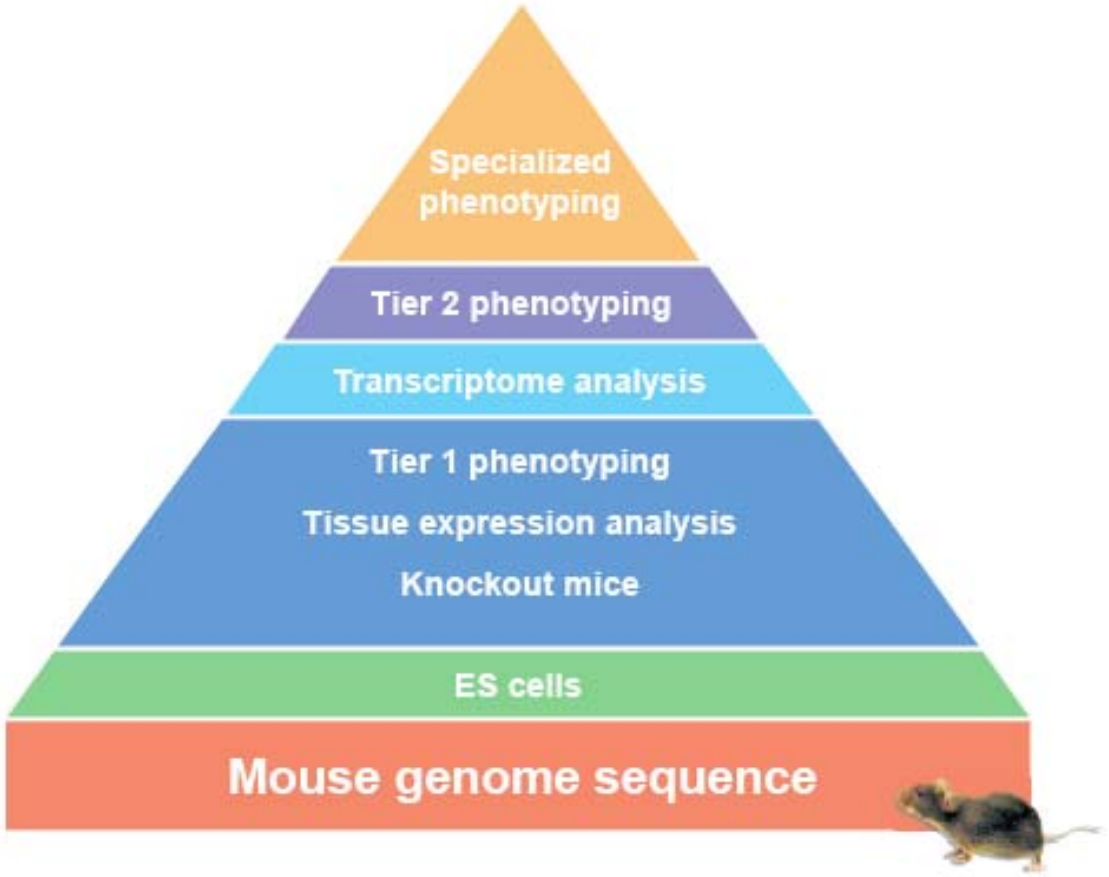
KOMP2
EVOLUTION OF THE VISION

Athens, Infra-frontier, IPAD-MD, IMPC

11-2017

The Knockout Mouse Project

- The vision of the knockout mouse project has evolved since it was first articulated in 2003
- Implementation of the vision over its three phases has been in response to community input, modulated by scientific, political, and financial issues.
- With the mandatory termination of Common Fund support (final award 2020) and the disruptive opportunity of CRISPR, it is time to develop a new vision for a mouse phenotyping project.



The vision for KOMP was articulated in a meeting at the Banbury Center, Cold Spring Harbor in 2003, calling for high throughput production of gene knockouts, and phenotyping, for every gene in the mouse genome.

Deliver ES cells : 2006-2010

The goal of Phase I was to deliver an ES cell library that would be readily available, with the intention of reducing the cost and waste inherent in retargeting.

