

The Jackson Laboratory

Leading The Search For Tomorrow's Cures

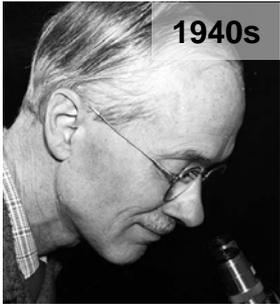


The Jackson Laboratory



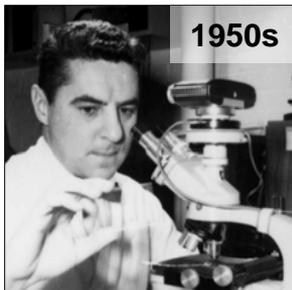
- **Research:** Genetics and biology of human disease
- **Resources:** JAX[®] Mice, JAX[®] Services, bioinformatics databases
- **Education:** World-class courses, conferences, and training programs

Human Health Advances



George Snell, PhD & Nobel Prize Recipient

- Discoveries of immune system function formed the foundation for **tissue and organ transplantation**



Leroy Stevens, PhD

- Laid the foundation for modern **embryonic stem cell research**



Elizabeth Russell, PhD

- Pioneered the use of **bone marrow transplants**

JAX[®] Mice: *The Gold Standard for Biomedical Research*

- Over 3,200 mouse models and growing
- Most well-characterized strains available
- Over 2.1 million mice shipped annually to 16,000 investigators in 60 countries
- Referenced ~100 new publications each week
- Unsurpassed animal health and genetic quality
- Over 75-years experience in mouse breeding and research



JAX[®] Services

- Facilities in Bar Harbor, ME and Sacramento, CA
- On site breeding & colony management
- Revolutionary cryopreservation & recovery
- Phenotyping & efficacy testing
- Genetic research services
- Surgical & preconditioning services



Making Sense of Mouse Nomenclature

Genetic Background Effects and the Importance of Genetic Stability



What's in a Name?



B6.129P2-*Apoa1*^{tm1Unc}/J

C57BL/6-Tg(APOA1)1Rub/J

Unique identifiers for....

Background strains
Relevant gene/allele
Technology used
Lab founder line
Research group
Lab maintaining colony

Nomenclature Rules and Resources

International Mouse Nomenclature Committee

Mouse Genome Informatics (MGI) Nomenclature Committee

Nomenclature help: **nomen@informatics.jax.org**

Resources

JAX[®] Mice and Services: **<http://jaxmice.jax.org/info/nomenclature>**

Tutorial: **<http://jaxmice.jax.org/nomenclature.html>**

Mouse Genome Informatics rules and guidelines:

<http://www.informatics.jax.org/mgihome/nomen/>

Mouse Nomenclature Basics

Mouse Gene - *Italics*, first letter capitalized

Adenomatosis polyposis coli = *Apc*

Leptin receptor = *Lepr*

Mouse Allele - *Italics*, superscripted

First letter capitalized if dominant - *Apc*^{*Min*}

First letter lower case if recessive - *Lepr*^{*db*}

JAX[®] Mice

- Inbreds
- Hybrids
- GEMM[™] Strains

Spontaneous, Transgenic, Targeted and
Congenics

Unique Characteristics of Inbred Strains

C3H/HeJ - severe retinal degeneration

AKR/J - high leukemia incidence

SJL/J - highly aggressive males

DBA/2J

- Audiogenic seizure susceptibility
- Develop hereditary glaucoma
- Low susceptibility to diet-induced atherosclerosis
- Extreme intolerance to and avoidance of alcohol & morphine

C57BL/6J

- Audiogenic seizure resistance
- Microphthalmia common
- High susceptibility to diet-induced atherosclerosis
- Preference for alcohol and morphine

Inbred Nomenclature Based on Phenotype

NOD Nonobese Diabetic

NU Nude

DW Dwarf



Nomenclature Based On Origin & Coat Color

Miss Abbie Lathrop's "pet shop" stock



C.C. Little (1921) mating of female 57



C57BL (Black)



C57BR (Brown)

