What’s in a Name?
Understanding the Basics and Research Value of Mouse Nomenclature

Technical Information Services
June 20, 2019
The Jackson Laboratory’s Mission

“To discover precise genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.”

Biomedical Research
Genetics, genomics and biology of human disease

Resources & Services
PRECLINICAL: Mouse models & research services (mouse breeding, model generation, cryopreservation, in vivo pharmacology, humanized mice, and more)

CLINICAL: Clinical genomics services and JAX Clinical Knowledgebase (JAX-CKB)

Education & Training
Courses, conferences, internships, pre-doctoral and post-doctoral training, live webinars, on-demand videos, on-site seminars and other programs
JAX™ Mice
The Gold Standard for Biomedical Research

- NIH-funded resource
- >11,000 strains and growing
  - >3 million mice shipped annually
- Unsurpassed genetic quality & animal health
- Best characterized & referenced ~100 new pubs/week
- Common inbred strains (C57BL/6J, BALB/cJ, B6.SJL-Ptprc<sup>a</sup> Pepc<sup>b</sup>/BoyJ) support development/collection of specialty strains and other valuable community research resources
Online Resources to Expedite Research

- JAX™ Mice Database
  www.jax.org/mouse-search

- Mouse Genome Informatics
  www.informatics.jax.org

- Mouse Phenome Database
  www.jax.org/phenome

- Others, including:
  JAX-Clinical Knowledgebase
  Mouse Tumor Biology Database
Today’s Learning Goals

- Understand nomenclature rules for different strains:
  - Inbred
  - Hybrid
  - Genetically engineered mutant mice (GEMM)

- Determine strain characteristics using only the strain name; use this information to determine the appropriate controls for a mutant strain

- Describe how genetic background can impact phenotype (and research outcomes)
What’s in a Name?

- Unique identifiers for
  - Genetic background
  - Relevant gene/allele
  - Technology used
  - Lab founder line
  - Research group
  - Lab maintaining colony

**Example:**
B6.129P2-Apoa1^{tm1Unc}/J
C57BL/6-Tg(APOA1)1Rub/J
Nomenclature Rules and Resources

- International Committee on Standardized Genetic Nomenclature for Mice

- Mouse Genome Informatics (MGI) Nomenclature Committee
  - Nomenclature help: nomen@informatics.jax.org

- Resources
  - JAX™ Mice and Services (Technical Support Nomenclature page)
    www.jax.org/jax-mice-and-services/customer-support/technical-support/genetics-and-nomenclature
  - Mouse Genome Informatics rules and guidelines
    www.informatics.jax.org/mgihome/nomen/
JAX™ Mice

- Inbreds
- Hybrids
- Genetically Engineered Mutant Mice (GEMM)
  - Spontaneous
  - Chemically Induced
  - Targeted
  - Transgenic
Inbred Strains

- Maintained by sibling (sister x brother) mating for 20 or more consecutive generations (F20+)
- Mice virtually genetically identical and homozygous at virtually every locus
  - Most genetically uniform mouse resource
- Best characterized strains
- Unique phenotypes
- Widely used as models of human disease

| Nomenclature for Mouse Strains | THE JACKSON LABORATORY |
Unique Characteristics of Inbred Strains

**C3H/HeJ** - severe retinal degeneration (*Pde6b*)
**AKR/J** - high leukemia incidence (AKV retrovirus)

<table>
<thead>
<tr>
<th>C57BL/6J</th>
<th>DBA/2J</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audiogenic seizure resistance</td>
<td>Audiogenic seizure susceptible</td>
</tr>
<tr>
<td>Microphthalmia common</td>
<td>Develop hereditary glaucoma</td>
</tr>
<tr>
<td>High susceptibility to diet-induced atherosclerosis</td>
<td>Low susceptibility to diet-induced atherosclerosis</td>
</tr>
<tr>
<td>Preference for alcohol and morphine</td>
<td>Extreme intolerance to and avoidance of alcohol and morphine</td>
</tr>
</tbody>
</table>
Inbred Nomenclature Based on Phenotype

