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

* Based upon a June 2007 survey of all PubMed citations
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?

Unique identifiers for....

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

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

C57BL/6-Tg(APOA1)1Rub/J
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*\(^{\text{Min}}\)
- First letter lower case if recessive - *Lepr*\(^{\text{db}}\)
JAX® Mice

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

- Strain maintained by sibling (sister x brother) mating for 20 or more consecutive generations
- Most genetically and phenotypically uniform mouse resource
- Well Characterized
- Unique phenotypes
- Widely used as models of human disease

Inbred lineage diagram based on by Petkov PM, et al., *Genomics, Volume 83, Issue 5, May 2004, Pages 902-911*
## Unique Characteristics of Inbred Strains

<table>
<thead>
<tr>
<th>Inbred Strain</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C3H/HeJ</strong></td>
<td>- severe retinal degeneration</td>
</tr>
<tr>
<td><strong>AKR/J</strong></td>
<td>- high leukemia incidence</td>
</tr>
<tr>
<td><strong>SJL/J</strong></td>
<td>- highly aggressive males</td>
</tr>
<tr>
<td><strong>DBA/2J</strong></td>
<td>- Audiogenic seizure susceptibility</td>
</tr>
<tr>
<td></td>
<td>- Develop hereditary glaucoma</td>
</tr>
<tr>
<td></td>
<td>- Low susceptibility to diet-induced atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>- Extreme intolerance to and avoidance of alcohol &amp; morphine</td>
</tr>
<tr>
<td><strong>C57BL/6J</strong></td>
<td>- Audiogenic seizure resistance</td>
</tr>
<tr>
<td></td>
<td>- Microphthalmia common</td>
</tr>
<tr>
<td></td>
<td>- High susceptibility to diet-induced atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>- Preference for alcohol and morphine</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Nnt deficient</th>
<th>Wild-type Nnt</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C57BL/6J</strong></td>
<td><strong>C57BL/6JEiJ</strong></td>
</tr>
</tbody>
</table>

Parent strain

Substrain Line #

Lab Maintaining Strain
Substrain Development

C57BL/6 Vendor

Lab A
- 24 Generations
- Sibling Matings

Lab B
- 14 Generations
- Sibling Matings

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

C57BL/6J  Chr 1  DBA/2J  X  Chr 1

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
Mouse Strain Nomenclature
Standard Abbreviations

- 129P3/J = 129P
- 129S1/SvImJ = 129S
- A/HeJ = AHe
- A/J = A
- AKR/J = AK
- BALB/cByJ = CBBy
- 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
- RIIIS/J = R3
- SJL/J = SJL or J
- SWR/J = SW

http://jaxmice.jax.org/info/hybrid_nomenclature
Hybrid Nomenclature

\[ \text{C57BL/6J} \times \text{DBA/2J} \]
\[ \downarrow \]
\[ \text{B6D2F1/J} \times \text{B6D2F1/J} \]
\[ \downarrow \]
\[ \text{B6D2F2/J} \]
JAX® Mice

- Inbreds
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  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

Type II Diabetes
Obesity, Hyperglycemia, Hyperinsulinemia, Insulin Resistance, Hyperphagia.

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

129P3/J-\textit{Lepr}^{db-3J}/J

Background Strain
Gene Affected
Allele Designation
Lab Maintaining Strain
Nomenclature for Targeted Mutations (“Knockouts”)

B6;129P2-Il2 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: B6;129P2-Il2tm1Hor/J
Donor strain: B6.129P2-Il2tm1Hor/J

Backcross to C57BL/6J five+ generations
## Genetic Background Effects
Interleukin 2 targeted mutation ("Knockout")

<table>
<thead>
<tr>
<th>Strain</th>
<th>Mortality</th>
<th>Colitis</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B6;129P2- il2&lt;sup&gt;tm1Hor&lt;/sup&gt; (original publication)</strong></td>
<td>4-9 wks</td>
<td>Progressive</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>B6.129P2-Il2&lt;sup&gt;tm1Hor/J&lt;/sup&gt;</strong></td>
<td>pre &amp; post wean loss, 10-25 weeks</td>
<td>Progressive</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>C.129P2(B6)-Il2&lt;sup&gt;tm1Hor/J&lt;/sup&gt;</strong></td>
<td>3-5 wks</td>
<td>None</td>
<td>Yes</td>
</tr>
</tbody>
</table>
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
Congenic 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+)

Percent Recipient Strain

Backcross Generation

Mixed background:
- 50% after 1 generation
- 75% after 2 generations
- 87.5% after 3 generations
- 93.8% after 4 generations
- 98.4% after 5 generations

Incipient Congenic:
- 96.9% after 5 generations
- 99.2% after 6 generations
- 99.6% after 7 generations
- 99.8% after 8 generations
- 99.95% after 10 generations

Congenic:
- 99.9% after 9 generations
- 99.98% after 10 generations
- 99.99% after 11 generations
- 99.99% after 13 generations
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

\textbf{B6.Cg-Tg(BCL2)22Wehi/J}

Background Strain

Transgenic

Gene expressed

Founder line number

Lab registration code

Lab Maintaining Strain

Original: \textbf{STOCK Tg(BCL2)22Wehi}
Genetic Modification Effect
B-cell Leukemia/Lymphoma 2 Induced Mutations

Transgenic Overexpression

Promoter: E mu $lgh$, immunoglobulin heavy chain

- B6.Cg-Tg(BCL2)22Wehi/J  B-cell lineage
- B6.Cg-Tg(BCL2)25Wehi/J  T-cell lineage
- B6.Cg-Tg(BCL2)36Wehi/J  B & T-cell lineages
### C57BL/6 Publications

Total 18,075 PubMed publications using C57BL/6 mice

<table>
<thead>
<tr>
<th>Substrain</th>
<th># of Citations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6J</td>
<td>7,660</td>
</tr>
<tr>
<td>C57BL/6N</td>
<td>586</td>
</tr>
<tr>
<td>C57BL/6Jlco</td>
<td>19</td>
</tr>
</tbody>
</table>

* Based upon an Oct 2007 survey of all PubMed citations without any limits (time, field, language, etc.)

Complete nomenclature benefits everyone!
Background
Environment
Genetic Modification
Genetic Drift

- Higher degree of exploratory behavior
- Increased susceptibility to...
- High fecundity
- Higher levels of blood enzyme...
- Increased tumor incidence
- High anxiety
- Resistance to...
- Larger body mass...
- Lower gene X expression
- Higher levels of blood enzyme...
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 (i.e., 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?

Muscular dystrophy

Species Diversity

1. Geospiza magnirostris
2. Geospiza fortis
3. Geospiza parvula
4. Certhidea alvacea

Phenotypic Diversity

Data Diversity

Aggravated Grad Student
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 ≠ C3H/HeNTac ≠ C3H/HeNCRlBR
The Jackson Laboratory’s Unique Genetic Stability Program

25 Year Supply Frozen Stock

Refresh every 5 generations

Foundation Stock

Embryos

Expansion & Distribution
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