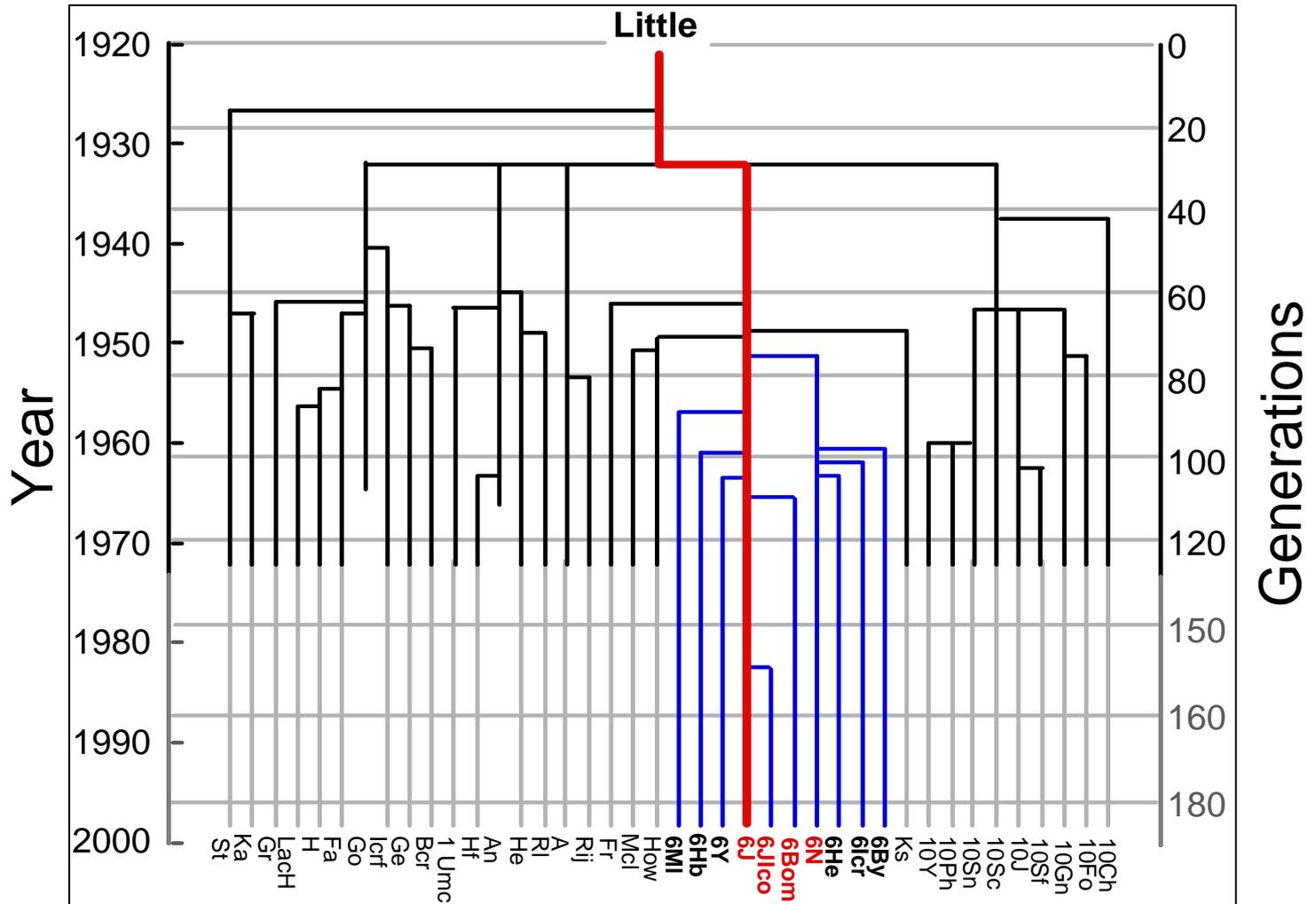


C57L (Leaden)



Substrains of C57BL

Institute for Laboratory Animal Research (ILAR) Lab Codes
http://dels.nas.edu/ilar_n/ilarhome/labcode



Substrain Nomenclature

Substrains: Branch of an inbred strain known or suspected to be genetically different from the parent colony.

