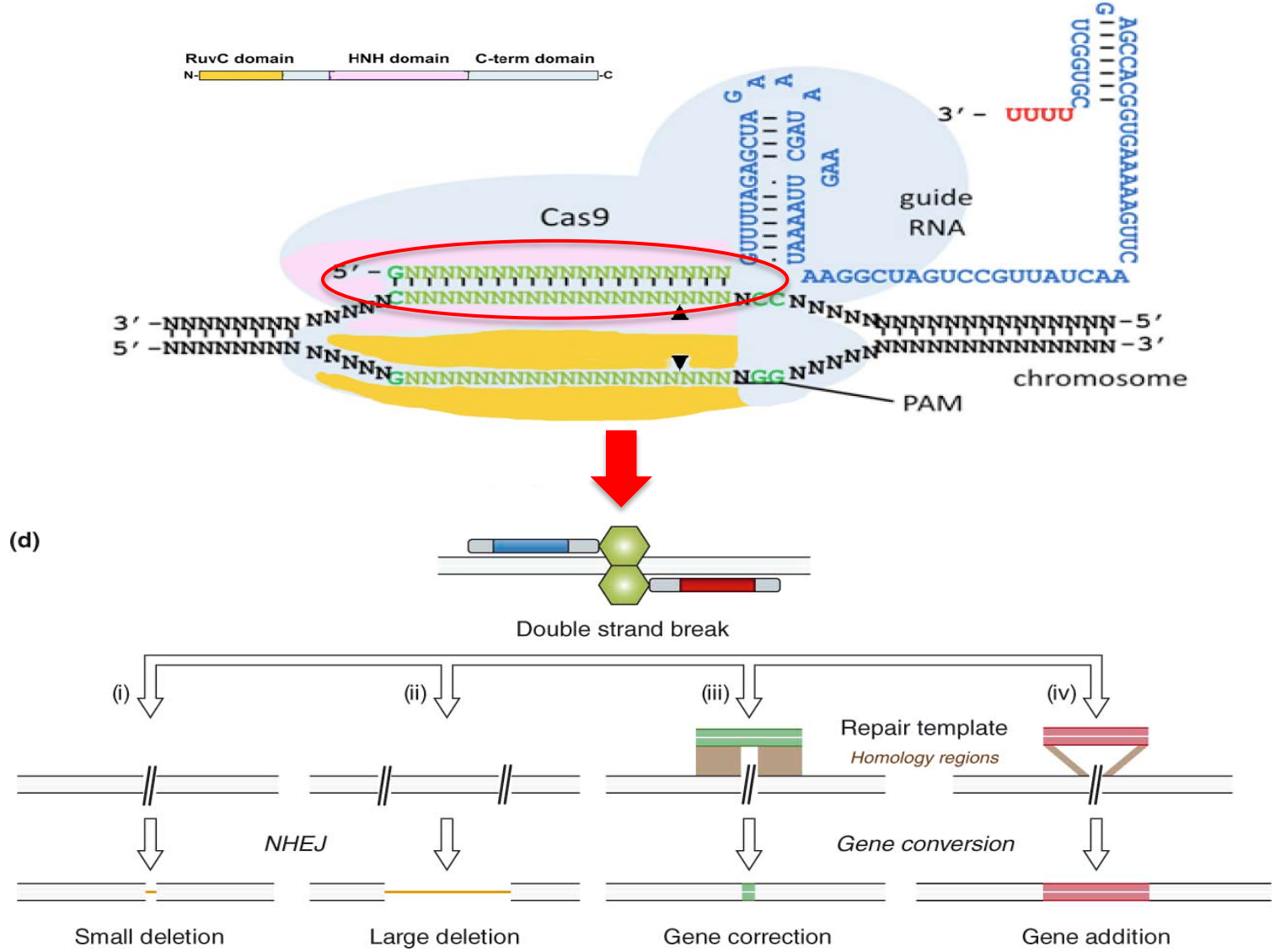
- *Significant, fully-validated resource for research community…*
  - *reagents, tools, SOP's, data, information, expertise*
  - *highly quality controlled (e.g., gender balance) processes*
  - *ensures reliability and reproducibility throughout*
  - *foundation of infrastructure, capacity, and capability*