All type of Targeted Alleles in MGI (knock-out, knock-in, reporter, floxed/Frt, other)

Total number of targeted alleles = 7,068
Number of these alleles available in IMSR = 1,109
Total unique genes with targeted allele(s) in IMSR = 706

Targeted Genes	*Targeted alleles/gene*	*Specific Genes*
2144	1	
761	2	
342	3	
146	4	
74	5	
40	6	
32	7	
13	8	
20	9	
12	10	
8	11	(Brca1, Cd79a, Cdkn2a, Cebpa, Il4, Nodal, Pdgfra, Xist)
7	12	(Catnb, Epor, Pdgfrb, Th, Tnf, Vegfa)
4	13	(Cftr, Efnb2, En1, Myf5)
6	14	(Brca2, Psen1, Fgfr3, Gnas, Grin1, Prnp)
2	15	(Runx1, Smad2)
4	16	(Erbb2, Fgfr2, Pparg, Gt(ROSA)26Sor)
1	17	(Met)
1	18	(H19)
1	19	(Hprt)
2	20	(Otx2, Trp53)
1	21	(Hdh)
0	22	
1	23	(Olfr151)
1	24	(Fgfr1)

Total unique genes with targeted knockout allele(s) = 3,622
60% of these genes have only 1 targeted allele
90% of these genes have 1-3 targeted alleles

~~Scientific~~
(Political)
Financial ✓

Deliver Mice & Phenotypes : 2011-2015

- Further cost saving with centralized mouse production
- Disseminate to focused phenotyping centers à la ENU model?
  - Candidate gene/disease gene selection?
- Community input: phenotype the “dark” genes
  - Abandon the candidate gene idea
- Standard phenotyping was achievable (Eumodic)
- Hint about pleiotropy
- R01 grant mechanism is not appropriate for this type of project

