



UNC Chapel Hill

Mutant Mouse Research Modeling Human Health & Disease

Terry Magnuson
Project Director, UNC MMRRC

DPCPSI U42OD010924

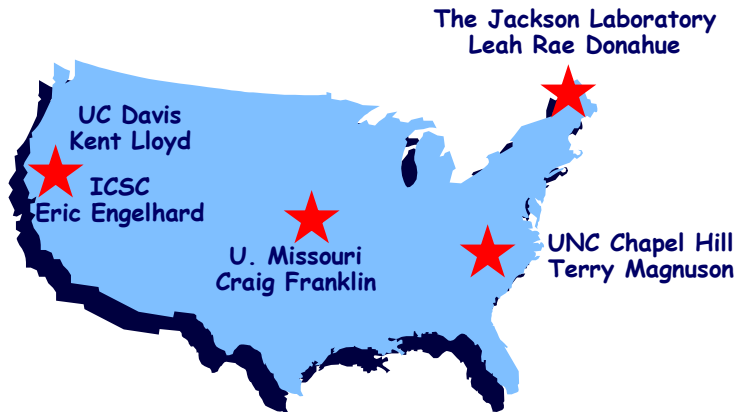
MMRRC
Mutant Mouse Regional Resource Centers
supported by the National Institutes of Health, Division of
Program Coordination, Planning, and Strategic Initiatives

a repository for the archiving
and distribution of mutant ES cells,
germplasm and mice

Find or donate your mouse model today
1-800-910-2291 mmrrc.org

A circular inset image showing a person's hands holding a small, light-colored mouse. The person's face is partially visible in the background.

MMRRC regional distribution facilities



Advantages to Researchers

- Secure against loss of strains
- Facilitates NIH sharing
- Saves research dollars

MMRRC Mission

- Import, archive, distribute genetically engineered mouse strains & ES cell lines
 - 3,851 strains/lines available for distribution
 - 7,281 orders; 2,750 unique strains/lines
 - Supporting projects funded by 15 different NIH Institutes
- Ensure quality control (genotype, health status)
- Consultation
- Research & Partnerships

Advantages to Facilities

- Colony management (saves space)
- Disaster plan management
- Health status

International Co-operation

Practices common to repositories

Identify & evaluate mouse strains

Acquire, archive & distribute

Quality control programs

Maintain & meet
national/international standards

Customer service & technical support

Provide special services

Coordination amongst repositories

Provide educational & training

Research & Partnerships

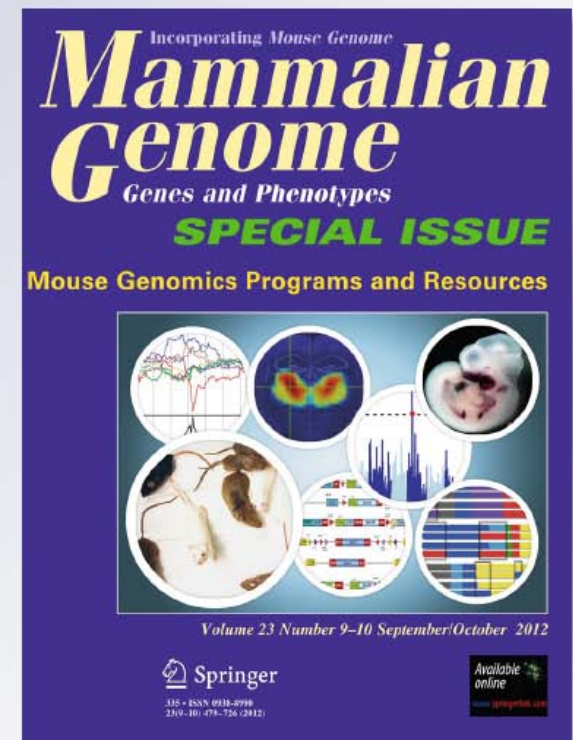
Centralized mouse repositories

**Leah Rae Donahue, Martin Hrabe de
Angelis, Michael Hagn, Craig Franklin,
K. C. Kent Lloyd, Terry Magnuson,
Colin McKerlie, et al.**

Mammalian Genome

ISSN 0938-8990
Volume 23
Combined 9-10

Mamm Genome (2012) 23:559-571
DOI 10.1007/s00335-012-9420-4



MMRRC Value Added Research & Partnerships

- **JAX: Genetic Resource Sciences**
Reproductive sciences, sperm cryo kit, Cre farm, disease panels, congenic panels
- **UCD: Mouse Biology Program**
ES, iPS cell derivation, gene targeting, speed congenics, phenotyping, KOMP
- **UM: Rat & Swine Resource Centers**
Rodent diseases, mucosal immunology, cryobiology
- **UNC: Systems Genetics**
Genotyping, sequencing, & informatics platforms, pipelines, & tools



Mutant Mouse Research Modeling Human Health & Disease

MMRRC

Immune
Response

CEGS

Mouse Phase I

Gnobiatic

Collaborative
Cross



Strain Certification

A service of the UNC Mutant Mouse Regional Resource Center

[Home](#)
[Strain Q/C](#)
[MMRRC Catalog](#)

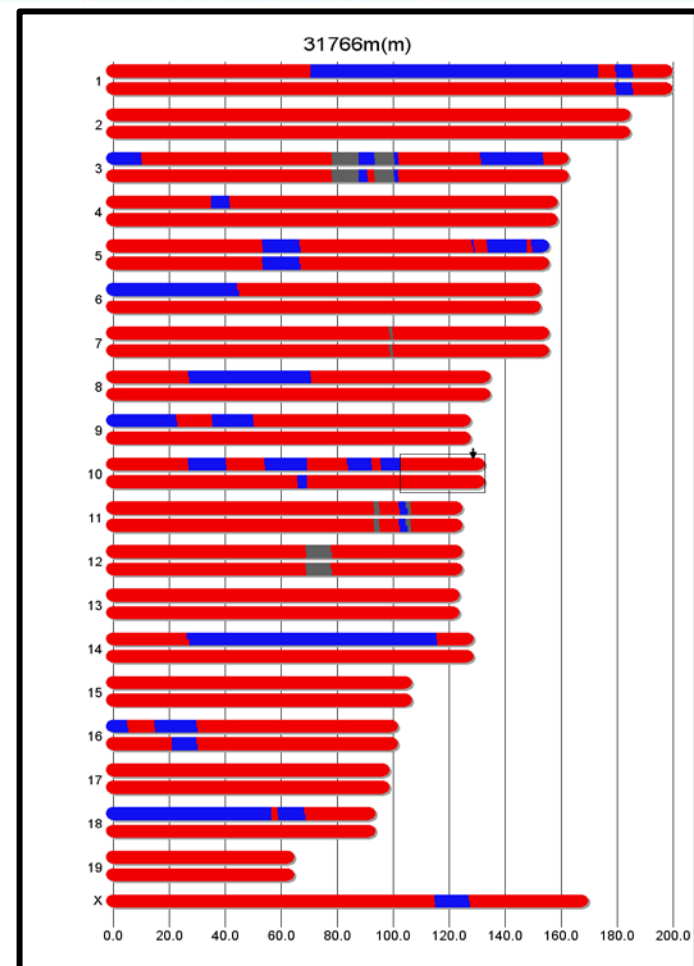
Mouse Universal Genotyping Array (80,000 SNPs)

MMRRC-specific computational tool for
haplotype reconstruction

129S6 (red) = ES cell strain of origin
for the mutation

BL/6 (blue) is the backcross

Gray: some other strain contamination





Strain Certification

A service of the UNC Mutant Mouse Regional Resource Center

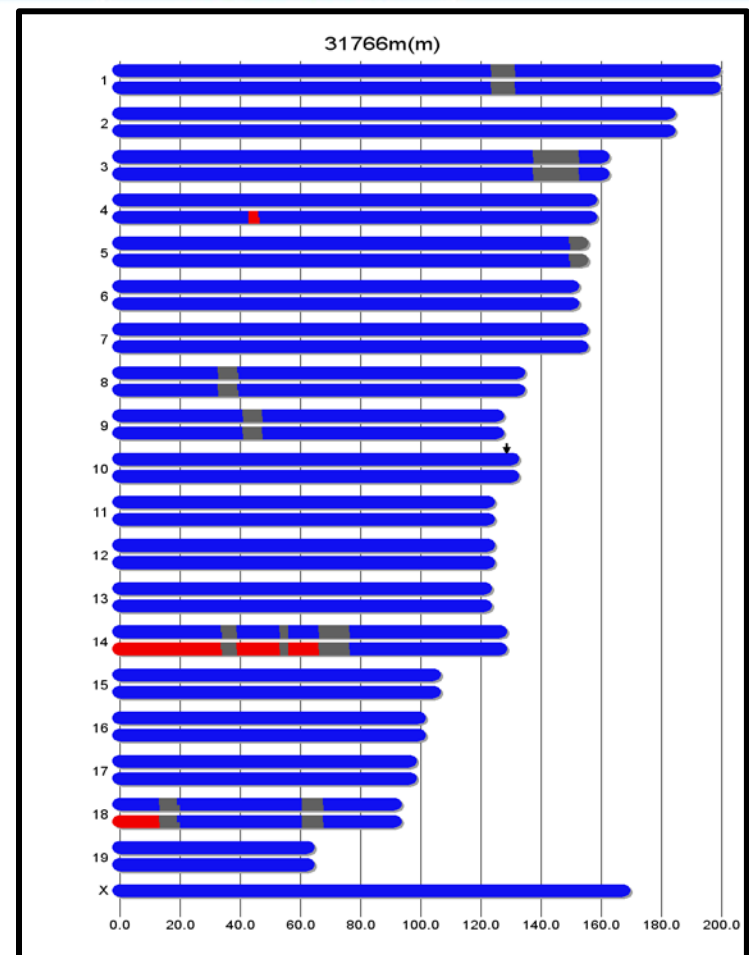
[Home](#)[Strain Q/C](#)[MMRRC Catalog](#)

