Production of an Encyclopaedia of Mammalian Gene Function

International Mouse Phenotyping Consortium

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The IKMC (EUCOMM, KOMP, NorCOMM and TIGM) have produced over 9,000 KO ES cell lines

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, Chr13:22210730-22311689

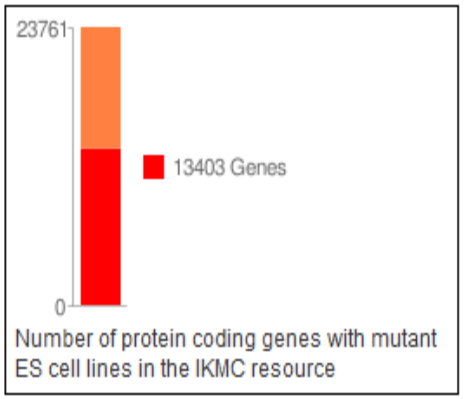
Browse IKMC database help

Use the following links to browse genes

- Browse by Gene Symbol
- Browse by Chromosome

Status

ES Cell Lines Progress



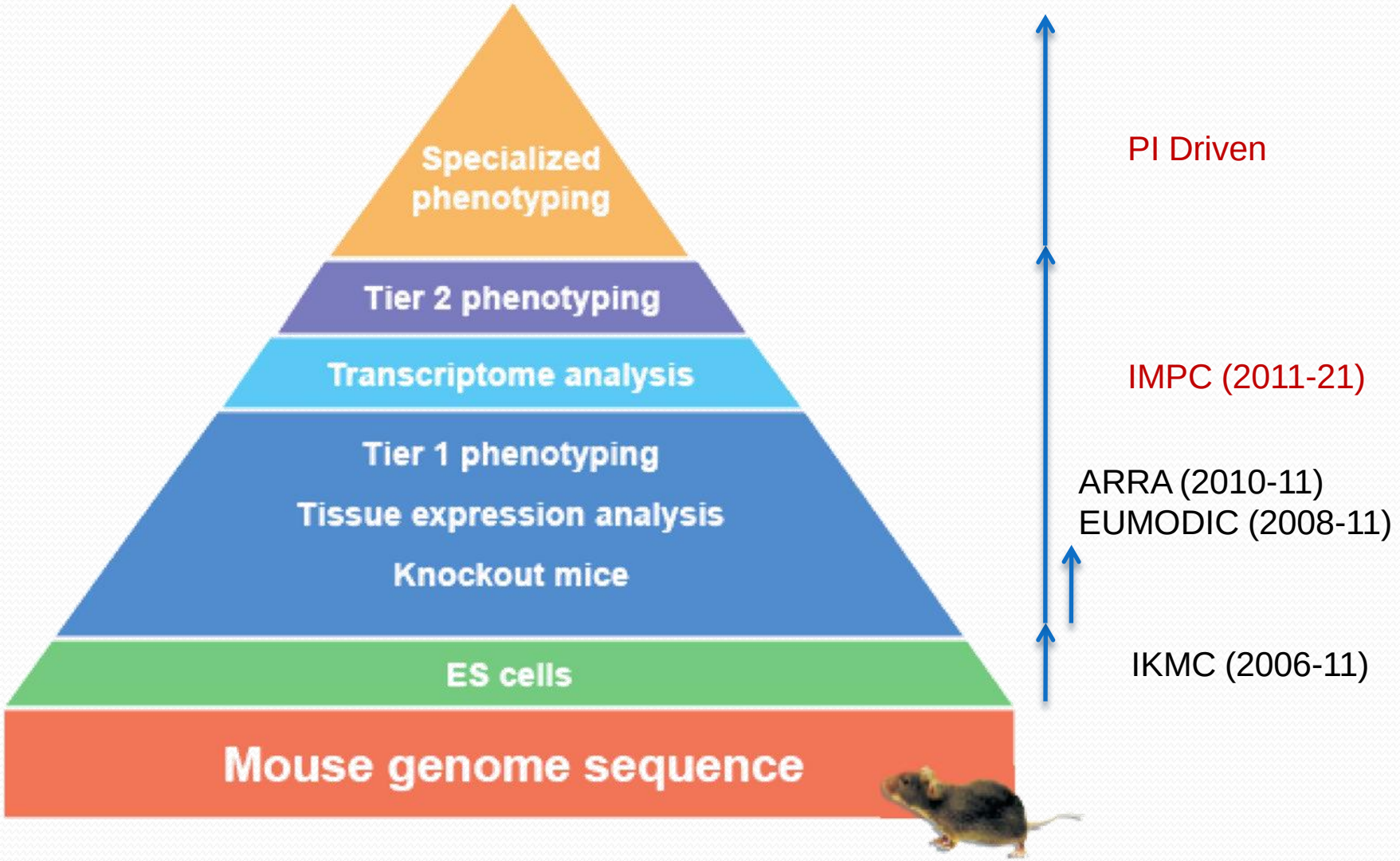
Number of protein coding genes with mutant ES cell lines in the IKMC resource