Scientific ✓
Political ✓
~~Financial~~

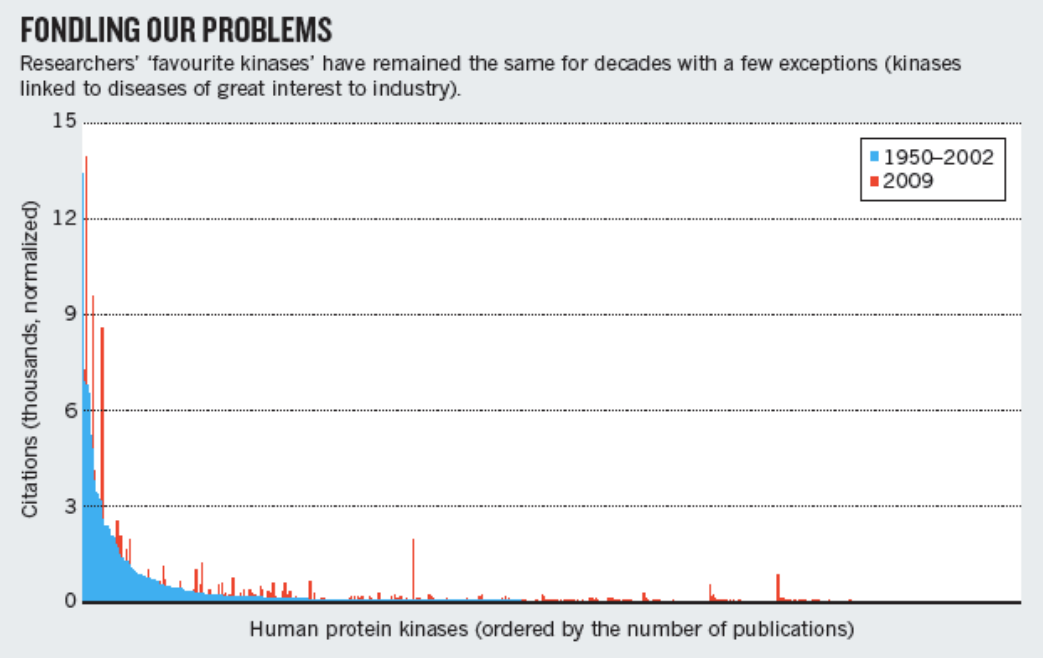
Deliver Mice & Phenotypes : 2011-2015

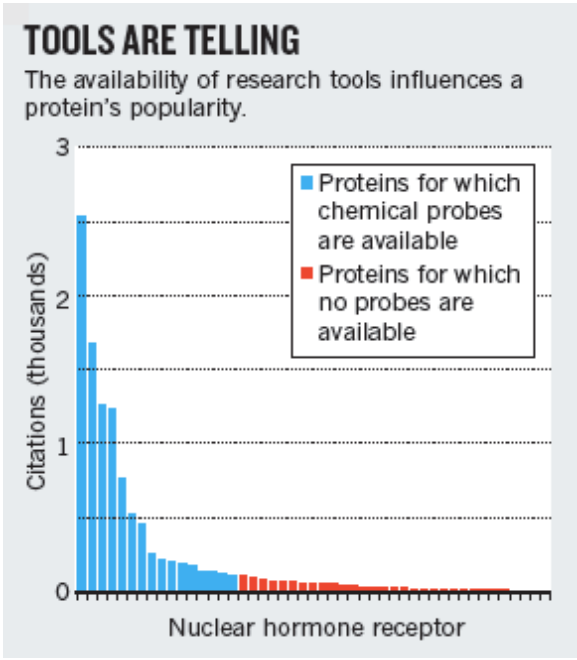
IMPC promotes access to unannotated genes by providing hypotheses and tools

Nature Commentary

Too many roads not taken

Most protein research focuses on those known before the human genome was mapped. Work on the slew discovered since, urge **Aled M. Edwards** and his colleagues.