Considered a substrain when....

- 1) Maintained separately from the parent colony for more than 20 generations
- 2) Genetic differences from the parent colony are discovered

Nnt deficient

C57BL/6J

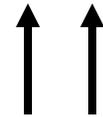
Parent strain

Substrain Line #

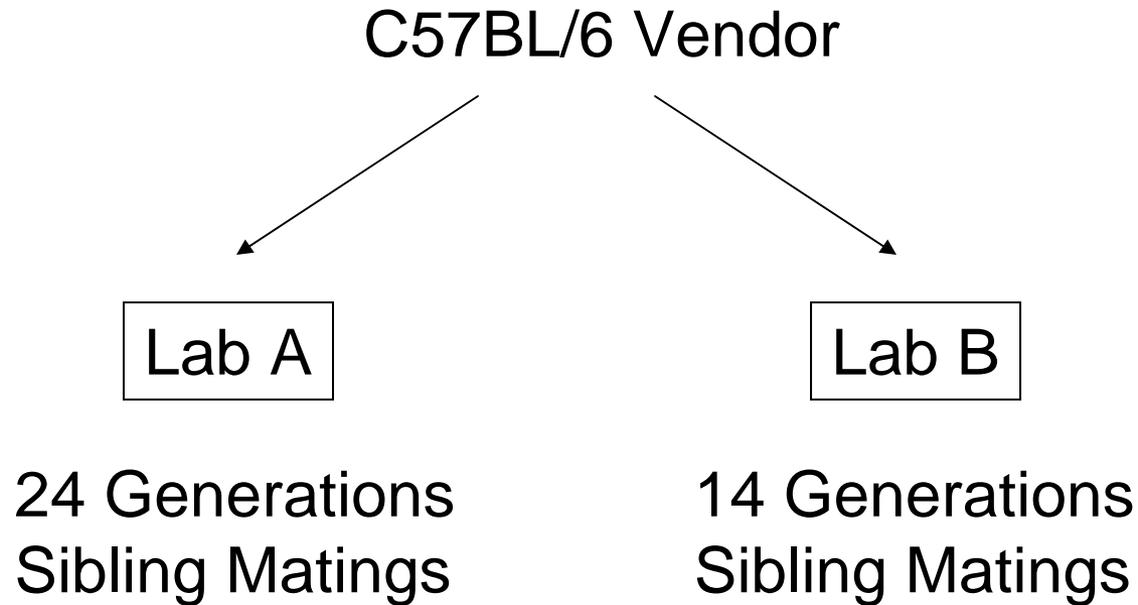
Lab Maintaining Strain

Wild-type Nnt

C57BL/6J*Ei*J



Substrain Development



38 Generations apart!

Resources for Inbred Strain Selection

JAX® Mice Strain Data Sheets

<http://jaxmice.jax.org/query/>

The Mouse Phenome Database

<http://www.jax.org/phenome>

Michael Festing's Database of Inbred Mice & Rats

http://www.informatics.jax.org/external/festing/search_form.cgi

PubMed literature searches

<http://www.pubmed.gov>

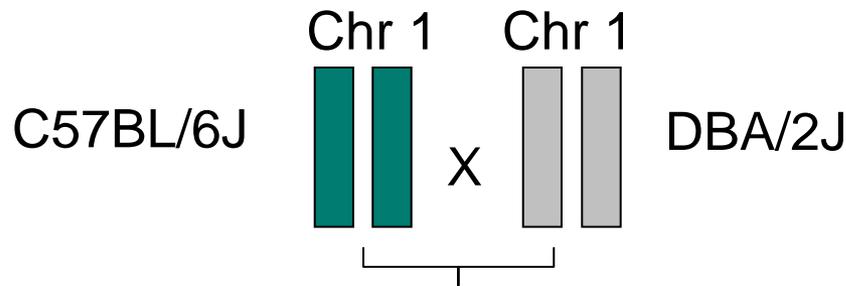
Online Books at MGI (Genetics, Origin, Anatomy, Coat Color)

