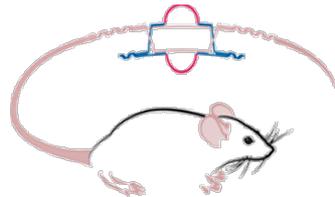
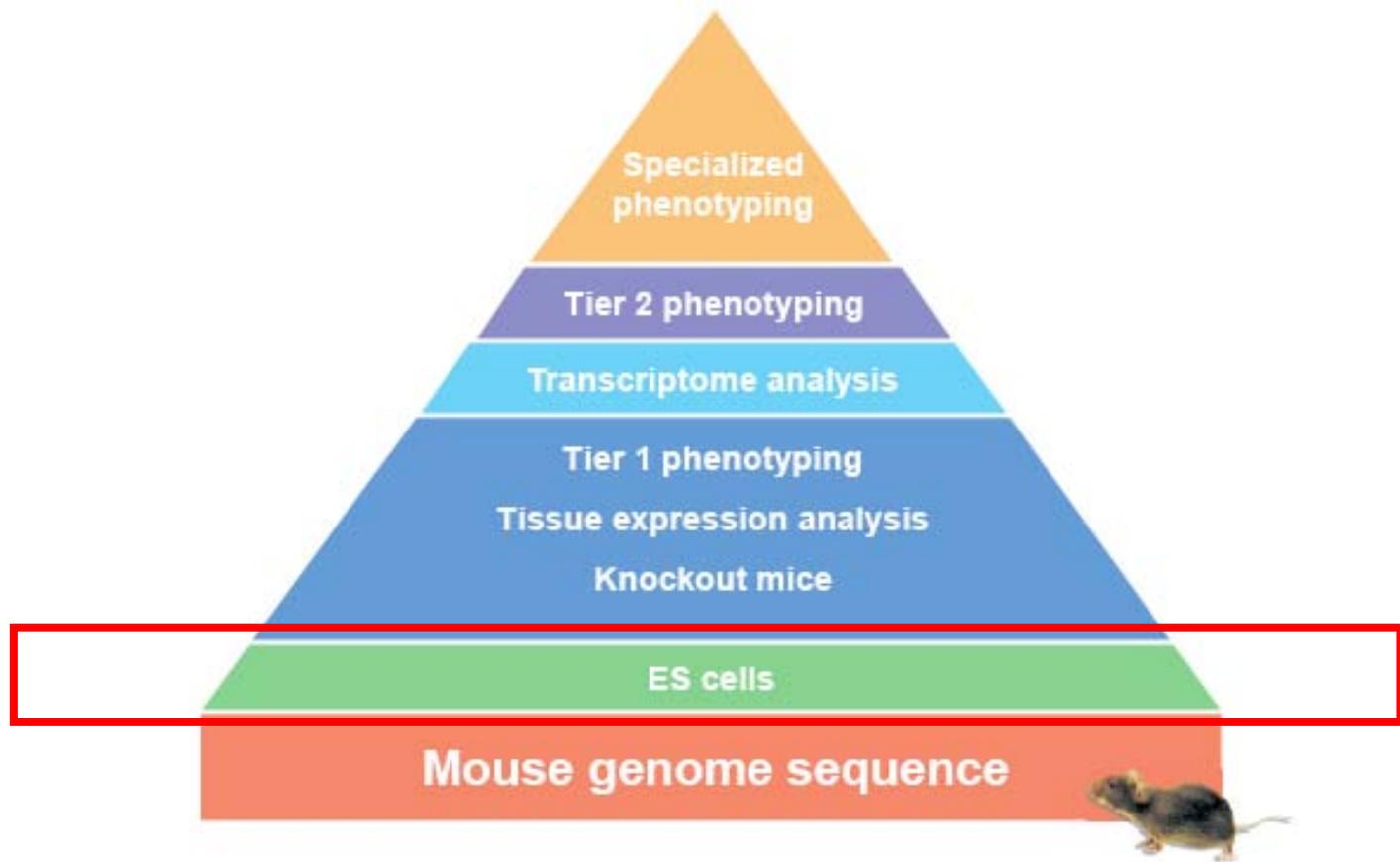


# Knockout Mouse Project (KOMP) and Knockout Mouse Production and Phenotyping (KOMP<sup>2</sup>)

Colin Fletcher, Ph.D.  
Kickoff Meeting, October 2011





A meeting at the Banbury Center, Cold Spring Harbor in 2003 published a proposal for high throughput Gene Knockouts and Phenotyping for every gene in the mouse genome.