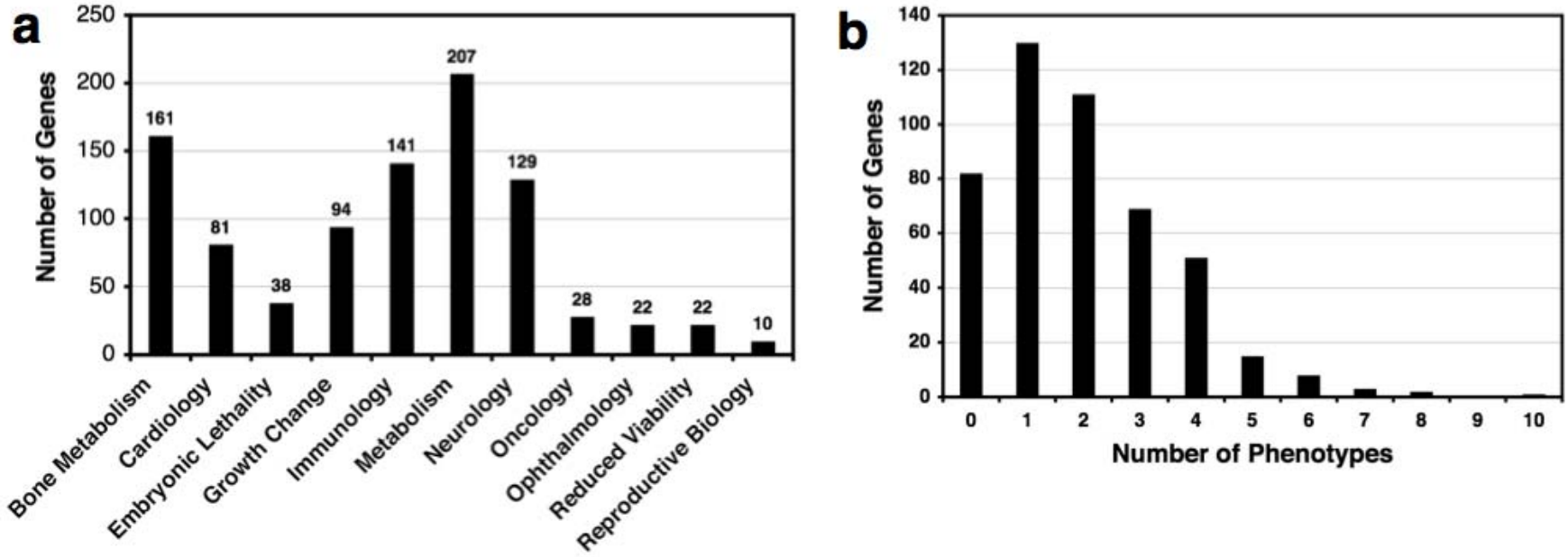




Deliver Mice & Phenotypes : 2011-2015

IMPC provides new insights into pleiotropy

472 Mouse knockouts were broadly phenotyped



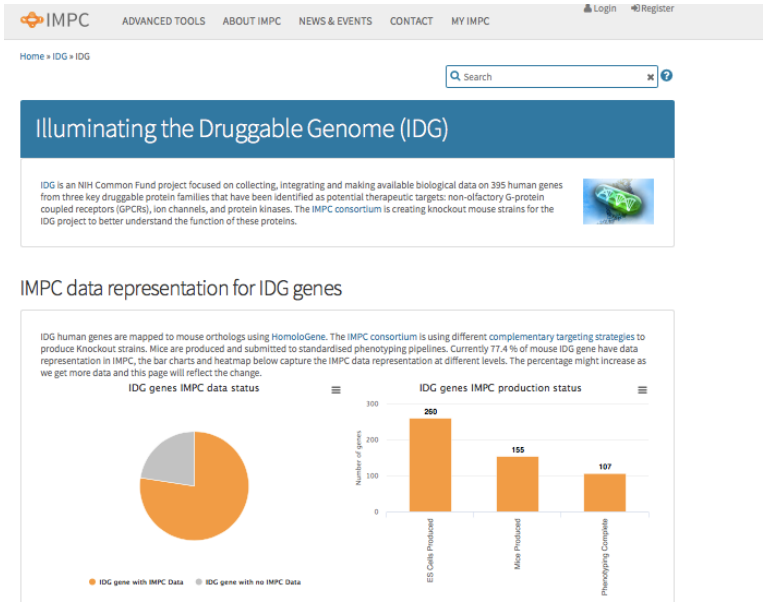
130 (27%) strains had 1 phenotype

245 (52%) strains had 2-5 phenotypes

Andy Peterson, Genentech

KOMP2 Integration Efforts : 2011-2015

- Community demand – Bloomsbury Report
  - Expansion into embryo imaging
- R01 community engagement
  - Embryo follow-on grants via NICHD
  - Bone grant via NIAMS
- NIH engagement
  - IDG collaboration



http://www.mousephenotype.org/data/collaborators/

Deliver the Phenotype Data : 2016-2020

- 2015 Second phase/renewal issues:
  - ✓Dark Genes
  - ✓Pleiotropy
  - ✓Sexual Dimorphism
  - ✓Rigor and Reproducibility
  - ✓Community Uptake
  - ✓CRISPR technology
  - ✓Late onset phenotypes

Scientific ✓
Political ✓
Financial ✓

Post KOMP – Precision Models

- KOMP will not be renewed in its current form
- 2021 Beyond KOMP
  - Allelic series
  - Genetic background/modifiers/sex
  - Environment
- Precision Medicine
  - Tailored treatment to the individual
    - Allele, Genome, Environment
- KOMP/CMG ASHG October 17, 2017
- KOMP/UDN TBD 2018
- Crispr-tunities
  - Model human disease alleles to understand mechanism
    - Confirm Gene ID, define pathophysiology
    - "allelic heterogeneity"
  - Nulls on other genetic backgrounds (modifiers)
  - Non-coding DNA – common disease variants