IKMC Gene Progress Summary

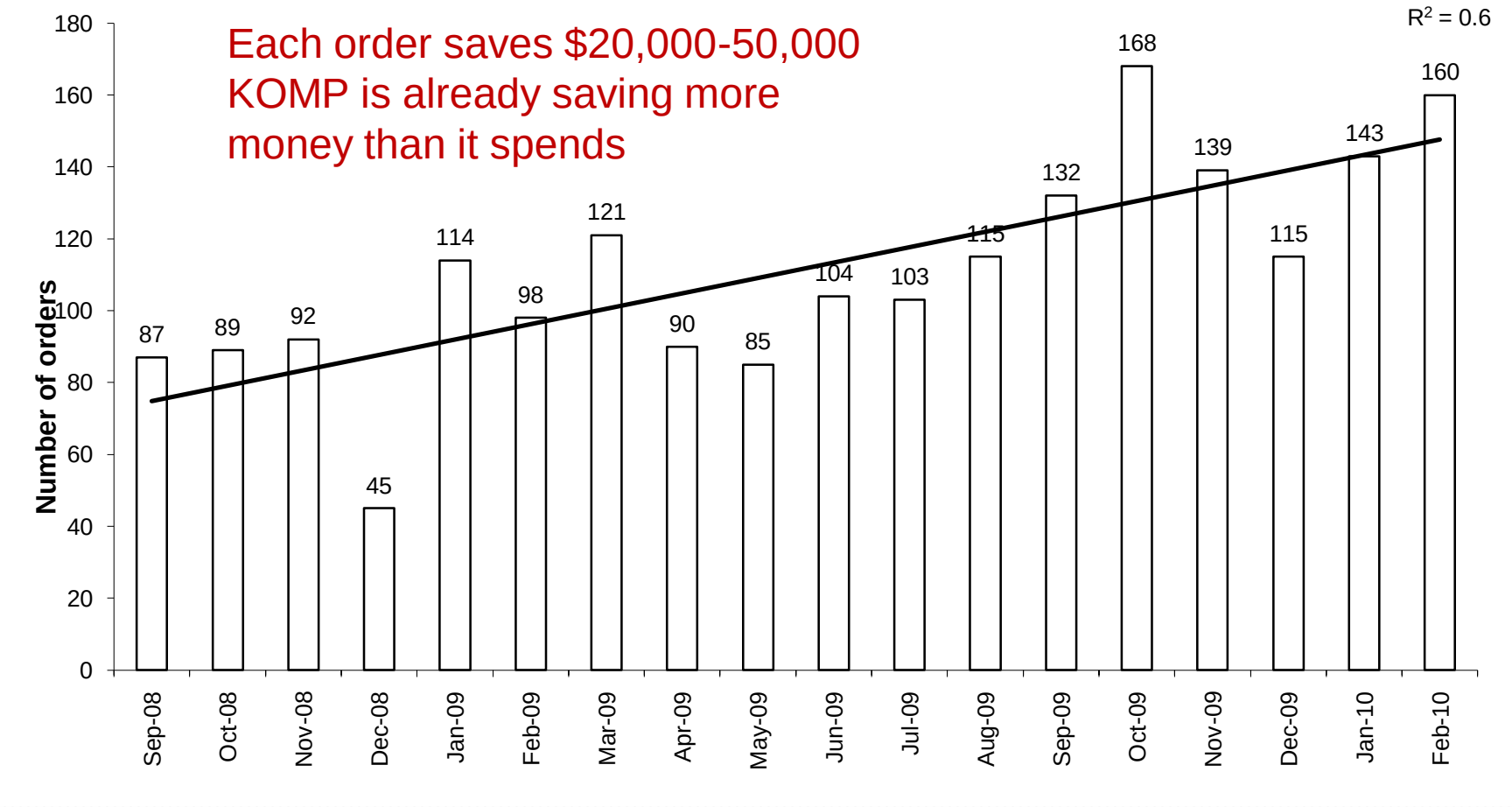
Total Genes	KOMP		EUCOMM	NorCOMM	TIGM
	CSD	Regeneron			
Project goal	5000	3500	8000	500	-
Vectors generated	5111	3327	4521	312	-
Vectors available	4842	2296	4521	312	-
ES cells generated	2674	1846	2443	45	-
ES cells available	1942	1136	2443	45	10699
Mutant mice generated	168	160	279	0	-
Mutant mice available	168	71	279	0	-

View details about this table View details about the acronyms used

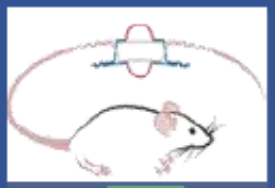
IMPC Vision


Specialized phenotyping
Tier 2 phenotyping
Transcriptome analysis
Tier 1 phenotyping
Tissue expression analysis
Knockout mice
ES cells
Mouse genome sequence
PI Driven
IMPC (2011-21)
ARRA (2010-11)
EUMODIC (2008-11)
IKMC (2006-11)

KOMP Customer orders by month
Late 2008 – early 2010



Knockout Mouse Phenotyping Program KOMP²



International Knockout Mouse Consortium (IKMC)

Mutate all protein-coding genes in mouse embryonic stem cells

Funded by NIH, EU, Wellcome Trust, Canada, Texas Enterprise Fund

Will be completed in two years

KOMP² --- Knockout Mouse Phenotyping Program

- **Standardized, broad phenotyping of 8,500 KO mice derived from IKMC ES cells**
- **Comprehensive definition of *in vivo* function of mammalian genes and identification of new models of disease**
- **Coordinated with other international activities**

FY10: Oct 2009 Planning Meeting, April 2010 Phenotyping Workshop

FY10: Continued Planning ($500K)

FY11-FY15: Pilot to create cost-efficient phenotyping pipeline -- 2,500 mutants in five years ($11M/yr Common Fund+ $11M/yr IC match)

Program Leaders: James Battey (NIDCD), Eric Green (NHGRI).