# KOMP

- *“...a high-throughput international effort to produce...knockouts for all mouse genes, and place these resources into the public domain.”*
- The KOMP was launched in 2006 by NIH
  - \$56.6 million over 5 years from the ICs
  - a goal of creating 8,500 ES cell lines
  - alleles are nulls or conditional-ready, contain reporter
- The EC launched EUCOMM, the European Conditional Mouse Mutagenesis Program in October 2005 (funded in Feb 2005)
  - 13 M Euros over 3 years
  - a goal of creating 8,000 mutants.
- KOMP and EUCOMM along with other international efforts formed the International Knockout Mouse Consortium (IKMC) and have jointly produced 14,000 mutant ES cell lines and made them available from public repositories.



# International Planning for Phenotyping the IKMC Resource

- 3 workshops: Rome in 2007, Bar Harbor and Toronto in 2008 to establish vision for an International Mouse Phenotyping Consortium & discuss international, coordinated phenotyping efforts – agreed that the way forward is to develop a business plan
- Medical Research Council/Wellcome Trust workshops in Nov 2008 and Oct 2009 to engage UK scientific community
- **NIH Phenotyping meeting, Bethesda October 2009 to discuss potential of launching Knockout Mouse Production and Phenotyping (KOMP<sup>2</sup>)**
- **Joint TCP-NIH meeting, Toronto, April 2010 to discuss phenotyping**
- IMPC-EUMODIC meeting, Barcelona, Feb 2011 to review EUMODIC progress
- EC-funded EUMODIC (Helmholtz, Munich; ICS, Strasbourg, MRC Harwell, WTSI) project is now doing broad-based phenotyping of 500 mutant lines – completion 2011

# A plan for international coordination

KOMP<sup>2</sup> is a founding member of the International Mouse Phenotyping Consortium (IMPC). It will provide:

- A coordinated plan for an international phenotyping effort
  - Phase I (2011-2016) scale up; Phase II full scale (2016-2021)
  - common and standardized phenotyping platforms
  - common QC standards
- A global resource of KO mice and associated database of gene function that will revolutionize research for the next 20-30 years
- A forum for exchange of information, collaboration and discussion among international mouse KO groups