- *Metabolomics profiling of select KOMP2 lines by KOMP2-BaSH*

- *Adopt CRISPR/Cas9 genome editing technology*

- *New, data-rich, intense phenotyping platforms*

# CRISPR Cas9




*Slide courtesy KOMP2-JAX*

# CRISPR Cas9

## *Eg:* KOMP2-DTCC data

| Mutation | # Genes | Mutation Confirmed (% of genes) | Efficiency per gene (by F0) |
|---|---|---|---|
| NHEJ | 19 | 18 (95%) | 10-100% |
| NHEJ + Point mutation by HDR | 6 | 6 (100%) | 6-71% |
| NHEJ + HR | 3 | 2 (66%) | 10-40% |

*NHEJ: non-homologous end joining; HDR: homology-directed repair; HR: homologous recombination*

## *KOMP2 at BaSH, JAX, & DTCC:*

- ✓ *NHEJ*
- ✓ *Point mutations*
- ✓ *LacZ insertion by homologous recombination*
- ✓ *Conditional mutagenesis*

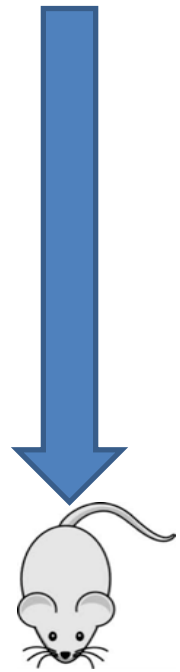
*Slide courtesy KOMP2-JAX, KOMP2-DTCC*

# CRISPR Cas9

**Conventional Gene targeting**

- Design and cloning
- ES cell targeting and screening
- Microinjection

(4-7 months, $9-12K)



Screen multiple litters for GLT

(Up to 6 months, $2-3K++)

Typical success rate: 60-70%

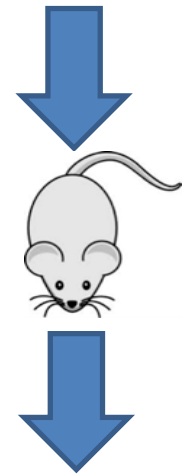
Abort or GLT

**Total cost: $25,000+**

Expansion

**CRISPR mutagenesis**

- Design and production of guides
- Microinjection (1 month, $2-3K)



Screen multiple litters for GLT

(Up to 3 months, $1K)

Typical success rate: 85-95%

Abort or GLT

**Total cost: ~$5-13,000**

Expansion

*Production Savings: ~$50% and ~50 weeks*

*Slide courtesy KOMP2-JAX, KOMP2-DTCC*

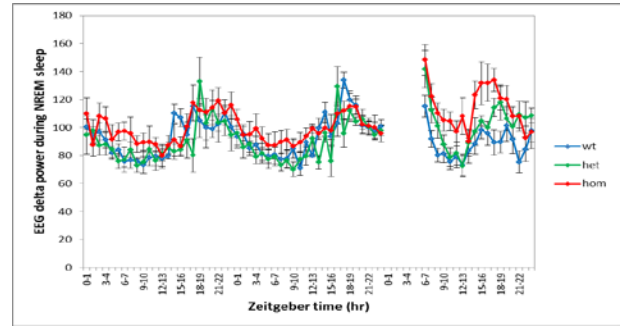
NIH National Institutes of Health
Office of Research Infrastructure Programs

The NIH Common Fund

# *Refinement of the Phenotyping Pipeline*

## Development of Phase 2 pipeline

Subgroup 1 **Behavior**
Subgroup 2 **Metabolism & markers**
Subgroup 3 **Morphology**
Subgroup 4 **Challenges**
Subgroup 5 **Ex vivo**
Subgroup 6 **Sick mouse**
Subgroup 7 **Telemetry**
Subgroup 8 **Automated image analysis**
Subgroup 9 **Immune phenotyping**



# *The CF KOMP$^2$ Project…*

## *discovering new knowledge about gene function*


## *Acknowledgements*

***KOMP$^2$ Centers (David West [CHORI], Lynette Bower [UCD], Colin McKerlie, Ann Flenniken, Lauryl Nutter [TCP], Sara Wells [MRC Harwell], Steve Murray [JAX])***

***DCC and MPI2 (Terry Meehan)***

***IMPC (Steve Brown, Mark Moore)***

***The MONARCH Initiative (Melissa Haendel)***

***NIH (Colin Fletcher, Ray O'Neill, Oleg Mirochnitchenko)***

NIH National Institutes of Health
*Office of Research Infrastructure Programs*

The NIH Common Fund