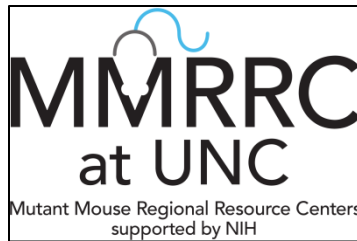
Mouse Universal Genotyping Array

129S6/red = mutation strain of origin

129S1/SvJ/blue = backcross strain

Gray: some other strain contamination

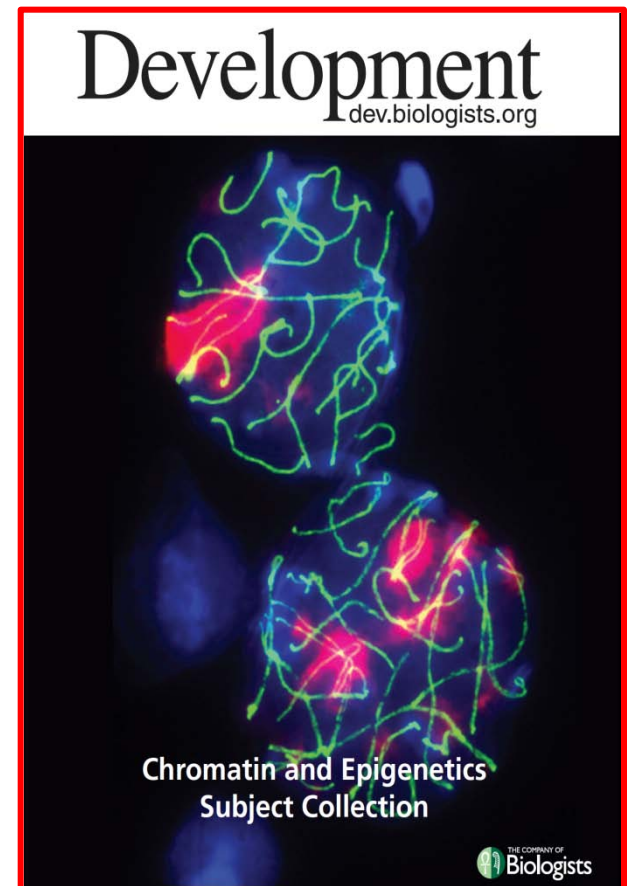




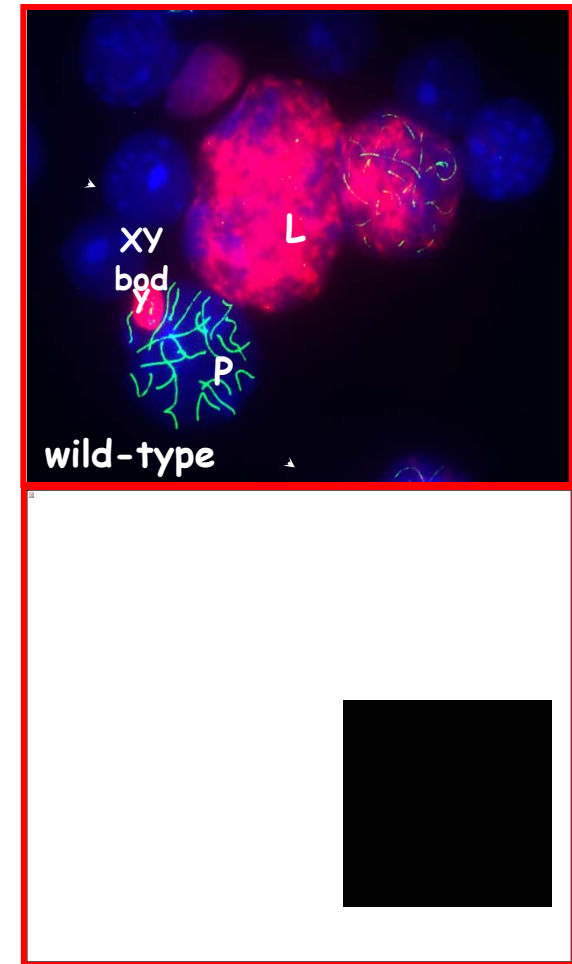
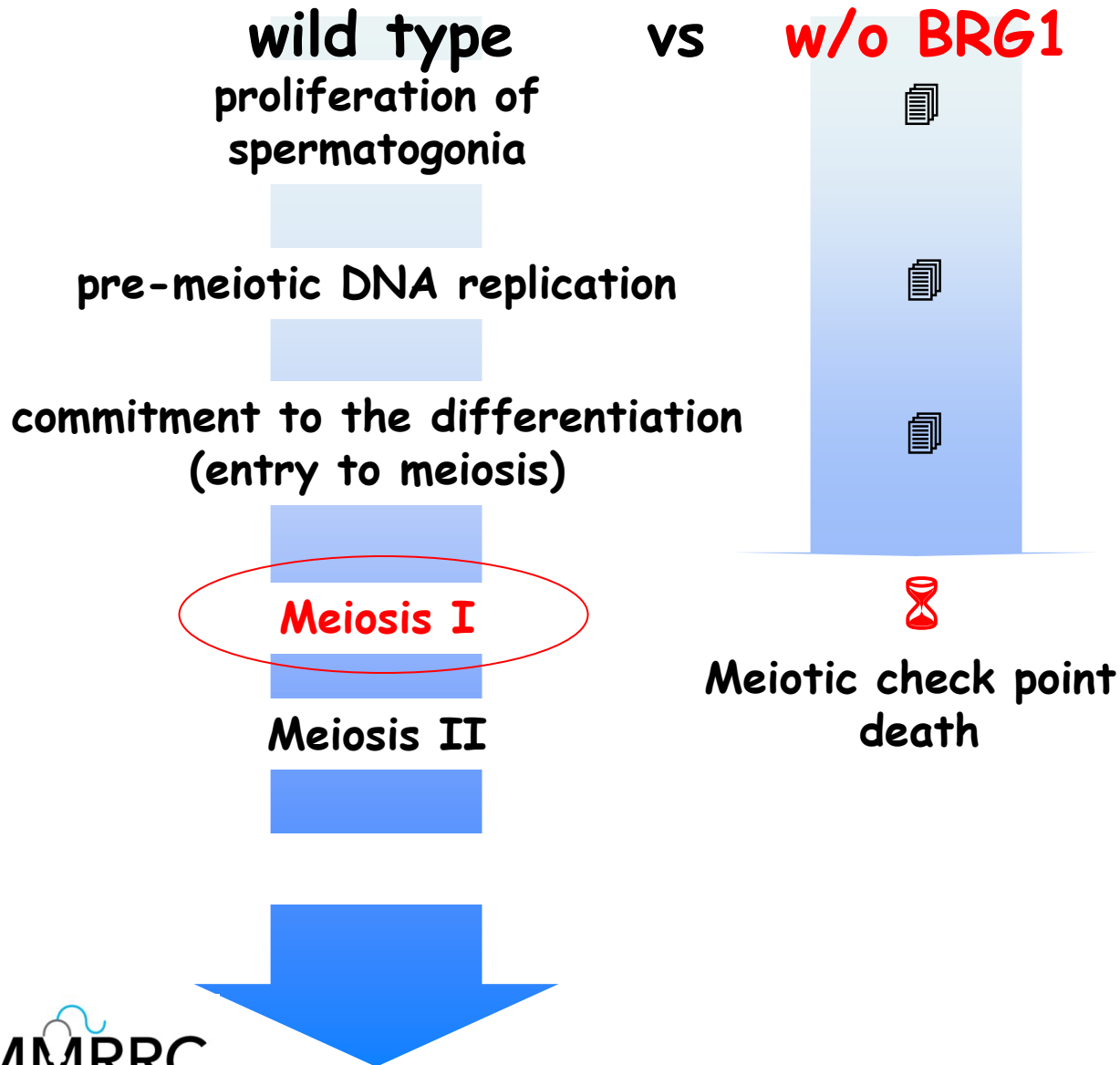
Epigenetics & Fertility

Kim, Y., Fedoriw, A. & Magnuson, T (2012)

An essential role for mammalian SWI/SNF
chromatin remodeling complex during male meiosis.
Development 139, 1133-1140