Why the IMPC

- Build a resource of KO mice and associated encyclopedia of gene functions
- Free thousands of researchers from tool generation
- This resource will be revolutionize research for the next 20-30 years
- Novel genes will be brought to light that would otherwise be ignored
- Potential for breakthrough discoveries

Targeted deletion of the 9p21 non-coding coronary artery disease risk interval in mice

Axel Visel1,2, Yiwen Zhu1, Dalit May1, Veena Afzal1, Elaine Gong1, Catia Attanasio1, Matthew J. Blow1,2,
Jonathan C. Cohen3, Edward M. Rubin1,2 & Len A. Pennacchio1,2

Vol 464| 18 March 2010| doi:10.1038/nature08801

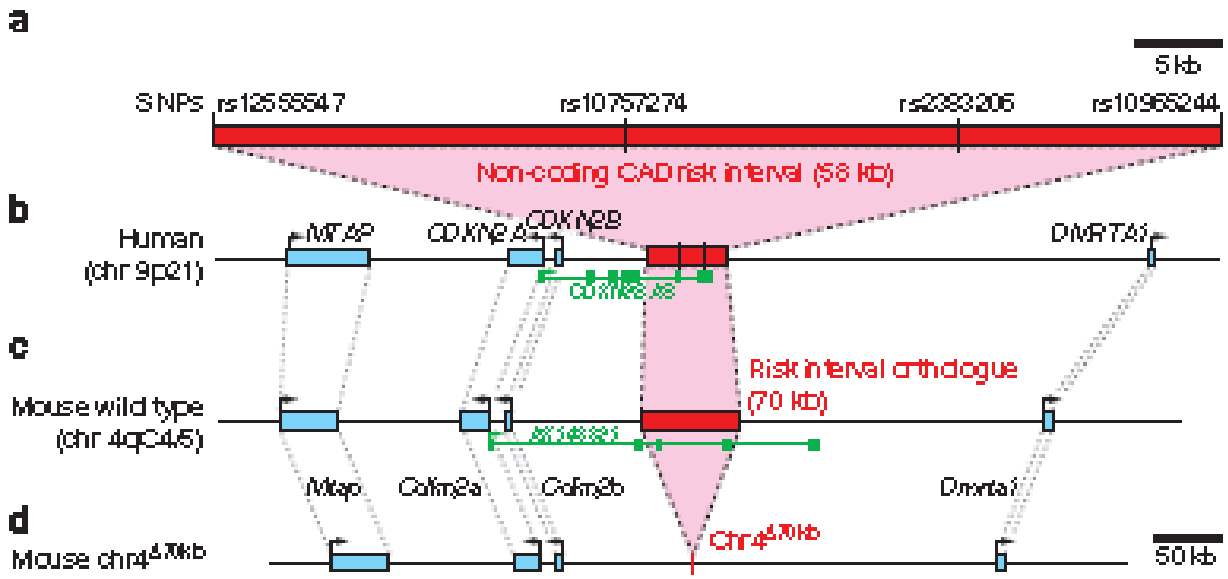


Figure 1 | Deletion of the non-coding region orthologous to the 58-kb CAD risk interval on human chromosome 9p21. a, Non-coding CAD risk interval with SNPs found to be most significantly associated with CAD in genome-wide association studies[1,2] and SNPs defining the boundaries of the linkage disequilibrium block. **b**, Overview of the human locus including

Variation in distant-acting regulatory sequences required for cardiovascular expression of CDKN2A and CDKN2B provides a plausible mechanistic model for the increased CAD risk associated with the 9p21 region independently of lipid leve

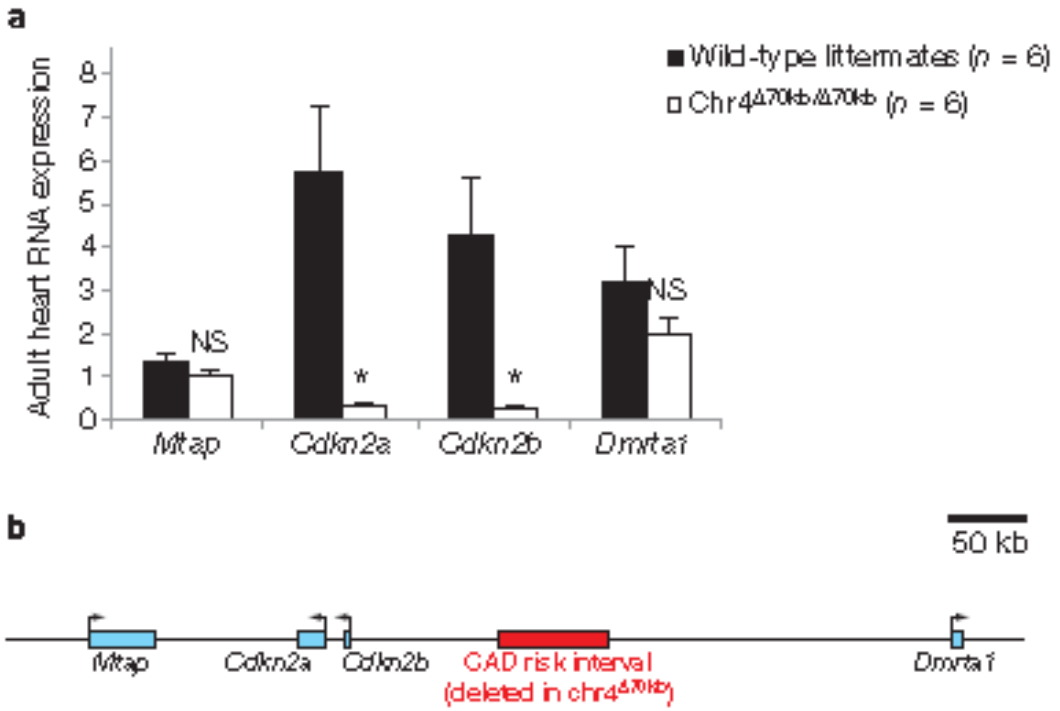


Figure 2 | Deletion of the CAD risk interval affects expression of neighbouring genes *Cdkn2a* and *Cdkn2b*. **a**, Expression levels of *Cdkn2a* (INK splice variant) and *Cdkn2b* are significantly reduced in heart tissue of chr4$^{\Delta 70kb/\Delta 70kb}$ mice. In contrast, expression of the neighbouring genes *Mtap* and *Dmrta1* is not significantly altered. Expression levels were normalized to the β-actin gene. NS, not significant. **b**, Overview of locus with locations of