https://www.youtube.com/watch?v=MxrCt7b6riU David Valle, ILAR, DC, Oct 5-6, 2017

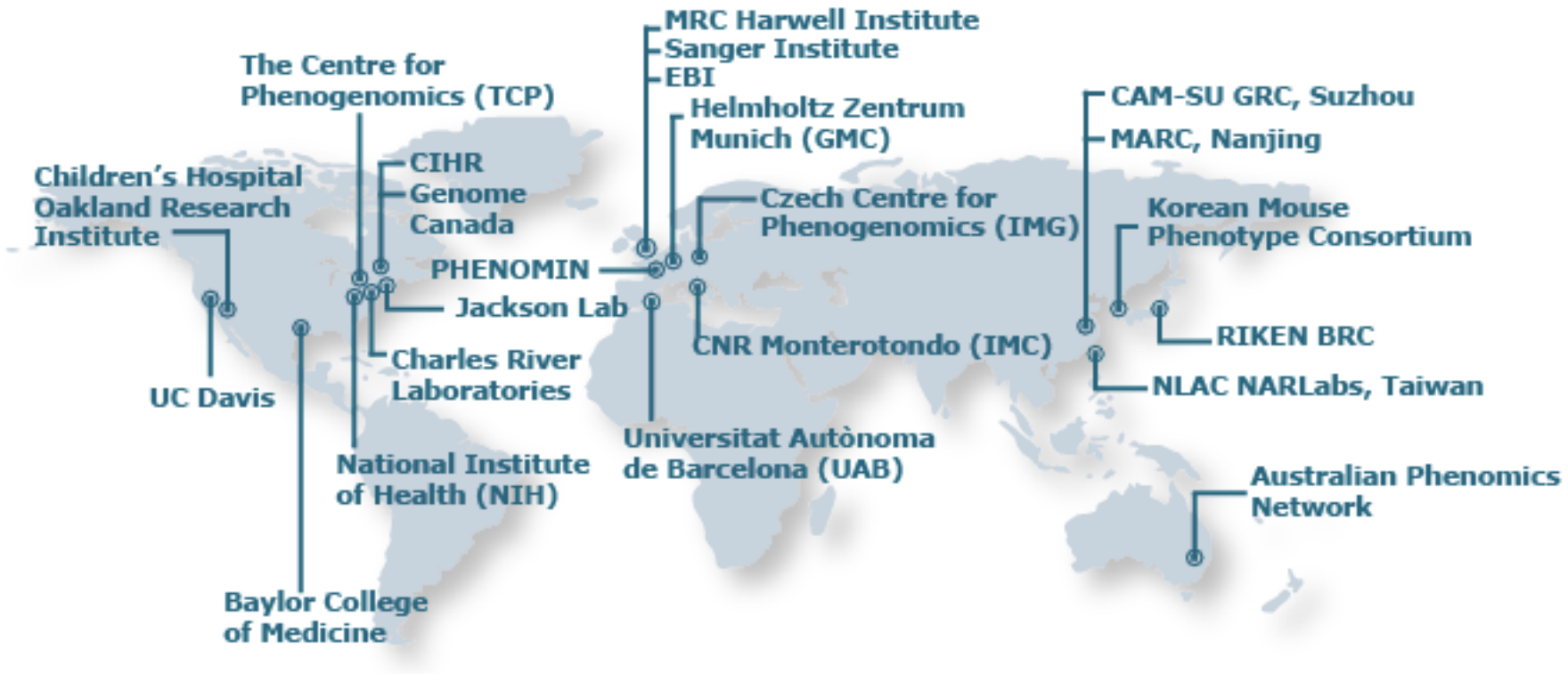
mPMI : 2021- 2025

mouse Precision Modeling Initiative

- Rationale
  - Rare disease alleles do not describe phenotypic scope
  - CRISPR therapeutic opportunity is confounded by partial penetrance of disease alleles.
- Deliverables
  - Disease allele B6N + DO/CC
  - Null allele B6N + DO/CC?
  - Disease allele + environmental challenge
- Requirements
  - Better align phenotyping assays with OMIM
  - Identify disease genes with allelic heterogeneity/PE
  - Predict discovery rate/extent of human disease genes
- Opportunities
  - Ex vivo disease modeling
  - Validation of environmental exposure correlations (*All of Us?*)

IMPC

International Mouse Phenotyping Consortium



www.mousephenotype.org