Epigenetics & Fertility

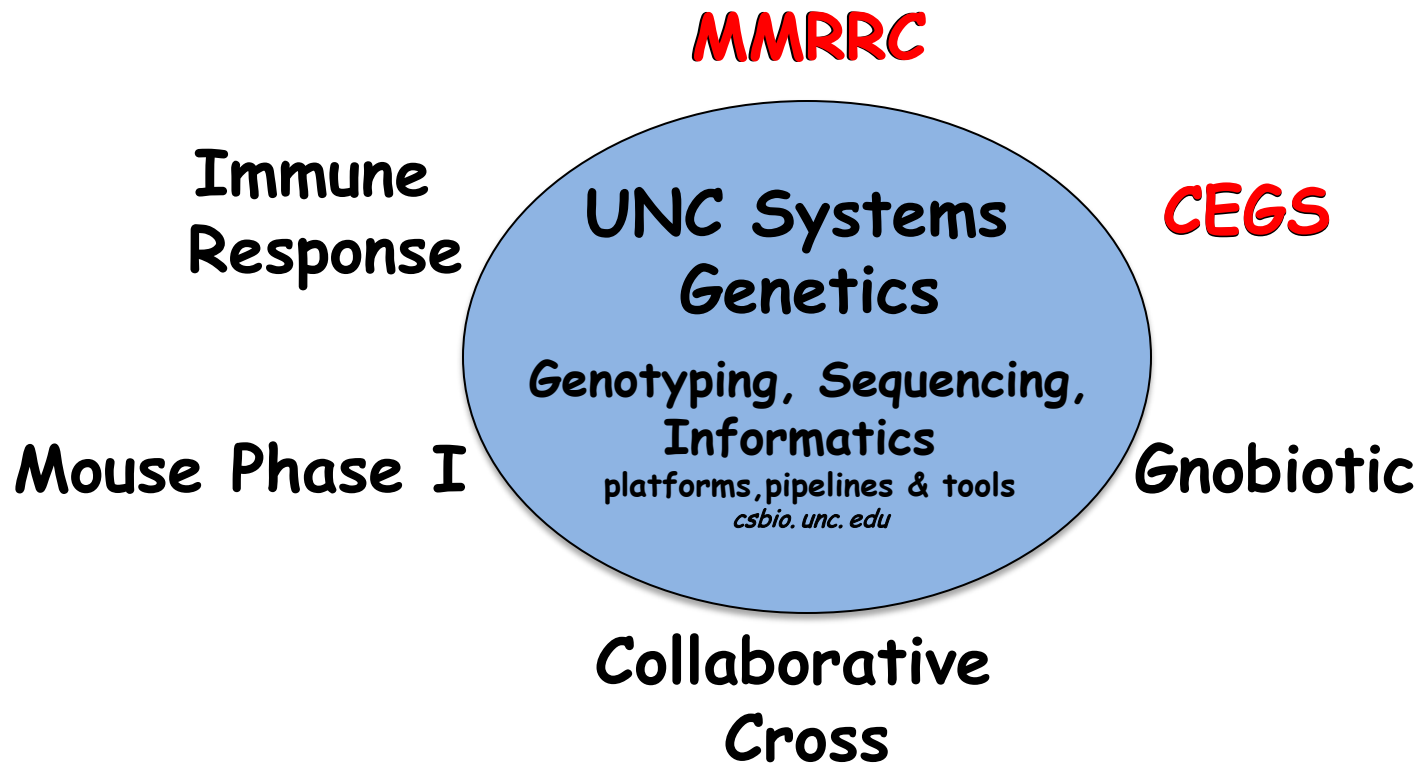


Double strand DNA
repair defect & chaotic
synapsis

Yuna Kim
Andy Fedoriw



UNC Chapel Hill



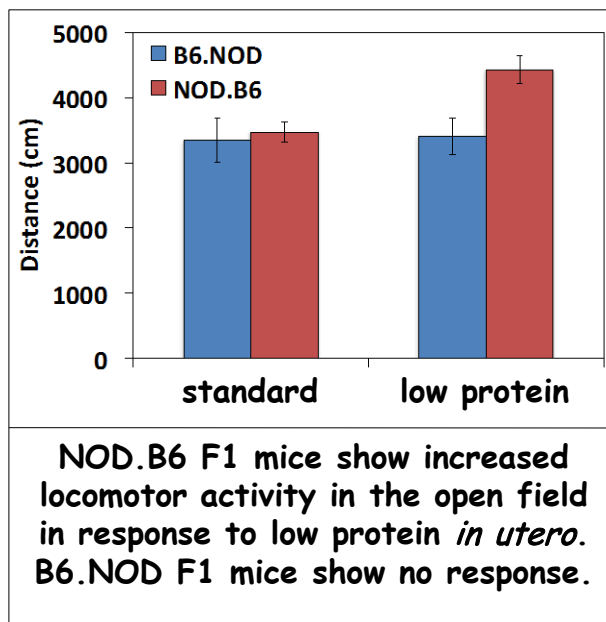


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Behavioral Phenotyping
Lisa Tarantino
CEGS
P50MH090338
P50HG006582

Effect of Prenatal Diet on Adult Behaviors

- B6.NOD & NOD.B6 reciprocal F1 mice
 - Diets: standard, low protein
- Mothers exposed to diet for 5 weeks prior to breeding & then throughout gestation until weaning
- Are there diet x strain interactions?

Diet x Strain Interaction





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Behavioral Phenotyping
Lisa Tarantino

Effect of Housing Environment on Behavior

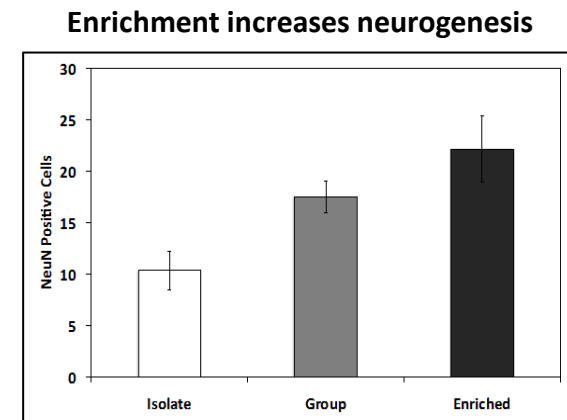
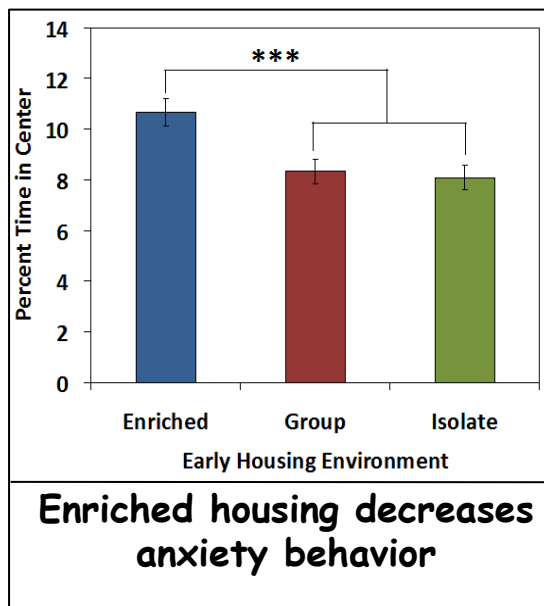
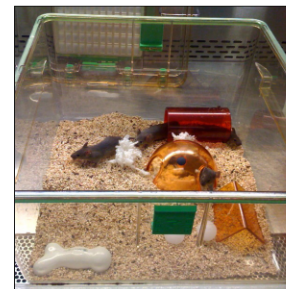
Isolation
Housing
(1 mouse,
standard cage)



Standard Group
Housing
(4 mice, standard
cage)

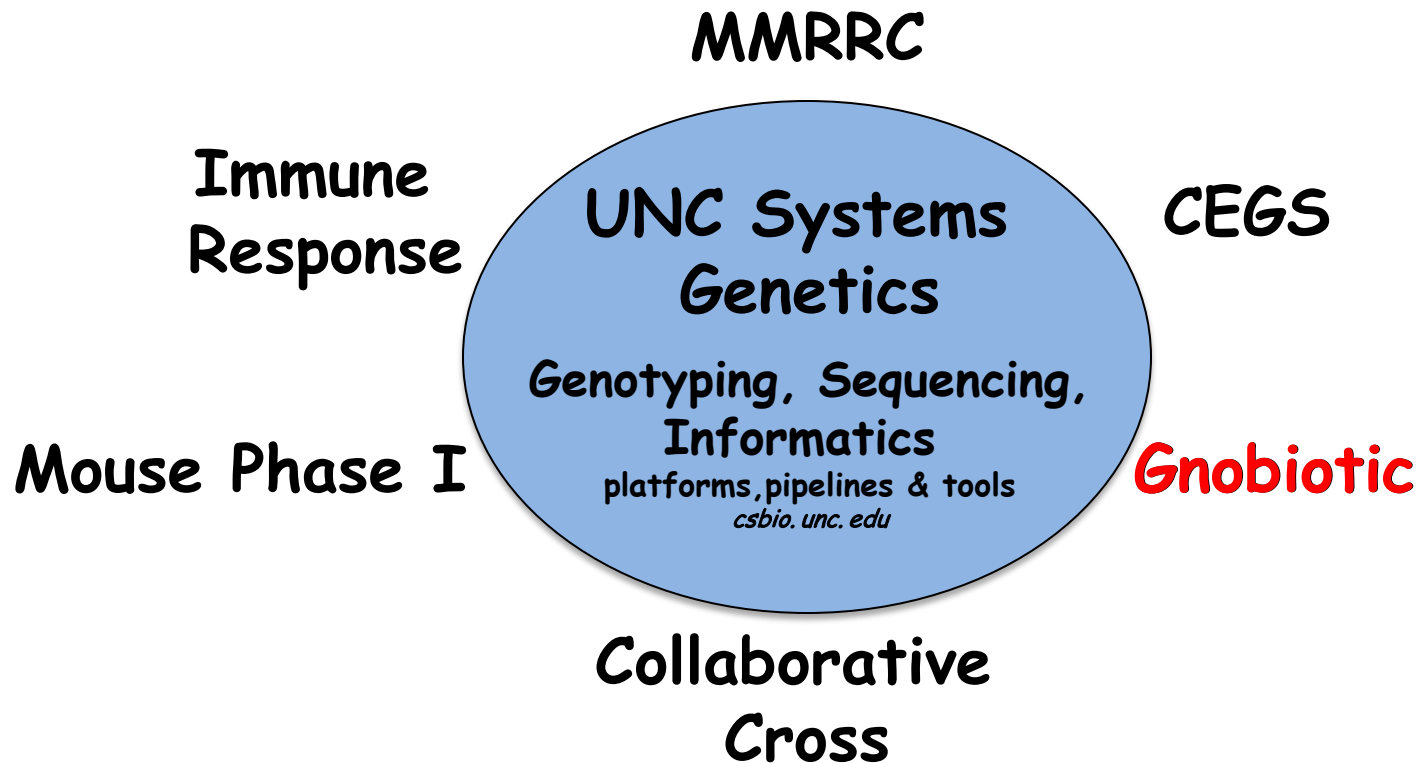


Enriched Group
Housing
(4 mice, enriched
cage)





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National Gnotobiotic Rodent
Resource Center
DPCPSI P40 OD010995
R. Balfour Sartor, M.D.
Director

Gnotobiotic Rodent Resource

Gnotobiotic (known life): germ-free or selectively colonized gut with defined microbial species

Host/microbial interactions

Physiologic & pathophysiologic responses to bacteria

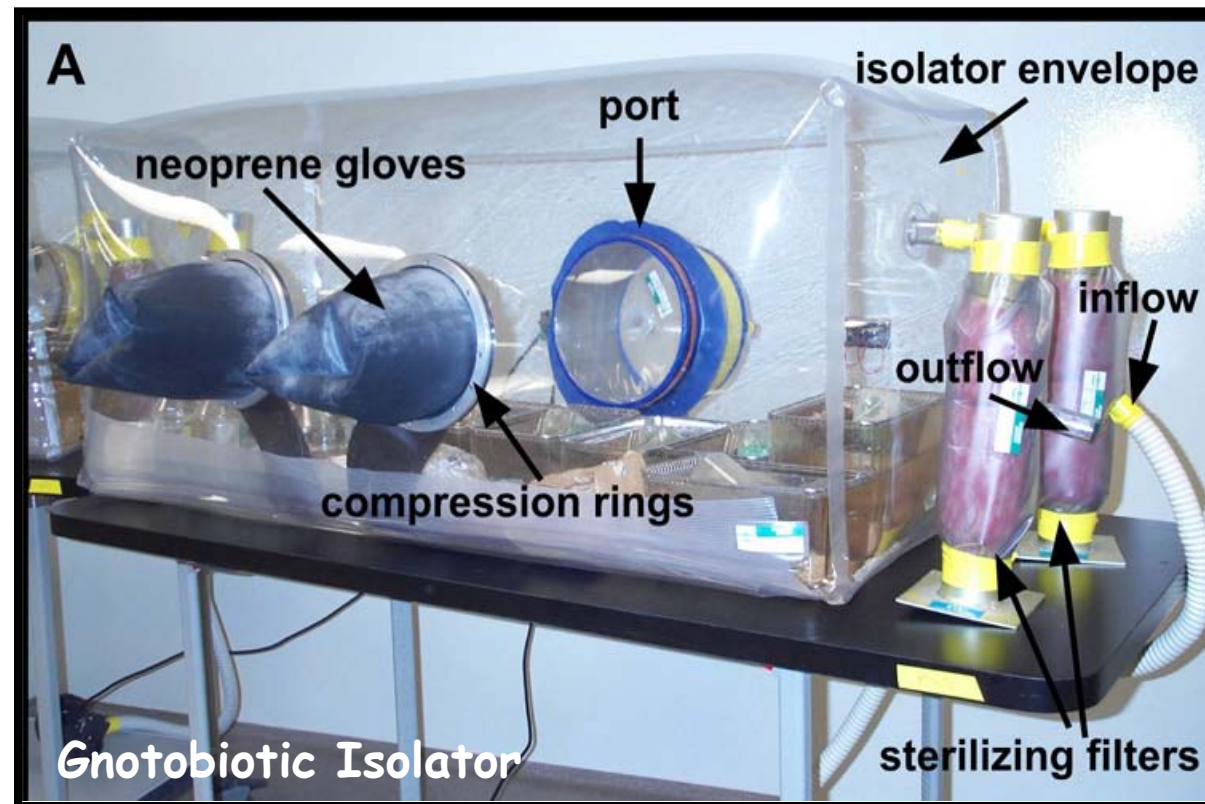
Functional effects of bacteria, virus & fungi with selective colonization