UPDATE 2-Amgen, Glaxo bone drug wins EU OK, shares rise

* Prolia approved for osteoporosis in women and men

STOCKS | REGULATORY NEWS | GLOBAL MARKETS | HEALTHCARE

* Amgen and Glaxo to share commercialization in Europe

* U.S. FDA to decide on drug by late July

* Glaxo rises 2 pct, Amgen up 0.7 pct (Adds details on analyst comments, U.S. applications, byline)

By Ben Hirschler and Ransdell Pierson

Fri May 28, 2010 11:22am EDT

Related News

PREVIEW-Immunotherapy for tumors key topic at cancer meeting
Tue, Jun 1 2010

Glaxo settles more Avandia lawsuits in U.S.
Tue, Jun 1 2010

The discovery program began in an Amgen lab when researchers observed that one of the knockout mice it had developed during gene disabling research work had grown huge. "We noticed, hey that's a really big
mouse," Amgen CEO Kevin Sharer recently told the Wall Street Journal.
"It's really got big bones."

The International Mouse Phenotyping Consortium (IMPC) Steering Committee

The Wellcome Trust (Dr. Michael Dunn)
The Medical Research Council (Dr. Nathan Richardson)
The Wellcome Trust Sanger Center (Dr. Allan Bradley)
MRC Harwell (Dr. Steve Brown)
European Commission (OPEN)
German Mouse Clinic/InfraFrontiers (Dr. Martin Hrabe de Angelis)
Toronto Centre for Phenogenomics (Dr. Colin McKerlie)
ICS (Strasbourg) (Dr. Yann Herault)
NIH: NHGRI (Dr. Eric Green) **NDCD** (Dr. James Battey)
Australia Phenomics Network (Adrienne McKenzie)

Other likely members:

The Jackson Labs China Italy (Monterotondo)
Czech Republic Japan
UAB (Barcelona) Korea?Taipai?

IMPC Progress

- *Addition of new members bringing total to 10*
  - *4 Funding Organizations*
  - *6 Mouse phenotyping Centers*
- *Response to community-wide surveys*
  - *Development of workshops*
    - *Embryology*
    - *Imaging Technologies*
- *Working to actively manage the coordination and development of the multiple centres*
- *Launch Phase II 2011?*

IMPC Activities

- ***Six mouse clinics so far; anticipate 10-12 worldwide.***
- ***Phase I (2011-2016) of the preparatory/development period ~4,000***
- ***Work to actively manage the coordination and development of the multiple centres***
- ***Evaluate a final scientific, management and governance plan for the full scale programme to commence in 2016***
- ***Launch Phase II 2016-2021 Completion of the Genome***