- Nonobese Diabetic  **NOD/ShiLtJ** *(001976)*
- Nude  **NU/J** *(002019)*
- Small  **SM/J** *(000687)*
Nomenclature Based on Origin and Coat Color

Miss Abbie Lathrop's “pet shop” stock

↓

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

↓

C57BL (Black)

↓

C57BR (Brown)

↓

C57L (Leaden)
Resources for Inbred Strain Selection

- JAX™ Mice Strain Data Sheets
  www.jax.org/jax-mice-and-services/find-and-order-jax-mice

- Michael Festing’s Database of Inbred Mice & Rats
  www.informatics.jax.org/external/festing/search_form.cgi

- Online Books at MGI (Genetics, Biology, Origin, Coat Color)
  www.informatics.jax.org/resources.shtml

- The Mouse Phenome Database
  http://phenome.jax.org/
Mouse Phenome Database
C57BL/6J – Best Characterized Strain

Mouse strain: C57BL/6J

JAX 000664  inbred  MGI / IMSR info  Availability: Readily Available

• Find data for C57BL/6J
  Search C57BL/6J data: [search]

• List all studies involving C57BL/6J (254)
• Find phenotypes where C57BL/6J is an outlier
• Download all measured phenotypes for this strain (more info)

• Retrieve SNPs for C57BL/6J
• Compare C57BL/6J vs. one other strain
What is Genetic Drift?

• “The constant tendency of genes to evolve even in the absence of selective forces. Genetic drift is fueled by spontaneous neutral mutations that disappear or become fixed in a population at random”
  
  ○ Lee Silver, “Mouse Genetics” Oxford University Press, 1995
  
  wwwinformatics.jax.org/silverbook/

• Genetic changes resulting from mistakes in meiosis or DNA repair
  
  ○ Single base changes
  ○ Deletions
  ○ Duplications
  ○ Inversions
Genetic Drift Promotes Diversity

Species Diversity

Phenotypic Diversity

muscular dystrophy

Data Diversity

Lama2^dy-2J
Substrains Develop Quickly

- Colonies separated by 20 or more generations
- Phenotypic or genetic differences are discovered

C57BL/6 Parent Colony

Lab A
Sibling Mating
10 Generations

Lab B
Sibling Mating
20 Generations

Generations add up!

Labs A & B are 30 generations apart!
C57BL/6 Substrain Divergence

**Substrains:** Branch of an inbred strain known or suspected to be genetically different from the parent colony.
# Reproducible Phenotype Differences

Data consistent from four IKMC phenotyping centers

<table>
<thead>
<tr>
<th>Description</th>
<th>HMGU M</th>
<th>F</th>
<th>ICS M</th>
<th>F</th>
<th>MRC Harwell M</th>
<th>F</th>
<th>WTSI M</th>
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<td>Calorimetry: Oxygen consumption</td>
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<td>Simplified IPGTT: Blood glucose concentration</td>
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<td>Simplified IPGTT: Glucose response AUC</td>
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<td>DEXA: Fat mass</td>
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<td>Modified SHIRPA: Locomotor activity</td>
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<td>Grip-strength: Forelimb grip strength measurement</td>
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<td>Rotarod: Latency to fall</td>
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<td>Rotarod: Passive rotation</td>
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<td>Acoustic Startle &amp; PPI:Global prepulse inhibition</td>
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Key:
- 0.01
- 0.001
- 1.0E-4
- 1.0E-5

No diff
No data available
No data loaded

Know Your Substrain
Use Proper Nomenclature

- C57BL/6J *Parent strain*
- C57BL/6NJ *Substrain designation*
  - NIH (N)
  - By (Dr. Bailey)
- C57BL/6NCrI *Laboratory maintaining the strain*
  - Jackson (J)
  - CrI (Charles River Laboratories)
- C57BL/6ByJ

Institute for Laboratory Animal Research (ILAR) Lab Codes
http://dels.nas.edu/global/ilar/Lab-Codes
C57BL/6 Publications

<table>
<thead>
<tr>
<th>SEARCH TERM</th>
<th>PUBMED ENTRIES</th>
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<tr>
<td>C57BL/6</td>
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<td>C57BL/6NHsd</td>
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<tr>
<td>C57BL/6NTac</td>
<td>95</td>
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</tbody>
</table>

**Complete nomenclature benefits everyone!**

Based on October, 2018 PubMed citations search (without limits)
Minimizing Genetic Instability

- Maintain pedigrees lines and detailed colony records
- Refresh breeders frequently (F5-10 generations)
- Avoid selection pressure
- Watch for phenotypic changes in controls
- Cryopreserve unique models!