Precise onset of colonization for kinetic analyses

Gene-microbiota interactions are important in many diseases

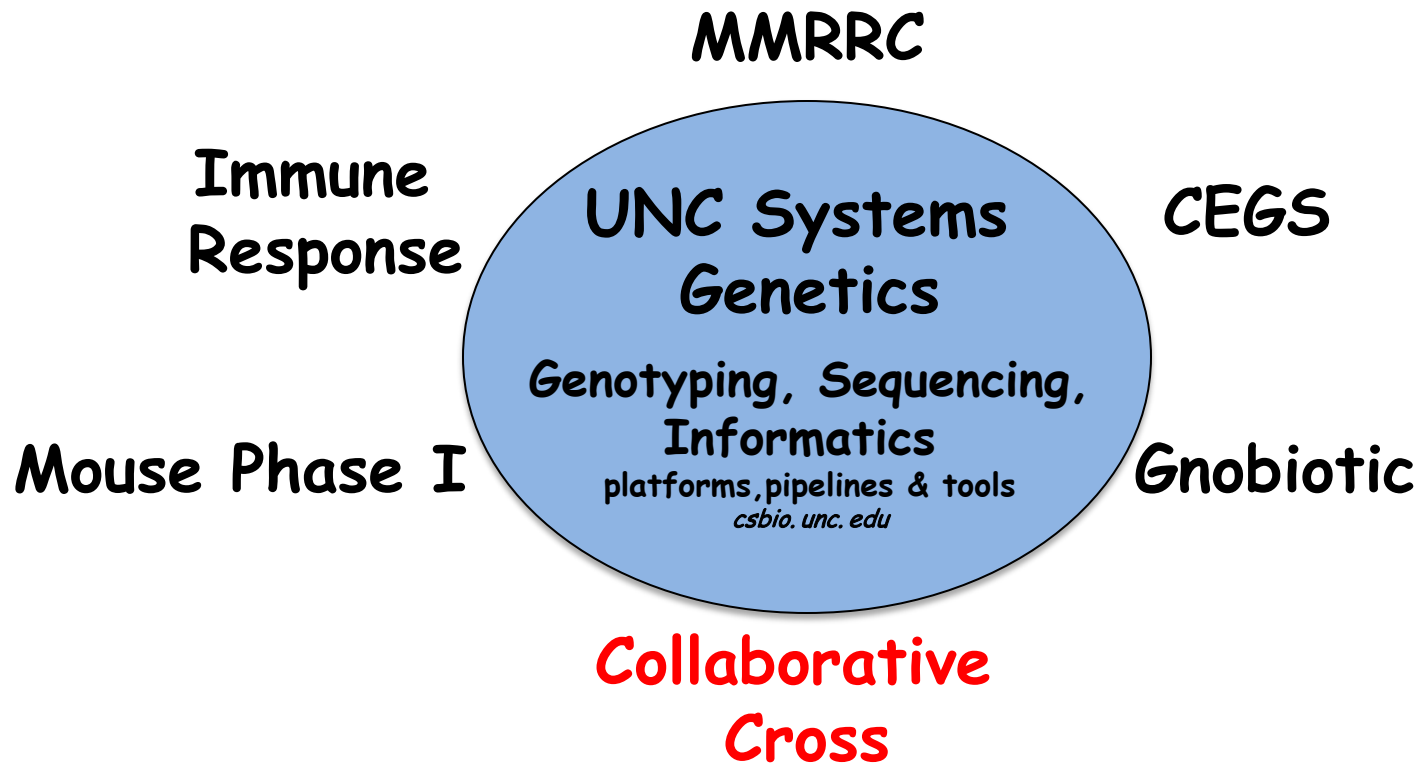
22 strains available

2011-2012 provided 2963 gnotobiotic mice to 60 PIs





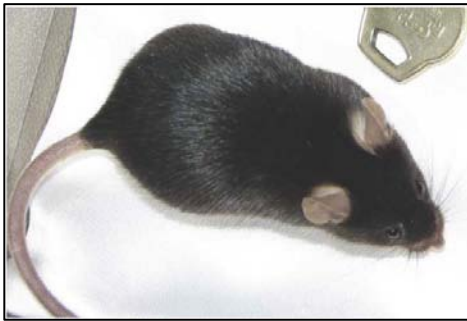
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Collaborative Cross Systems Genetics & Predictive Biology in Mouse



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Systems Genetics
Fernando Pardo Manuel de Villena
NCI, NIMH, NHGRI, NIAID, NICHD