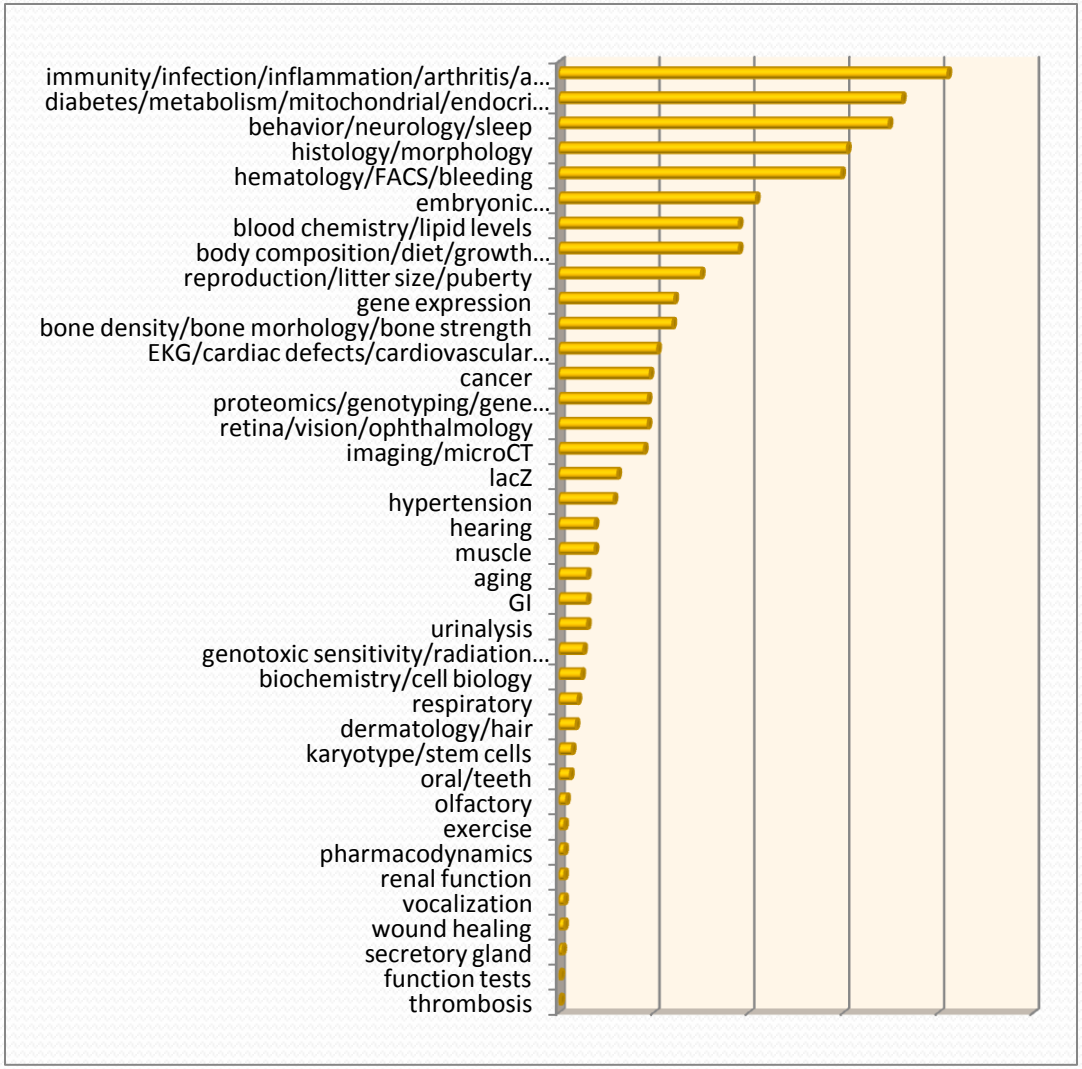
IMPC Phenotyping Proposal

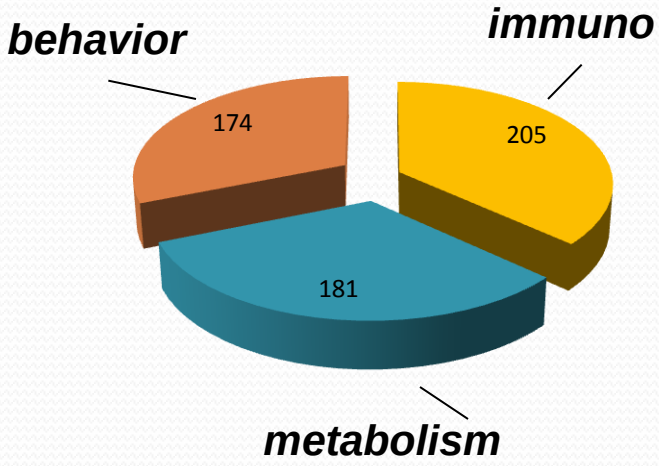
The proposal will be shaped by:

- **EUMODIC results**
- **The Sanger MGP**
- **Publicly available data (Lexicon and Deltagen)**
- **ENU screens phenotyping results**
- **Survey Results from UK, NIH, EU**
- **Recommendations from workshops in the UK and US**
- **Future workshops in Europe, US, Canada and UK**

Survey Summary Report

Question #2: Thinking beyond your laboratory, what do you see as the 3 essential tests, analyses, and/or examinations that would most likely reveal the utility of a mutant mouse line in your field? Two caveats: the numbers of mice used per test are limited to 5-10 and the tests must be high throughput (100's/y).

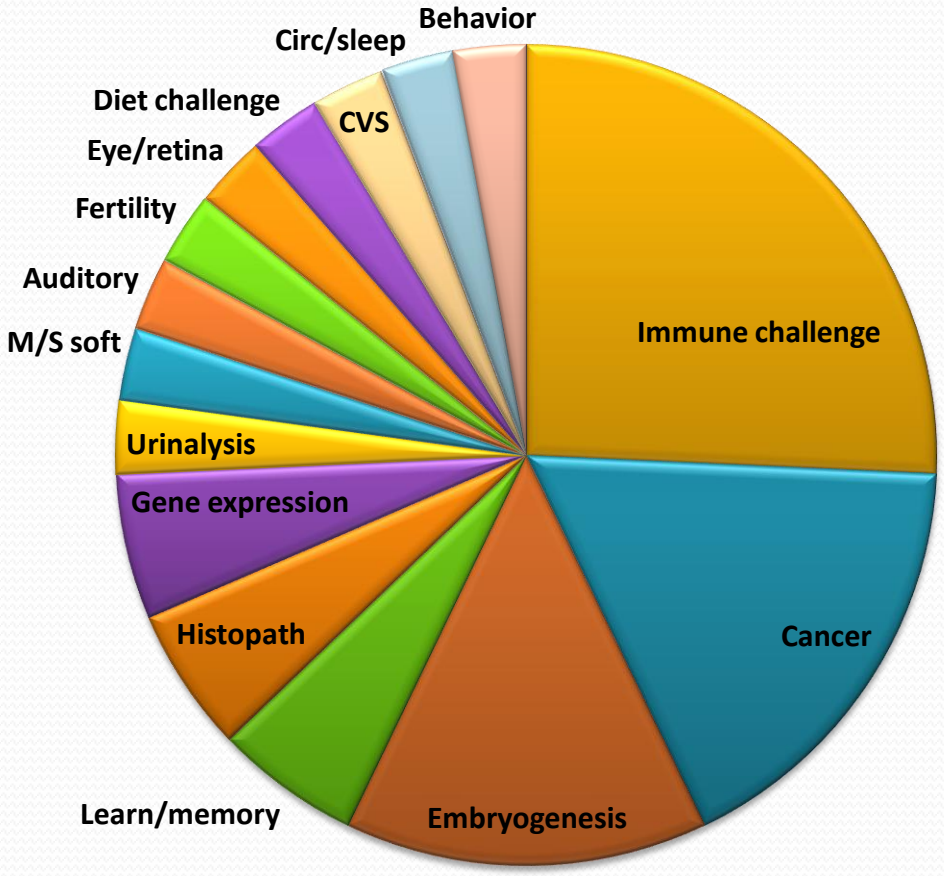




MMRC Survey Conducted by Kent Lloyd

Survey Summary Report

What is missing?