Genetic change can’t be stopped, but it can be slowed down!
The Jackson Laboratory
Patented Genetic Stability Program

Frozen embryos used to refresh foundation stock every five generations

US patents 7592501, 8110721
JAX™ Mice

- Inbreds
- Hybrids
- Genetically Engineered Mutant Mice
  - Spontaneous
  - Chemically Induced
  - Targeted
  - Transgenic
Hybrids F1 and F2

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

Hybrid Vigor!
Hybrids F1 and F2

C57BL/6J $\times$ DBA/2J

- Uniform genotype/phenotype
- Tissue transplant host from parental strains
Hybrids F1 and F2

C57BL/6J  \( \times \)  DBA/2J

F1

Hybrid Vigor!

- Uniform genotype/phenotype
- Tissue transplant host from parental strains
Hybrids F1 and F2

- Uniform genotype/phenotype
- Tissue transplant host from parental strains

- Random allele distribution
- Approx control for mutants on mixed background

Chr 1 from three siblings

C57BL/6J \( \times \) DBA/2J

F1 \( \times \) F2

Hybrid Vigor!
Hybrid Nomenclature

\[ \text{C57BL/6J} \times \text{C3H/HeJ} \]
\[ \downarrow \]
\[ \text{B6C3F1/J} \times \text{B6C3F1/J} \]
\[ \downarrow \]
\[ \text{B6C3F2} \]

Standard Nomenclature Abbreviations for Top Inbred Strains

- 129S1/SvImJ = 129S
- A/J = A
- AKR/J = AK
- BALB/cJ = C
- C57BL = B
- C57BL/6J = B6
- C57BL/6JEi = B6Ei
- C57BL/10 = B10
- C57BR/cdJ = BR
- C57L = L
- C3H/HeJ = C3
- C3HeB/FeJ = C3Fe
- DBA/2J = D2
- SJL/J = SJL or J
- SWR/J = SW

Nomenclature for Mouse Strains | THE JACKSON LABORATORY

30
Name this strain:
Cross between BALB/cJ female and A/J male

A. AC/J
B. ACF1/J
C. BA/J
D. CA/J
E. CAF1/J
F. CAF2/J

BALB/cJ (000651) × A/J (000646)
Name this strain:
Cross between BALB/cJ female and A/J male

A. AC/J
B. ACF1/J
C. BA/J
D. CA/J
E. CAF1/J
F. CAF2/J

BALB/cJ (000651) × A/J (000646) → CAF1/J (100003)
JAX™ Mice

- Inbreds
- Hybrids
- Genetically Engineered Mutant Mice
  - Spontaneous or chemically Induced
  - Targeted
  - Endonuclease
  - Transgenic
Genetically Engineered Mutant Mice

Evaluate function(s) of a single gene

- Spontaneous and chemical induced mutations
  - Random, altered gene function

- Targeted Mutation (tm)
  - “Knockout” or “Knockin”
  - Targeted DNA construct, loss-of-function

- Endonuclease Mediated Mutation (em)
  - CRISPR/Cas, ZFN, TALEN

- Transgenic (Tg)
  - (Randomly) inserted DNA construct, “over-expression”
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*\textsuperscript{Min}
  - First letter lower case if recessive - *Lepr*\textsubscript{db}
**Type II Diabetes**
Obesity, Hyperglycemia, Hyperinsulinemia, Insulin Resistance, Hyperphagia.