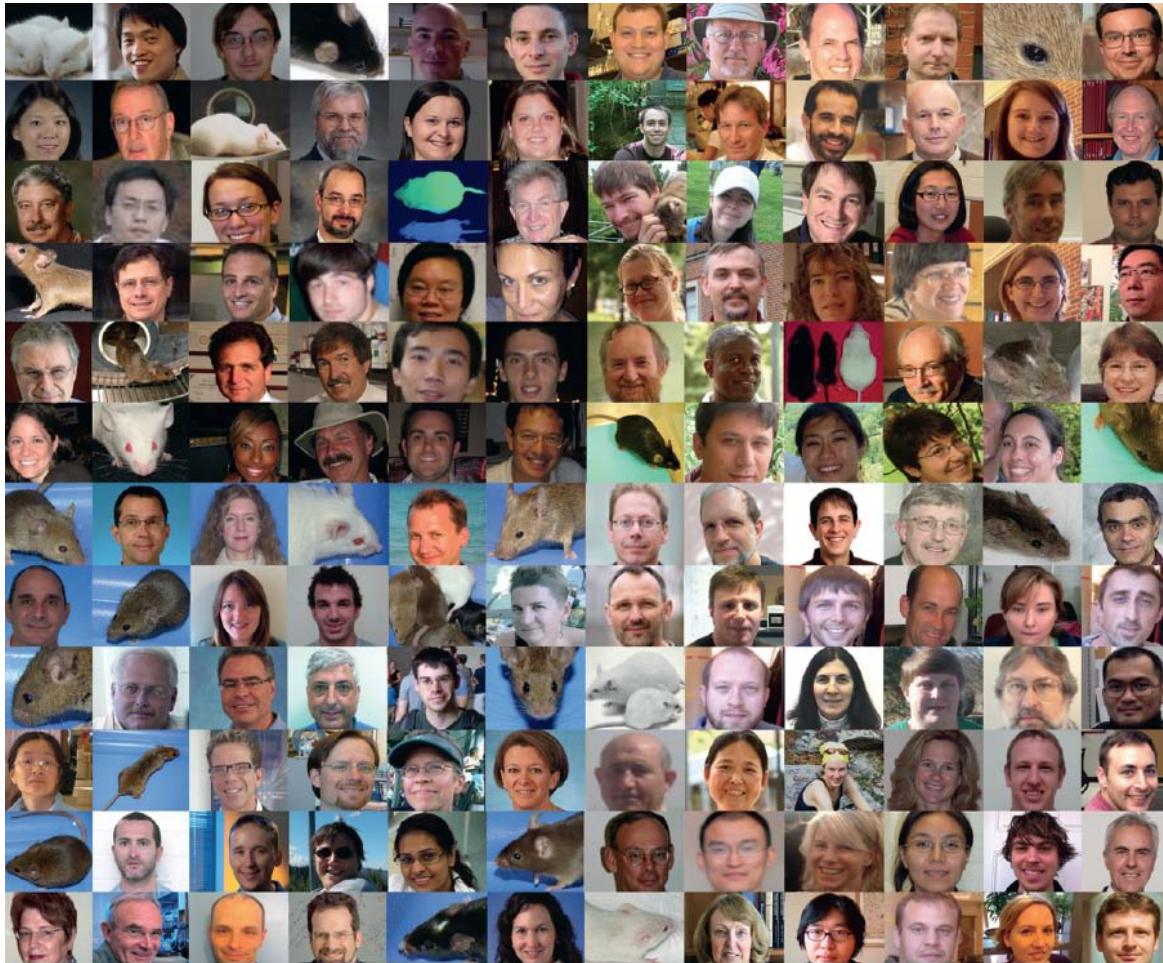


C57BL/6J

=



Systems Genetics & Predictive Biology in Mouse



Genomic variability

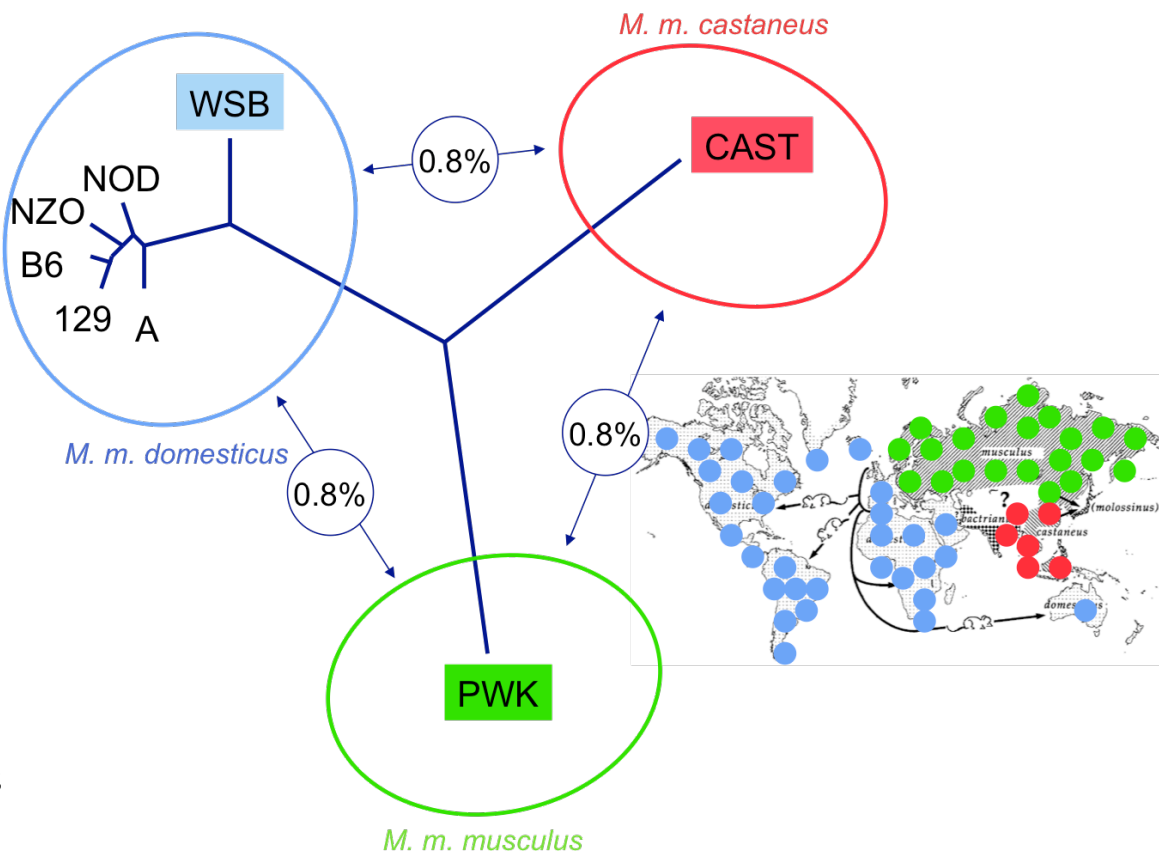
≠



C57BL/6J



Systems Genetics & Predictive Biology in Mouse



Collaborative Cross:

8 Founder lines

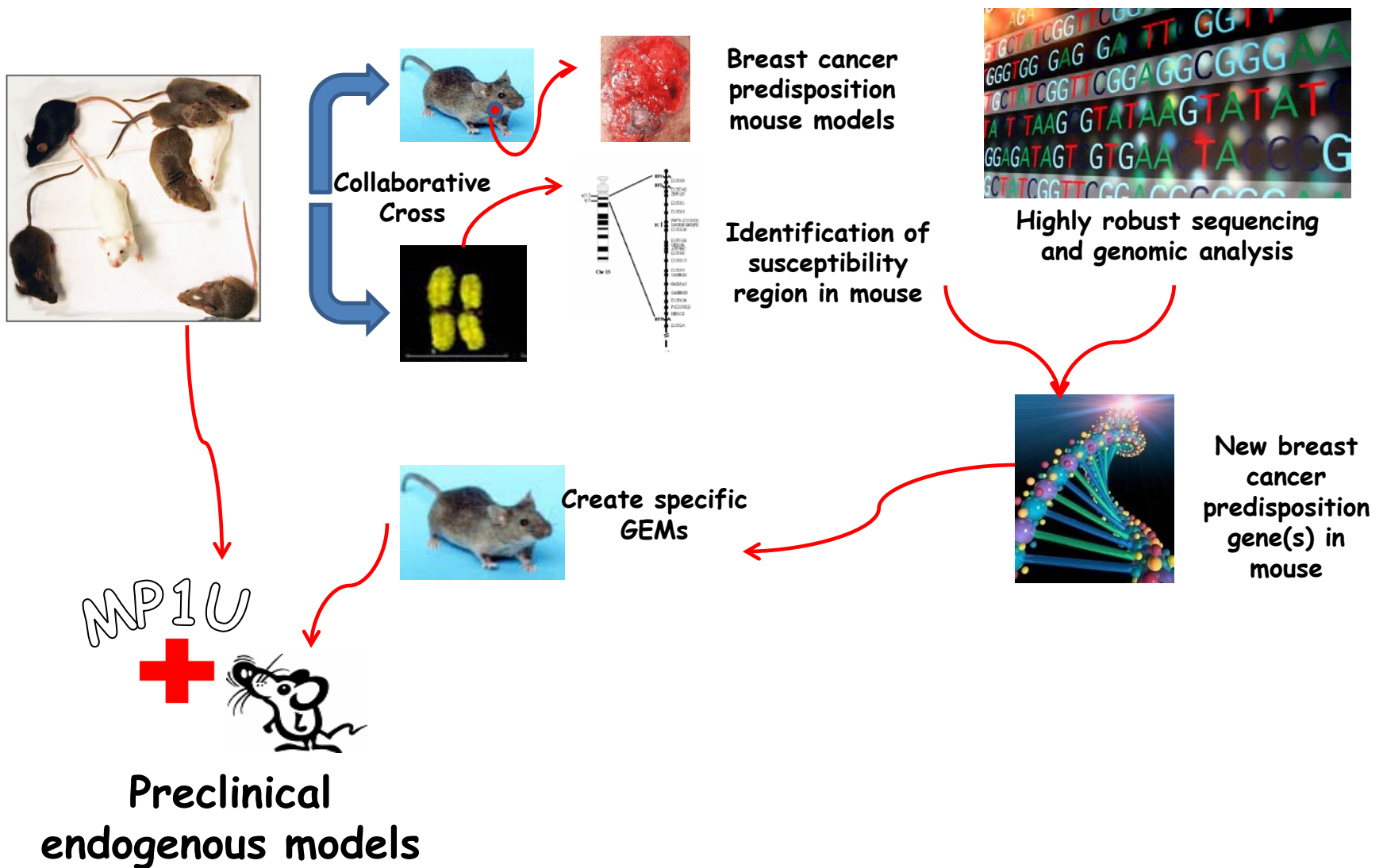
Funnel breeding scheme

Genomic randomization

Diverse populations that are genetically reproducible

Integration of phenotyping & genomic analyses

Systems Genetics & Predictive Biology in Mouse



UNC Mouse Phase I Unit

Endogenous mouse models



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Mouse Phase I Unit
Ned Sharpless, PI
Chuck Perou, PI

- **Research Areas of Focus include:**

- Innovative Therapies and Delivery Systems
- Mechanisms of Drug Resistance
- Tumor Profiling using Next Gen Technologies
- Novel Tumor Imaging Modalities
- Environmental and Genetic Factors of Tumorigenesis

Diseases Represented

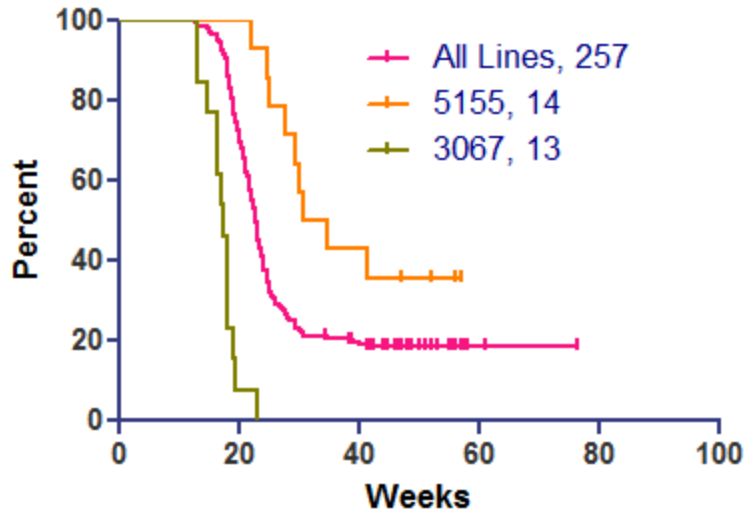
- Breast
- Melanoma
- Lymphoma & Leukemia
- Bladder
- Ovarian
- Lung

UNC Mouse Phase I Unit

Studying Cancer in a Highly Diverse Population using the Collaborative Cross



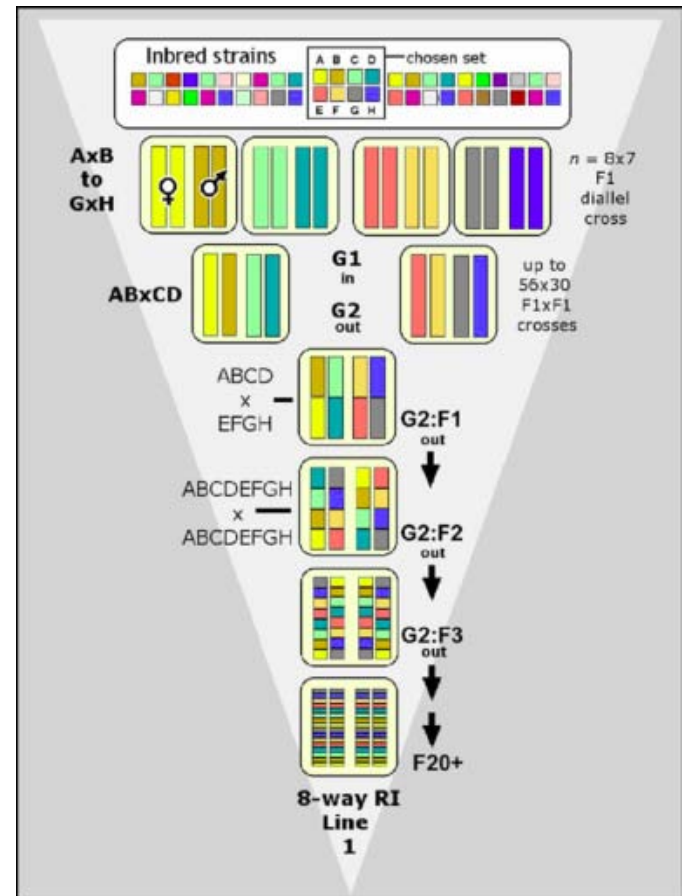
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Kaplan-Meier Plot showing Cancer Free Survival Mice Prone to Breast Cancer in Different Genetic Backgrounds.

Different CC lines were mated with a GEMM breast cancer model to study dominant genetic modifiers of tumor latency.