MMRC Survey Conducted by Kent Lloyd
>2000 e-mails and ~300 respondents

Cost Components: MLC, MRC, Harwell

Mouse Production & Archiving: £21,690
Generation of mice from ES Cells Archiving the mouse line
Viability and Fertility testing Breeding of cohort of 8M & 8F mutants
Housing for phenotyping cohort (8M & 8F mutants & 4 WT controls)

Gene Expression: £1100
Adult WM Embryo WM

Metabolism: £1300
High Fat Diet
Challenge
IPGTT
DEXA
Weight Curve
Calorimetry
Full Clinical
Chemistry

Behaviour: £500
SHIRPA
Open Field
Grip Strength
Rotarod

Behavior/Sensory: £400
Hot Plate
PPI
Opthalmoscope
Slit lamp

Haematology: £80
RBC
WBC
Platelet Counts
etc

Immune: £1,060
FACS of PBL
IgG Levels

Cardiovascular: £1100
Non invasive blood
pressure ECG
Echocardiograph
Heart Weights

Bones & Development: £350
Dysmorphology
Weight Curves
Faxitron

Total Cost: £27,580

Key Areas of Unmet Need

Cancer	Aging	Embryology
• Need longer time line to study • Fits with aging • Challenge?	• Critical need cited in all surveys and workshops • Strongly augments: Cancer, Cardiovascular, Metabolic, Neurodegeneration and Bone Research	• A rich source of phenotype data • ~30% KOs E.L. • Very Specialized Skill Sets Req. • Need HTP approach • Meeting at TCP April 9-10