# Rationale for a Large-scale KOMP<sup>2</sup>

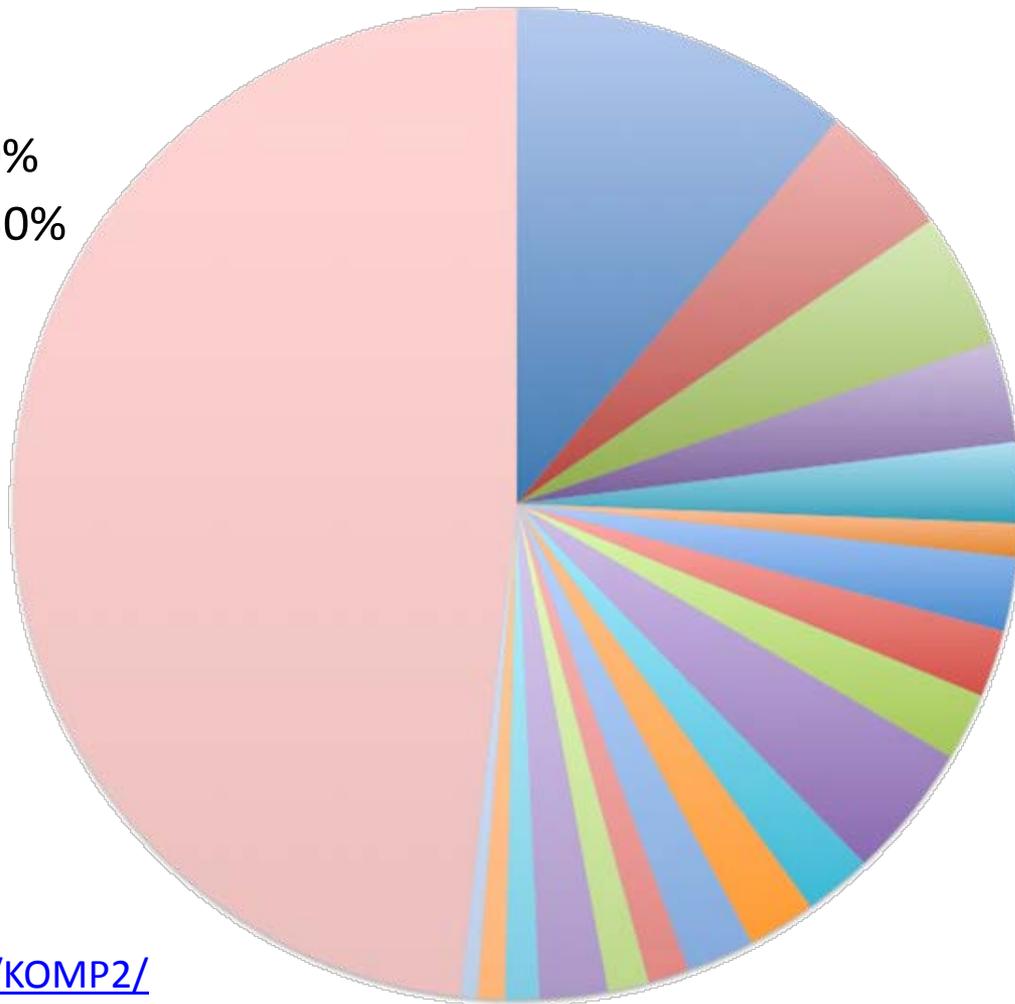
Supporting a broad phenotyping effort would provide the following advantages:

- Eliminate the redundancy and waste inherent in the “cottage industry” approach
- Each mutant mouse will be characterized for a broad set of phenotypes to allow direct comparisons & result in a thorough description of gene function.
- Novel genes will be brought to light that would otherwise be ignored
- 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.
- Potential for breakthrough discoveries

# Co-Funding from Common Fund and ICs

- Funding:

- NIH Common Fund – 50%
- Participating NIH ICs – 50%
- \$110M over five years



- Common Fund Website:

- <http://commonfund.nih.gov/KOMP2/>

# KOMP<sup>2</sup> Production RFA

The RFA calls for one to three mouse production centers with a total network capability of converting 500 IKMC ES cell lines per year to mouse strains, for a total of 2,500 over five years.

Production centers were also requested to:

- Remove the neo<sup>R</sup> cassette prior to breeding
- Breed cohorts of mice for phenotypic analysis
- Cryopreserve embryos or sperm and ship to the KOMP repository
- Perform LacZ staining on adult mice and embryos
- Monitor and report if the homozygous mice are viable and fertile
- Plan for determining embryonic lethality (before or after E12.5)

# KOMP<sup>2</sup> Phenotyping RFA

The RFA calls for two to four mouse phenotyping centers with a total network capability of phenotyping 500 mouse strains per year, for a total of 2,500 over five years.

Phenotyping Centers were requested to:

- Coordinate with the production centers to obtain mice or germplasm
- Demonstrate past experience in high throughput, broad-based phenotyping
- Justify phenotyping tests and plans for future tests
- Demonstrate IT capability to collect and deliver data to a DCC
- Agree to work in a consortium to standardize SOPs and coordinate with the IMPC



# KOMP<sup>2</sup> Data Coordination Center and Data Base (DCCDB) RFA

Goals of the RFA are to develop and implement a Data Coordination Center and Database (DCCDB) as part of the Knockout Mouse Phenotyping Project (KOMP<sup>2</sup>)

The DCCDB will be funded primarily to:

Develop, house, and maintain databases to track the progress of the pipelines for producing the knockout mice from ES cells

Collect all phenotype data generated at the phenotyping centers

Organize and maintain SOPs and track versions protocols

Provide QA and QC of data

Develop or coordinate data visualization tools

Coordinate these efforts with the International Mouse Phenotyping Consortium (IMPC)

Deliver this information to the members of the KOMP<sup>2</sup> research network, NIH staff, and the public via a single integrated web portal of phenotype data

# KOMP/KOMP<sup>2</sup> Timeline