Genetic strain background is a major determinant of tumor susceptibility.



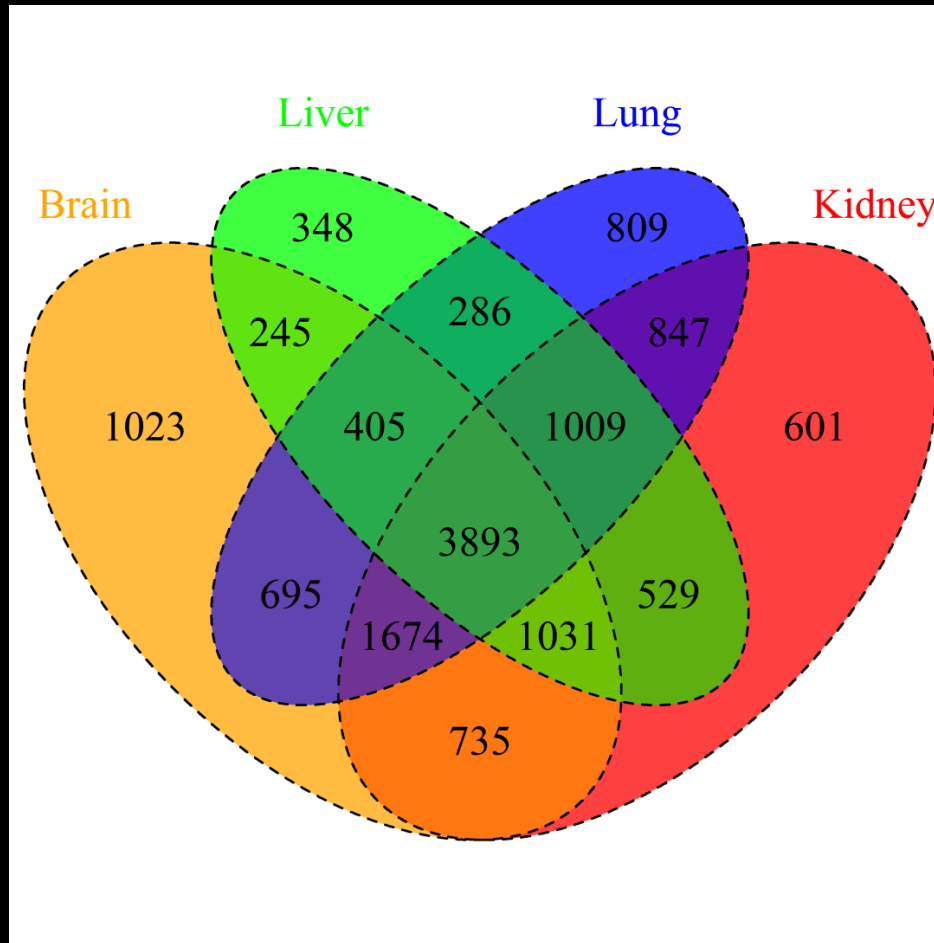
The Collaborative Cross complements the KOMP project
 (model to study consequences & molecular mechanisms of human regulatory variation)

Human		
GWAS	eQTL	ENCODE
Mostly SNPs in introns & intergenic regions	Significantly enriched for GWAS associations	GWAS hits are enriched in functional regulatory regions
Regulatory Variation		

Mouse
KOMP & ENU
Null & missense mutations
Gene Function

Mouse
Collaborative Cross
Most genes have at least one <i>cis</i> regulatory variant that results in differential gene expression
Reg. Variation

Evidence of regulatory variation in the Collaborative Cross



Number of differentially expressed genes with a *cis* regulatory variant in three of the CC founders (CAST/EiJ, PWK/PhJ and WSB/EiJ)

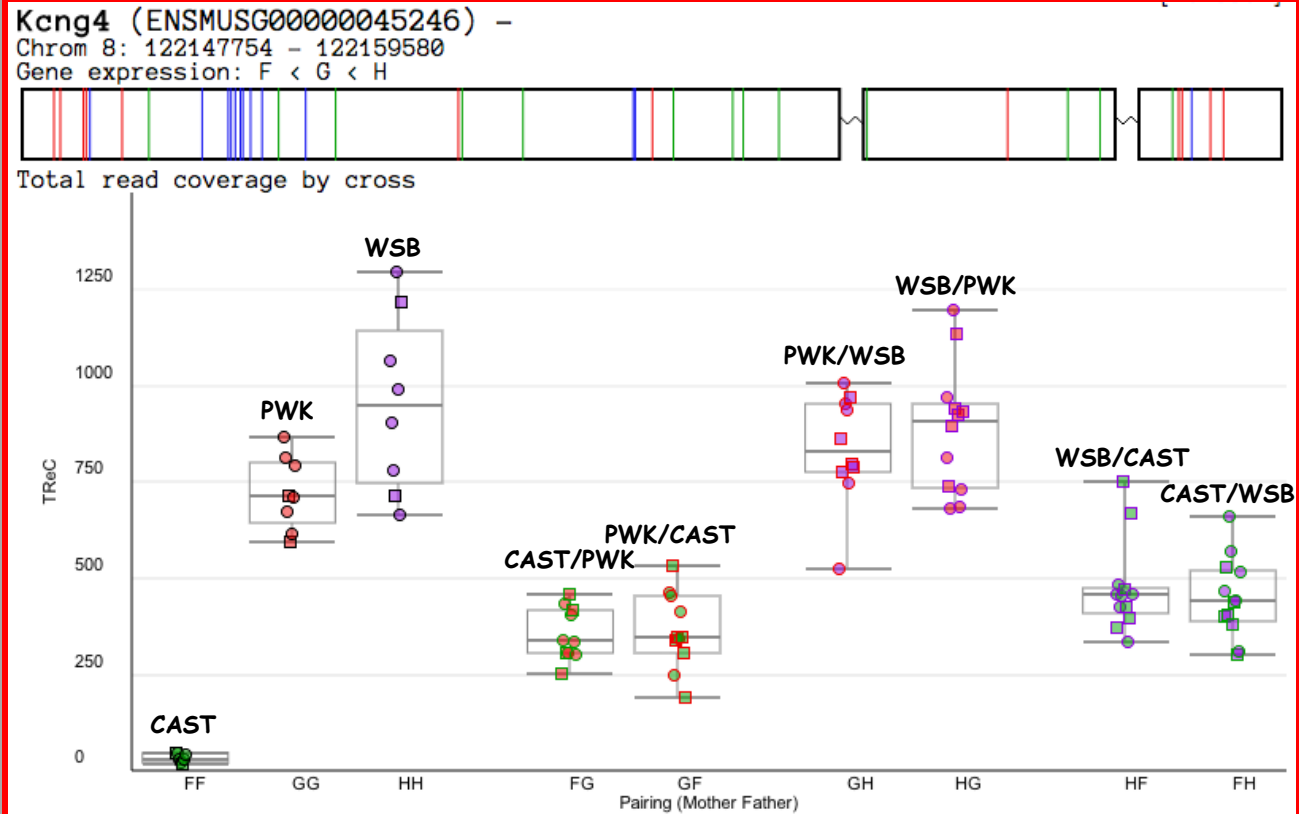
Cis regulatory strain effect on gene expression