http://www.informatics.jax.org/mgihome/resources/online_books.shtml

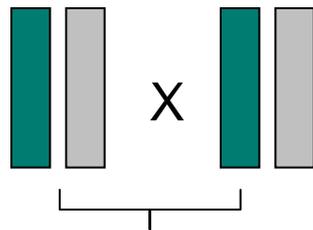
JAX[®] Mice

- Inbreds
- Hybrids
- GEMM[™] Strains
Spontaneous, Transgenic, Targeted, and
Congenics

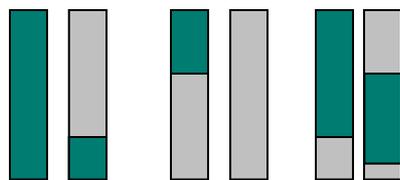
Hybrids -F1 and F2



Hybrid Vigor!
Tissue transplant hosts
from parent strains



F1 -uniform genotype/phenotype



F2 –random distribution of alleles,
excellent control for mutant strains
on a mixed background

Chr 1 from three F2 siblings

Mouse Strain Nomenclature Standard Abbreviations

- 129P3/J = 129P
- 129S1/SvImJ = 129S
- A/HeJ = AHe
- A/J = A
- AKR/J = AK
- BALB/cByJ = CBy
- BALB/cJ = C
- C57BL = B
- C57BL/6J = B6
- C57BL/6JEi = B6Ei
- C57BL/10 = B10
- C57BR/cdJ = BR
- C57L = L
- CBA/CaGnLe = CBACa
- CBA/J = CBA
- C3H/HeJ = C3
- C3HeB/FeJ = C3Fe
- DBA/1J = D1
- DBA/2J = D2
- NZB/BINJ = NZB
- NZW/LacJ = NZW
- RIIS/J = R3
- SJL/J = SJL or J
- SWR/J = SW

Hybrid Nomenclature

C57BL/6J x DBA/2J



B6D2F1/J x B6D2F1/J



B6D2F2/J



JAX[®] Mice

- Inbreds
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- GEMM[™] Strains

Spontaneous, Transgenic, Targeted and
Congenics

GEMM™ Strains

★ Evaluate single gene function(s) in normal & diseased pathways

Spontaneous Mutation

Random, altered gene function

Targeted Mutation (**tm**) (“Knockout”)

Targeted DNA construct, loss-of-function



Transgenic (**Tg**)

(Randomly) inserted DNA construct, “overexpression”

Congenic – Mutation or transgene placed on a pure inbred background

Spontaneous Mutant Strain Nomenclature



129P3/J-*Lepr*^{db-3J}/J

Background Strain

Gene Affected

Allele Designation

Lab Maintaining Strain

Type II Diabetes

**Obesity, Hyperglycemia, Hyperinsulinemia,
Insulin Resistance, Hyperphagia.**

**Diabetes severity highly dependent on genetic
background: *C57BLKS/J*, *C57BL/6J*, *129P3/J***

Nomenclature for Targeted Mutations (“Knockouts”)

B6;129P2-//2^{tm1Hor}/J



Background (mixed)

Targeted gene

Targeted mutation

Line number

Lab registration code

Lab maintaining strain

129 Nomenclature at <http://jaxmice.jax.org/info/bulletin/bulletin01.html>

Nomenclature for Targeted Mutations (“Knockouts”)

Recipient strain

Donor strain

B6;129P2-*Il2*^{tm1Hor}/J

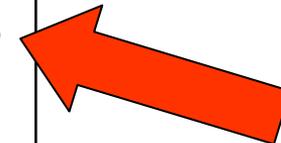
Backcross to C57BL/6J five+ generations

B6.129P2-*Il2*^{tm1Hor}/J

Genetic Background Effects

Interleukin 2 targeted mutation (“Knockout”)