New Areas and Cost Challenges

Respiratory: £441
Plethysmograph Challenge

Aging: **£18,617** New cohort
production and cage costs for 18 months

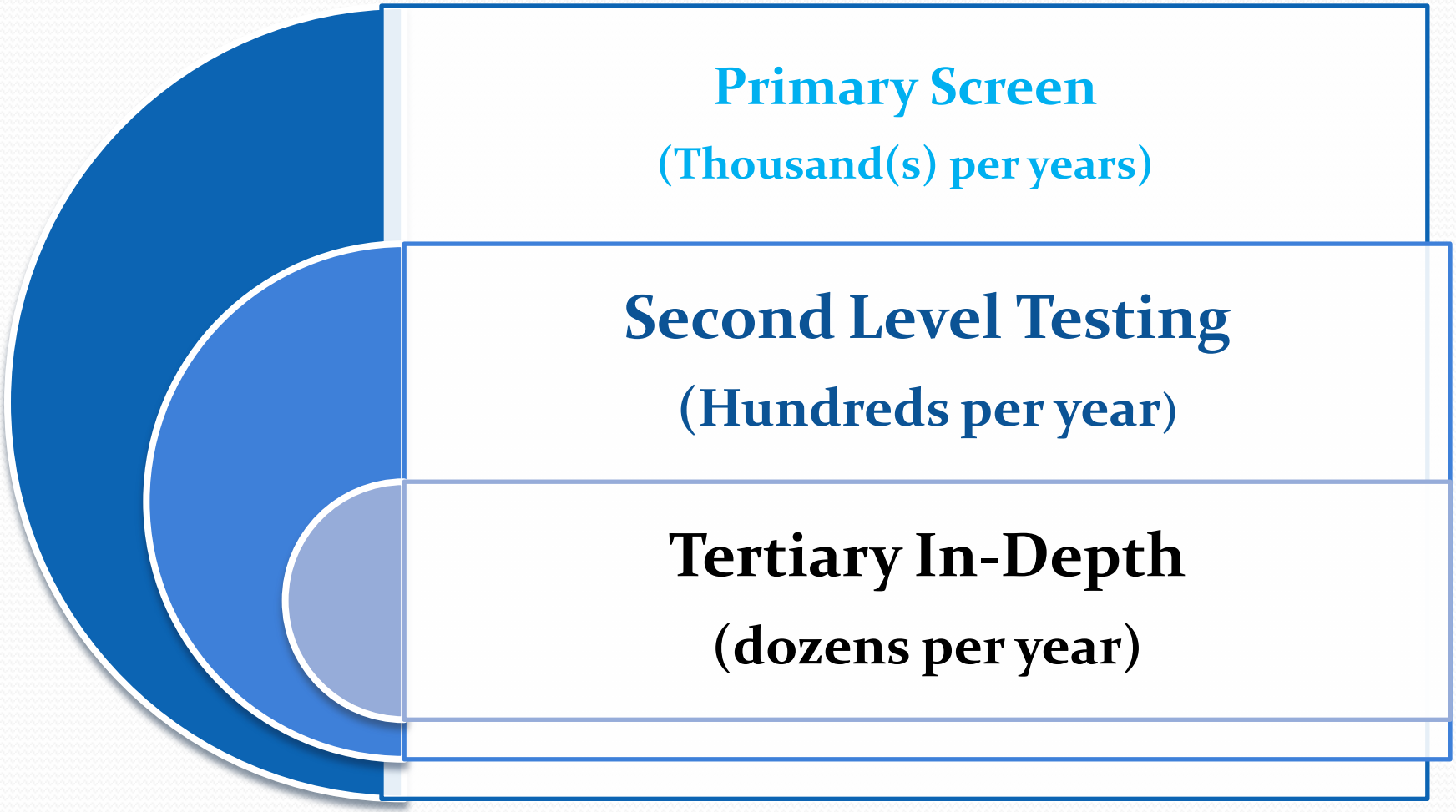
Embryology: **?????$$$$$$**

Immunology Challenge
Infectious vs defined antigen
?????$$$$$$

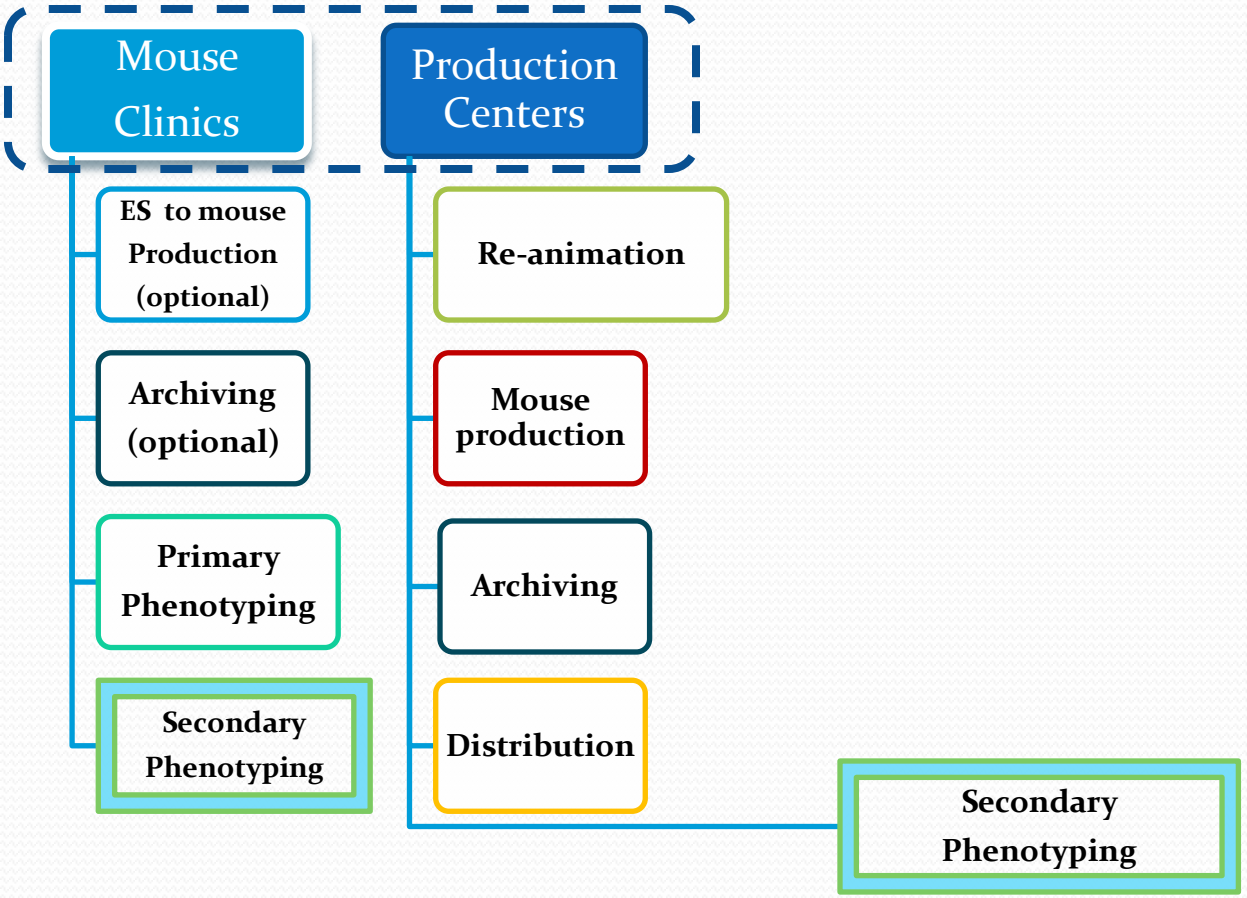
IMPC Phenotyping

- Core group of tests at all centres
- Agreed upon minimum cohort size (7?)
- Test and recommend additions to or dropping phenotypic tests from the pipeline
- Groups are encouraged to add tests to the phenotyping platform where possible
- Each centre is encouraged to incorporate a challenge assay or assays to the platform
- Each centre should develop networks of collaborators
- MRI and/or micro CT likely to be added
- Incorporate study of embryonic lethals