Kcng4

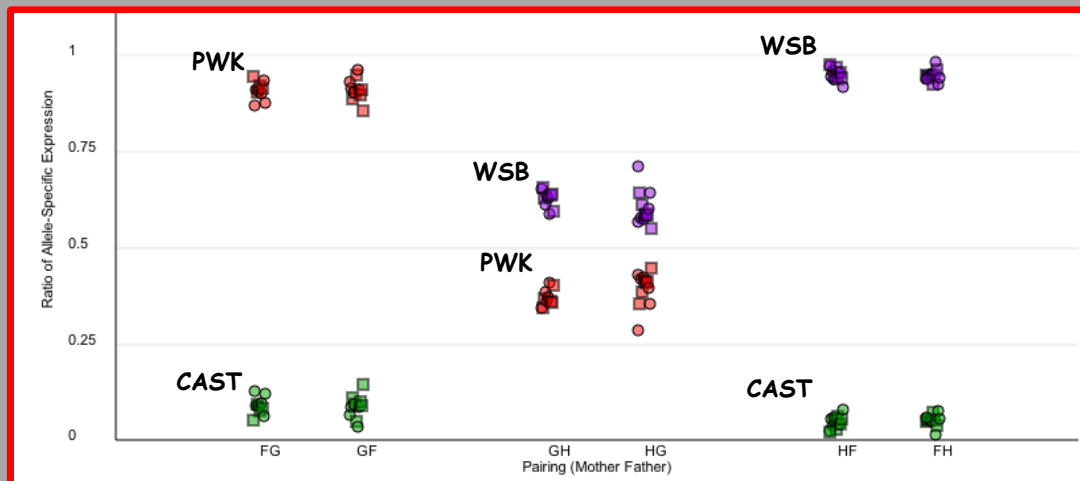
Allele-specific
expression

CAST/EiJ, PWK/PhJ,
WSB/EiJ

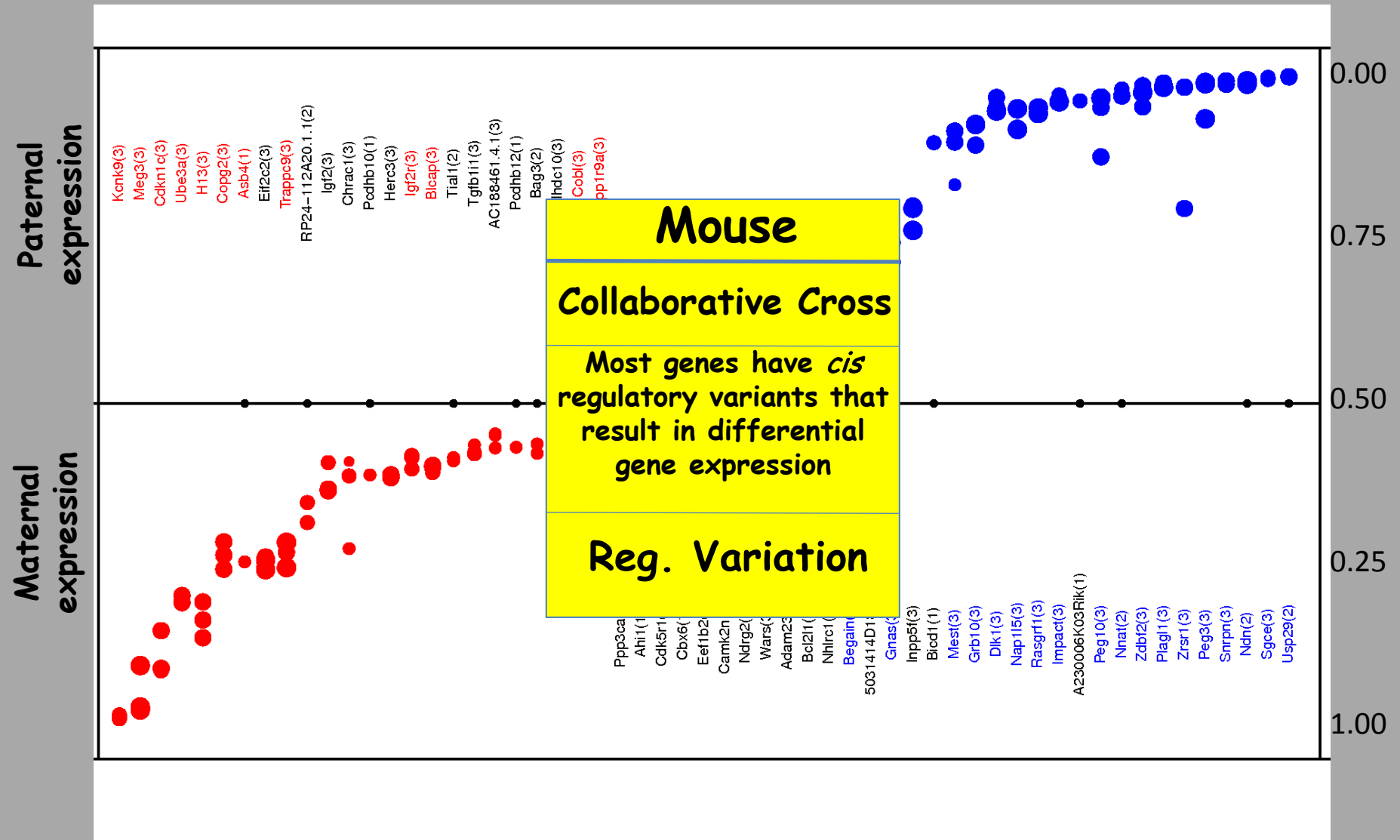
Total read count
(RNAseq)



Allele specific reads in
reciprocal F1 hybrids
(RNAseq)



Cis regulatory strain effect on gene expression in the brain




Each circle represent the ratio in reciprocal F1 hybrids between CAST/EiJ, PWK/PhJ and WSB/EiJ.

February 2012

GENETICS

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Collaborative Cross Panel

The CC is a diverse, well-powered population of mice that is being developed to study the genetic architecture of complex traits. It is composed of 10 founder strains, each with a unique genetic background, which are being crossed to create a population of mice with a wide range of genetic variation. This population is being used to study the genetic architecture of complex traits, such as behavior, metabolism, and disease susceptibility.

GSA

Genetic Science Association

Ten Years of the Collaborative Cross

David H. Thornton and Gary A. Churchill

The Collaborative Cross (CC) is a population of mice that is being developed to study the genetic architecture of complex traits. It is composed of 10 founder strains, each with a unique genetic background, which are being crossed to create a population of mice with a wide range of genetic variation. This population is being used to study the genetic architecture of complex traits, such as behavior, metabolism, and disease susceptibility.

The Genome Architecture of the Collaborative Cross Mouse Genetic Reference Population

Colleen E. Cawthon

The Collaborative Cross (CC) is a population of mice that is being developed to study the genetic architecture of complex traits. It is composed of 10 founder strains, each with a unique genetic background, which are being crossed to create a population of mice with a wide range of genetic variation. This population is being used to study the genetic architecture of complex traits, such as behavior, metabolism, and disease susceptibility.

Quantitative Trait Loci Association Mapping by Imputation of Strain Origins in Multifounder Crosses

Amel J. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Quantitative Trait Loci (QTL) association mapping is a powerful tool for identifying the genetic architecture of complex traits. In multifounder crosses, the genetic architecture is more complex than in traditional crosses, and the use of imputation to infer strain origins can improve the power of QTL mapping.

Genotype Probabilities at Intermediate Generations in the Construction of Recombinant Inbred Lines

Amel H. Zaitoun

Recombinant Inbred Lines (RILs) are a valuable resource for studying the genetic architecture of complex traits. The construction of RILs involves the repeated crossing of two parental strains, and the use of genotype probabilities at intermediate generations can improve the accuracy of the RIL construction process.

Varying Coefficient Models for Mapping Quantitative Trait Loci Across Recombinant Inbred Intercrosses

Amel H. Zaitoun

Quantitative Trait Loci (QTL) mapping is a powerful tool for identifying the genetic architecture of complex traits. Varying coefficient models can be used to map QTLs across different recombinant inbred intercrosses, allowing for the identification of QTLs that are specific to certain crosses.

High-Resolution Genetic Mapping Using the Mouse Diversity Outbred Strains

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

The Mouse Diversity Outbred (DO) strains are a population of mice that is being developed to study the genetic architecture of complex traits. They are composed of 10 founder strains, each with a unique genetic background, which are being crossed to create a population of mice with a wide range of genetic variation. This population is being used to study the genetic architecture of complex traits, such as behavior, metabolism, and disease susceptibility.

A General Bayesian Approach to Analyzing Diallel Crosses of Inbred Strains

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Diallel crosses are a type of cross in which two parental strains are crossed to create a population of offspring. A general Bayesian approach can be used to analyze diallel crosses, allowing for the identification of QTLs that are specific to certain crosses.

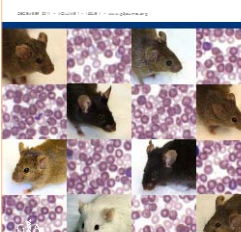
Imputation of Single-Nucleotide Polymorphisms in Inbred Mice Using Local Phylogeny

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Single-Nucleotide Polymorphisms (SNPs) are a type of genetic variation that can be used to study the genetic architecture of complex traits. Imputation of SNPs in inbred mice can be done using local phylogeny, allowing for the identification of SNPs that are specific to certain inbred strains.

G3

Genetic Science Association



Ten Years of the Collaborative Cross

David H. Thornton and Gary A. Churchill

The Collaborative Cross (CC) is a population of mice that is being developed to study the genetic architecture of complex traits. It is composed of 10 founder strains, each with a unique genetic background, which are being crossed to create a population of mice with a wide range of genetic variation. This population is being used to study the genetic architecture of complex traits, such as behavior, metabolism, and disease susceptibility.

Genetic Analysis of Hematological Parameters in Inbred Lines of the Collaborative Cross

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Hematological parameters are a type of physiological trait that can be used to study the genetic architecture of complex traits. Genetic analysis of these parameters in inbred lines of the Collaborative Cross can be used to identify QTLs that are specific to certain inbred strains.

Genome-Wide Association Mapping of Quantitative Traits in Outbred Mice

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Genome-Wide Association Mapping (GWAS) is a powerful tool for identifying the genetic architecture of complex traits. In outbred mice, GWAS can be used to identify QTLs that are specific to certain outbred strains.

Expression Quantitative Trait Loci for Extremal Host Response to Influenza A in Pre-Collaborative Cross Mice

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Expression Quantitative Trait Loci (eQTLs) are a type of genetic variation that can be used to study the genetic architecture of complex traits. Expression eQTLs for extremal host response to influenza A in pre-Collaborative Cross mice can be used to identify QTLs that are specific to certain pre-Collaborative Cross mice.

Transcriptome Atlases of Mouse Brain Reveal Differential Expression Across Brain Regions and Genetic Backgrounds

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Transcriptome atlases are a type of genetic variation that can be used to study the genetic architecture of complex traits. Transcriptome atlases of mouse brain can be used to identify QTLs that are specific to certain brain regions and genetic backgrounds.

Accelerating the Inbreeding of Multi-Parental Recombinant Inbred Lines Generated by Sibling Matings

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Recombinant Inbred Lines (RILs) are a valuable resource for studying the genetic architecture of complex traits. Accelerating the inbreeding of multi-parental RILs generated by sibling matings can improve the efficiency of the RIL construction process.

HTreeQA: Using Semi-Perfect Phylogeny Trees in Quantitative Trait Loci Study on Genotype Data

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

HTreeQA is a software tool that can be used to analyze genotype data. It uses semi-perfect phylogeny trees to identify QTLs that are specific to certain genotype data.

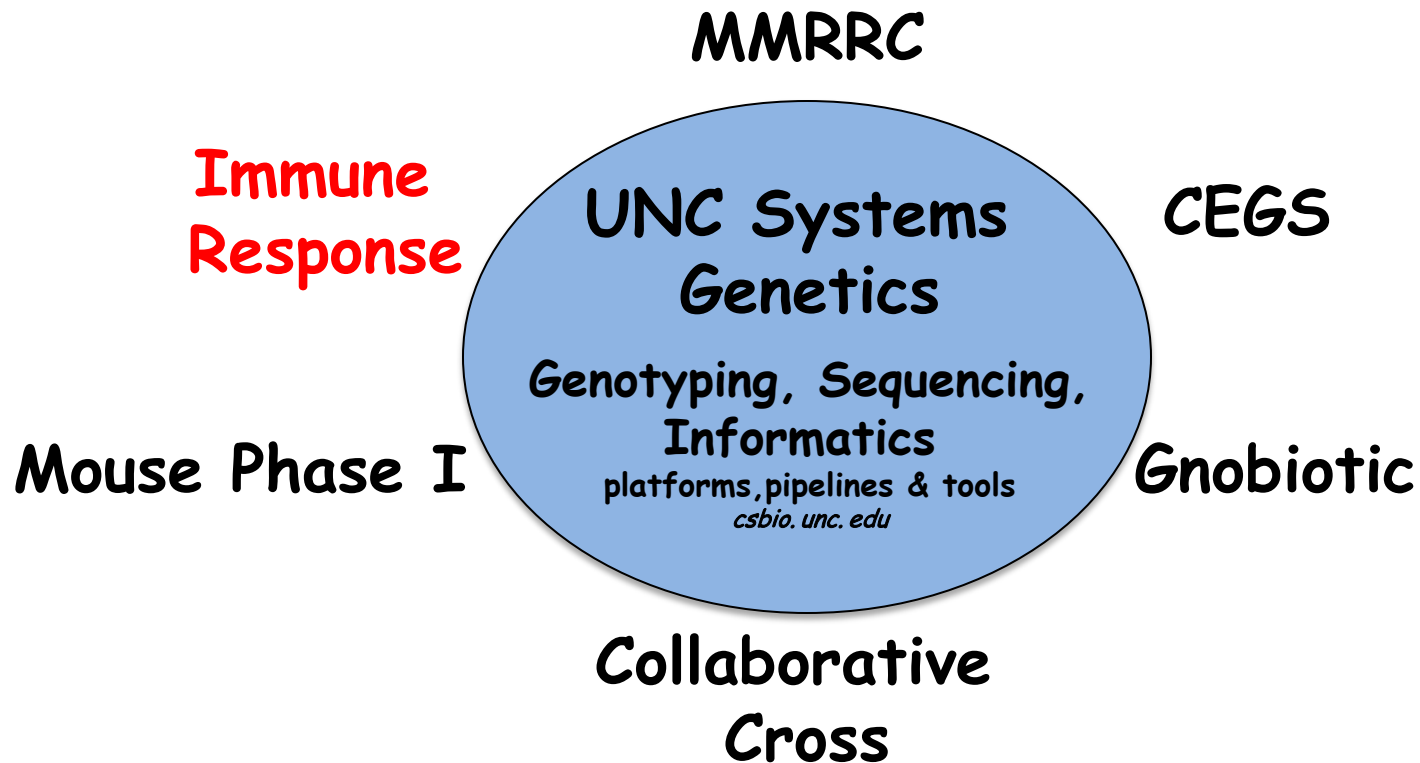
Haplotype Probabilities in Advanced Intercross Populations