Strain	Mortality	Colitis	Anemia
B6;129P2- <i>Il2</i>^{tm1Hor} (original publication)	4-9 wks	Progressive	Yes
B6.129P2-<i>Il2</i>^{tm1Hor}/J	pre & post wean loss, 10-25 weeks	Progressive Heath status dependent	Yes
C.129P2(B6)-<i>Il2</i>^{tm1Hor}/J	3-5 wks	None	Yes



Environmental Effects

Housing Conditions- Interleukin 10 Knockout

- Conventional
Severe inflammatory bowel (colitis), rectal prolapse, poor breeding
- Germ Free or Specific pathogen free (SPF)
No abnormal symptoms, normal breeding

Drug treatment

- Anti parasitic drugs such as ivermectin can alter strain behavior
Davis et al., Lab Animal Sci 49:288-296, 1999

Experimental design- obese strains

- Over handling obese mice causes stress related weight loss

Congenetic Strains

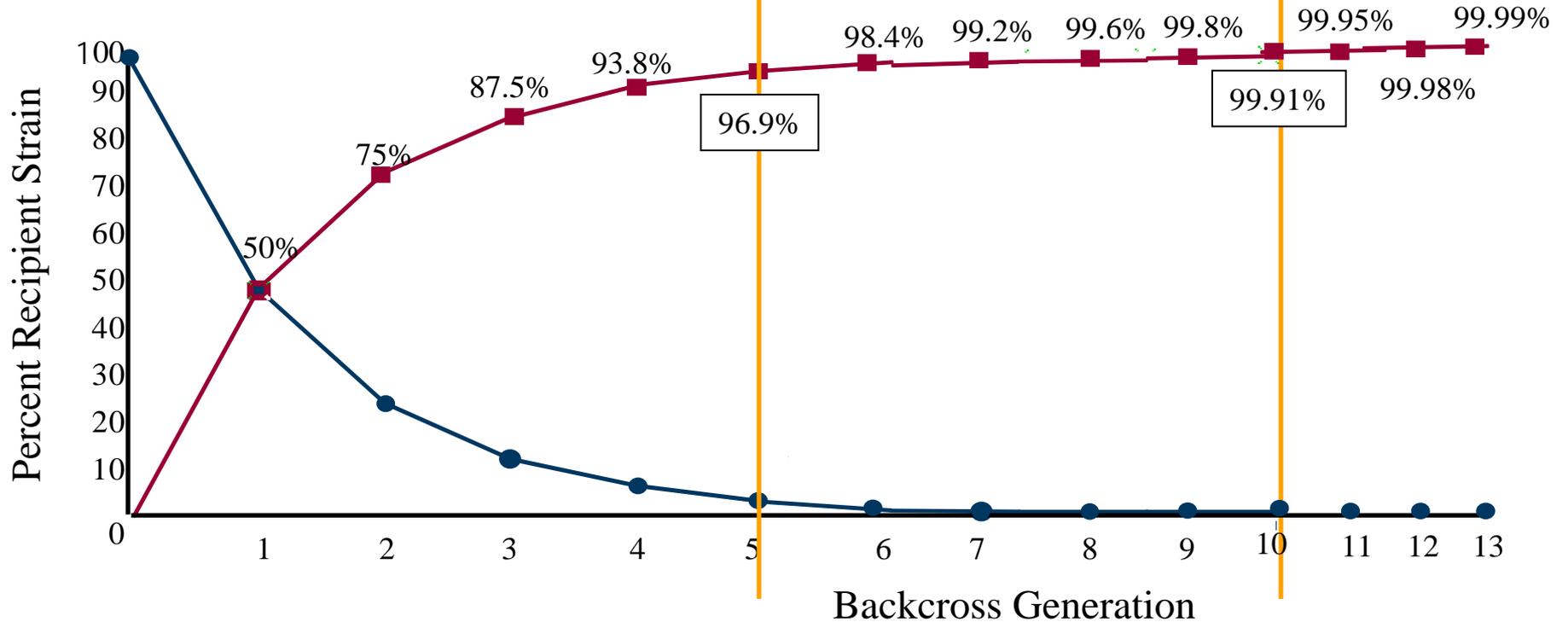
- ★ Genetic uniformity reduces phenotypic variability
 - Transfer mutation or transgene onto inbred background
 - Repeated backcrosses of a donor (mutant) strain to an inbred (recipient) strain
 - Maintain as homozygotes and use inbred control
 - Create multiple strains on different inbred backgrounds
 - Allows examination of modifier genes
 - N10 generation time takes 2 to 3 years or use speed congenics (1 to 1.5 years)