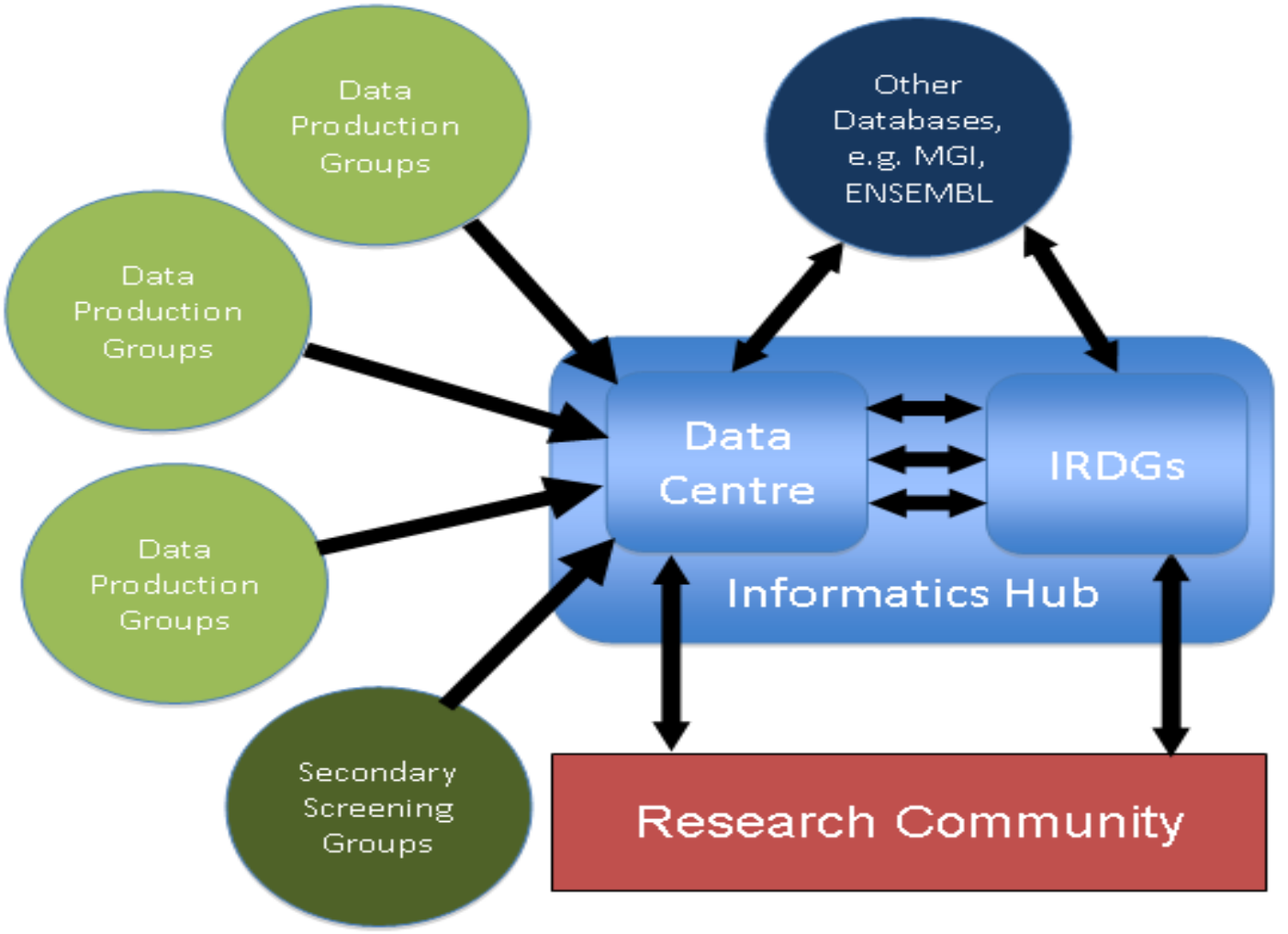
Phenotyping Progression



Mouse Phenotyping and Production/Distribution Centers



Informatics Organization



IMPC Next Steps

Informatics	• Form Steering Committee • Develop Requirements Document
Mice	• Explore new ways to lower mouse costs • Continue exploring commercial options
Tech Dev	• Form Tech Development Group • First Tasks: Imaging Recommendation (&Pathology) • Embryonic Lethal Analysis
Phenotyping	• Develop final plan for IMPC Pipeline • Operating plan for review of pipeline
Challenge Models	• Working groups in each area • Devise how to test models at centers

IMPC Cost Projections

Reasearch Groups	Yearly Output	Totals	Yearly Cost	Total Cost
WTSI	200	1000	£ 6,000,000.00	£ 30,000,000.00
Harwell	100	500	£ 3,000,000.00	£ 15,000,000.00
Infrafrontiers: ICS,GMC	150	750	£ 4,500,000.00	£ 22,500,000.00
NIH Group1	250	1250	£ 7,500,000.00	£ 37,500,000.00
NIH Group2	250	1250	£ 7,500,000.00	£ 37,500,000.00
TCP	100	500	£ 3,000,000.00	£ 15,000,000.00
Totals	1050	5250	£ 31,500,000.00	£157,500,000.00
Cost per line		£ 30,000		
Total Cost Phase I		£ 157,500,000		

IMPC Phase II Projections

Phenotyping Output

Research Groups	Yearly Output	Totals
APN	150	750
China (Nanjing)	200	1000
China (group 2)	200	1000
CZECH R	150	750
GMC	150	750
Harwell	150	750
ICS	150	750
NIH Group1	600	3000
NIH Group2	600	3000
TCP	250	1250
UAB	200	1000
WTSI	200	1000
Totals	3000	15000

Project Costs

Cost per line		£ 15,000
Total Cost Phase IV		£ 225,000,000
Cost per line		£ 20,000
Total Cost Phase IV		£ 300,000,000
Cost per line		£ 25,000
Total Cost Phase IV		£ 375,000,000

Next 3 years (2010-2013)

- *EUMODIC project will come to completion*
- *UC, Davis has funding to support the creation and limited analysis of 312 KO mouse lines*
- *The WTSI is funded to analyse 200 KO lines per year*
- *MLC Harwell planning to analyse 100 KO lines per year*
- *Toronto Centre for Phenotyping (TCP) has capacity to produce and analyse 100-200 KO mouse lines per year.*
- *InfraFrontiers is developing the vital infrastructure for the continuation and expansion of mouse*
- *Phenotyping New centres at UAB (Barcelona) and the Czech Republic will be constructed and come online*
- *NIH has raised funding to launch Phenotyping*