Amel H. Zaitoun, Amel H. Zaitoun, and Amel H. Zaitoun

Haplotype probabilities are a type of genetic variation that can be used to study the genetic architecture of complex traits. Haplotype probabilities in advanced intercross populations can be used to identify QTLs that are specific to certain advanced intercross populations.



UNC Chapel Hill



Systems Genetics of Infectious Diseases and Immunology



UNC Chapel Hill
Infectious Disease
Ralph Baric, PI
Mark Heise, PI

Program Overview

A systems genetic approach to identify & study interactions between polymorphic genes regulating the host response to pathogen challenge.

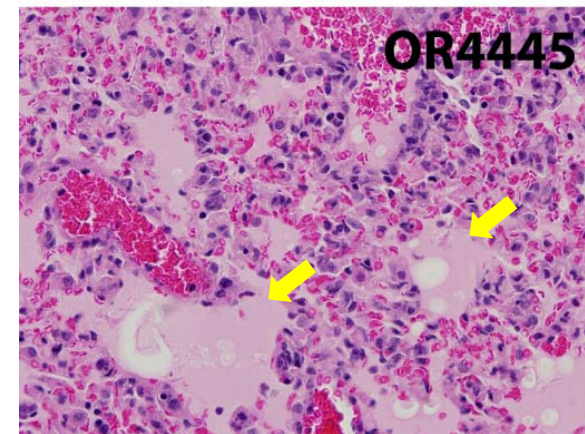
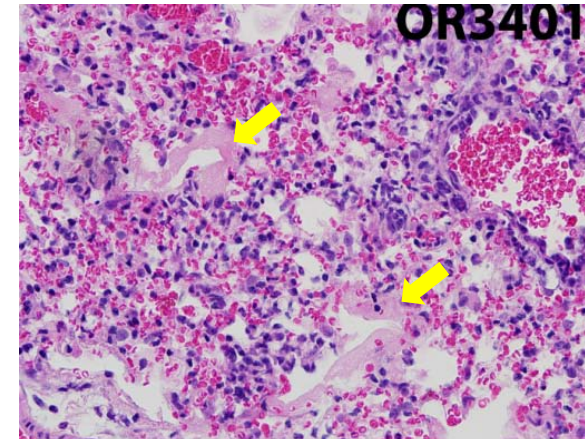
- **Systems Pathogenomics of Acute Respiratory Infection**
(U54 AI081680)
 - Identification of polymorphic host genes that control susceptibility to respiratory virus infection in young and aged individuals
- **Systems Immunogenetics of Biodefense Pathogens in the Collaborative Cross** (U19 AI100625)
 - Identification of polymorphic genes that control the immune response to SARS, Influenza virus, 7 West Nile virus

Improved Models of Human Disease

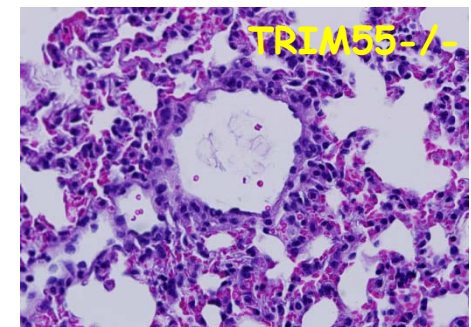
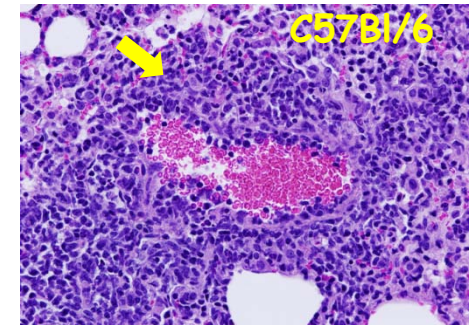
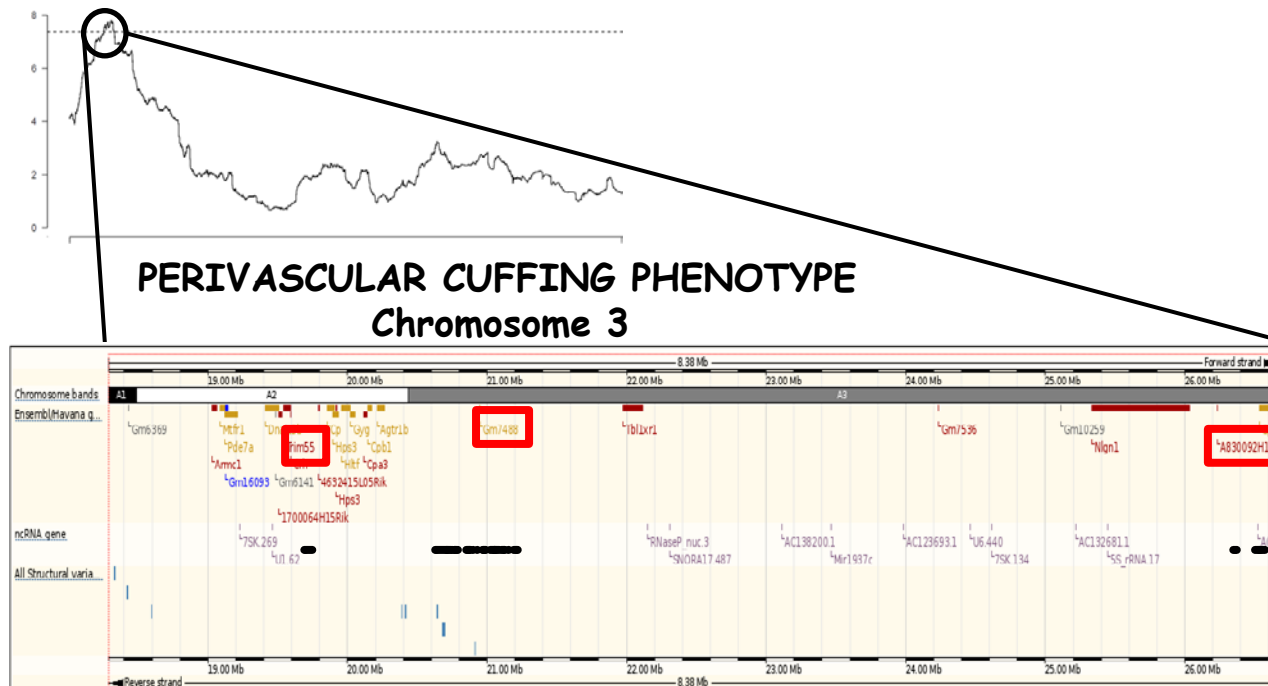


UNC Chapel Hill
Ralp Baric
Mark Heise

- **SARS-Coronavirus atypical pneumonia & acute respiratory distress syndrome (ARDS)**
 - characterized by hyaline membranes/diffuse alveolar damage (DAD) in humans
- **Standard inbred mouse lines (e.g. C57Bl/6 or Balb/c) do not reproduce these aspects of human disease.**
- **Approximately 15% of CC lines exhibit severe ARDS**
 - Better models for testing therapeutics
 - System for mapping genes associated with virus-induced ARDS

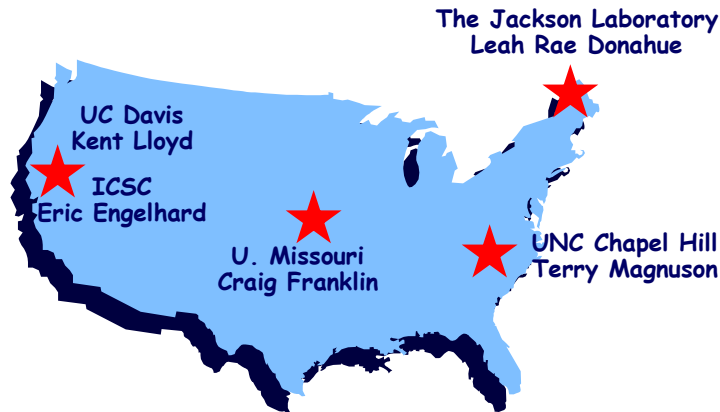


Identification of Novel Genes/Pathways Associated with Virus-Induced Disease



- QTL scan for vascular cuffing within the lungs of SARS-Coronavirus infected mice & identified a QTL peak on Chr. 3
 - 8.5 Mb region
 - 23 genes and 13 ncRNA
- Driven by C57Bl6 & WSB/EiJ alleles associated with severe cuffing
- Informatics analysis narrowed to 1 gene, 1 pseudogene, + 1 noncoding RNA
 - Trim55, GM7488 (pseudogene), AC107456.1(ncRNA)
 - Validation in TRIM55 knockout mice (reduced vascular cuffing)

Mutant Mouse Research Modeling Human Health & Disease



Advantages to Researchers

- Secure against loss of strains
- Facilitates NIH sharing
- Saves research dollars

MMRRC Mission

- Import, archive, distribute genetically engineered mouse strains & ES cell lines
(3851 strains available for distribution)
- Ensure quality control
(genotype, health status)
- Consultation
- Research & Partnerships

Advantages to Facilities

- Colony management
(saves space)
- Disaster plan management
- Health status