Backcrossing

**Mixed background
(N1-N4)**

**Incipient Congenic
(N5-N9)**

**Congenic
(N10+)**



Nomenclature for Transgenics

C57BL/6-Tg(ACTB-EGFP)131Osb/J

Background Strain

Transgenic

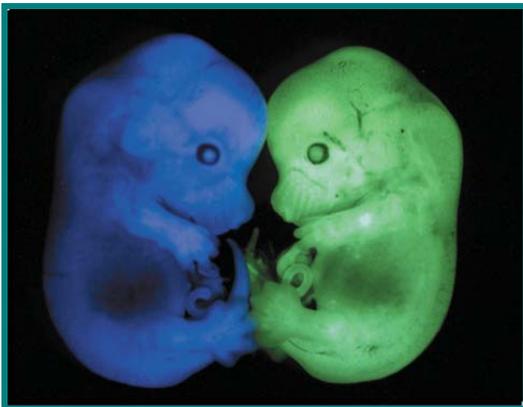
Promoter

Gene expressed

Founder line number

Lab registration code

Lab Maintaining Strain



Nomenclature for Transgenics

B6.Cg-Tg(BCL2)22Wehi/J

Background Strain

Transgenic

Gene expressed

Founder line number

Lab registration code

Lab Maintaining Strain

Original: STOCK Tg(BCL2)22Wehi

Genetic Modification Effect

B-cell Leukemia/Lymphoma 2 Induced Mutations

Transgenic Overexpression

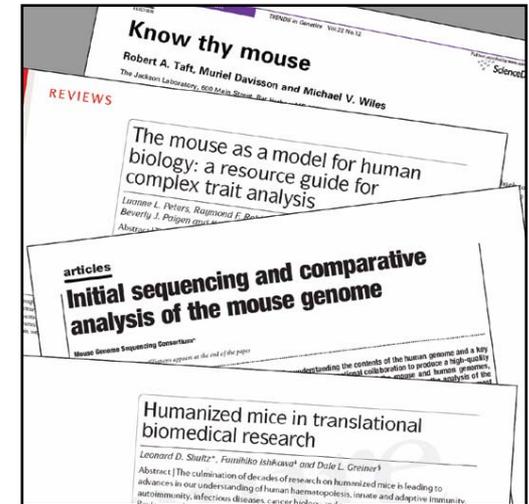
Promoter: E mu *Igh*, immunoglobulin heavy chain

B6.Cg-Tg(BCL2) 22 Wehi/J	B-cell lineage
B6.Cg-Tg(BCL2) 25 Wehi/J	T-cell lineage
B6.Cg-Tg(BCL2) 36 Wehi/J	B & T-cell lineages

C57BL/6 Publications

Total 18,075 PubMed publications using C57BL/6 mice

Substrain	# of Citations*
C57BL/6J	7,660
C57BL/6N	586
C57BL/6Jlco	19



Complete nomenclature benefits everyone!

Higher degree of exploratory behavior.....

Lower gene X expression

Higher levels of blood enzyme.....

Background
Environment
Genetic Modification
Genetic Drift

Increased susceptibility to.....

High fecundity

Larger body mass...

Resistance to.....

Increased tumor incidence

High anxiety

The Dynamic Genome

Genetic Drift

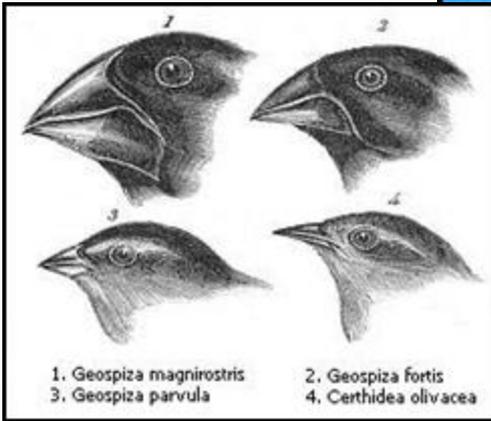
Fundamental tendency of any allele to vary randomly in frequency over time due to statistical variation alone.

Small populations are subject to more drift than large ones because departure from the norm (ie mutation) in one individual causes a disproportionately greater deviation from the norm.

Natural selection

Tendency of beneficial alleles to become more common, and detrimental ones less common, over time.

Genetic Instability...Friend or Foe?



Species Diversity



Phenotypic Diversity

Aggravated
Grad Student

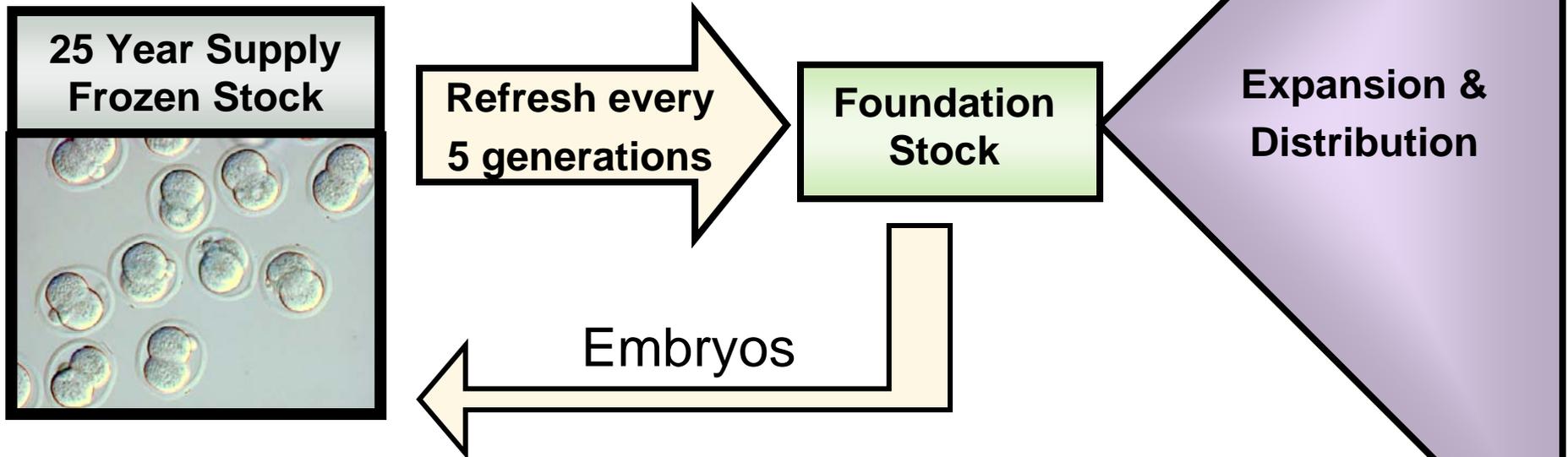


Data Diversity

Minimizing Genetic Instability

- Maintain detailed colony records
- Watch for phenotypic changes in controls
- Test breeder stocks for genetic purity
- Avoid selection pressure
- Cryopreserve unique models!
- Replace breeders frequently (F5-10 generations)
- **NOTE: C3H/HeJ \neq C3H/HeNTac \neq C3H/HeNCrIBR**

The Jackson Laboratory's Unique Genetic Stability Program



Take me home.....



- Know your nomenclature
- Use complete nomenclature in your publications
- Research your strain background
- Consider analyzing mutations on multiple backgrounds
- Consider that genetic drift can alter phenotype
- Adhere to strict colony management practices
- Replace breeders from trusted vendor regularly!

The Jackson Laboratory

Nomenclature experts:

nomen@informatics.jax.org

Need help?

micetech@jax.org