*Diabetes severity is genetic background dependent:*

\[
C57BLKS/J \quad > \quad C57BL/6J \quad > \quad 129P3/J
\]

**Spontaneous Mutant Strain Nomenclature**

<table>
<thead>
<tr>
<th>129P3/J-\textit{Lepr}^{db-3J}/J</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background Strain</strong></td>
</tr>
<tr>
<td><strong>Gene Affected</strong></td>
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<tr>
<td><strong>Allele Designation</strong></td>
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<tr>
<td><strong>Lab Maintaining Strain</strong></td>
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</tbody>
</table>
## Nomenclature for Targeted Mutations (“Knockouts”)

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

<table>
<thead>
<tr>
<th>Background (mixed)</th>
<th>Targeted gene</th>
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</thead>
<tbody>
<tr>
<td><strong>Targeted mutation</strong></td>
<td><strong>Allele designation</strong></td>
</tr>
<tr>
<td><strong>Lab registration code</strong></td>
<td><strong>Lab maintaining strain</strong></td>
</tr>
</tbody>
</table>

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**129 Nomenclature Resource**

**Nomenclature for Mouse Strains** | THE JACKSON LABORATORY
Nomenclature for Targeted Mutations: Mixed vs congeneric

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

Backcross to C57BL/6J five+ generations

Why Is This Important??!!
Genetic Background Can Impact Phenotype

Interleukin 2 targeted mutation ("Knockout")

<table>
<thead>
<tr>
<th>Strain</th>
<th>Mortality</th>
<th>Colitis</th>
<th>Anemia</th>
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<tbody>
<tr>
<td>B6;129P2-IL2tm1Hor</td>
<td>4-9 wks</td>
<td>Progressive</td>
<td>Yes</td>
</tr>
<tr>
<td>(original publication)</td>
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<tr>
<td>B6.129P2-IL2tm1Hor/J</td>
<td>pre &amp; post wean loss, 10-25 weeks</td>
<td>Progressive</td>
<td>Yes</td>
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<tr>
<td>C.129P2(B6)-IL2tm1Hor/J</td>
<td>3-5 wks</td>
<td>None</td>
<td>Yes</td>
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</table>

Congenic Strains

Genetic uniformity reduces phenotypic variability

- Transfer mutation or transgene onto uniform inbred background
  - Ten generations of 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 2-3 years
  - JAX Speed Congenic Service 1-1.5 years

Speed Congenic Service | THE JACKSON LABORATORY
Backcrossing
Traditional Methods

<table>
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<tr>
<th>Backcross Generation (N)</th>
<th>Mixed background (N1-N4)</th>
<th>Incipient Congenetic (N5-N9)</th>
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<tr>
<td>1</td>
<td>50%</td>
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<tr>
<td>2</td>
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<td>13</td>
<td>99.99%</td>
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</table>

- **B6.Cg-Gt(ROSA)26Sor^tm9(CAG-tdTomato)Hze/J (Stock # 007905)**
- **B6.Cg-Gt(ROSA)26Sor^tm9(CAG-tdTomato)Hze/J (Stock # 007909)**

**Speed Congenic Service | THE JACKSON LABORATORY**
JAX™ Speed Congenic Service
(N5) ~15 months

Congenic Following ~5 backcrosses

Traditional Congenic (N10+)
~30 months
Linked DNA Carryover

Mutation

Successive Backcrossing
Nomenclature for Targeted Mutations: 2nd Heritable allele

B6.129P2(SJL)-Myd88<sup>tm1Defr</sup>/J

Exon 3 flanked by loxP

Crossed to Cre deleter strain to remove exon 3

B6.129P2(SJL)-Myd88<sup>tm1.1Defr</sup>/J

Exon 3 deleted (KO)
What is the difference between these strains?

B6;129S- $Tnf^{tm1Gkl}$/J (003008)
B6.129S- $Tnf^{tm1Gkl}$/J (005540)
CByJ.129S(B6)- $Tnf^{tm1Gkl}$/J (007082)

A. Allele  
B. Genetic background  
C. Type of genetic modification  
D. Number of times backcrossed  
E. Control selection  
F. Phenotype
Nomenclature for Endonuclease-generated alleles

C57BL/6NJ-\(Fxn^{em1J}\)/J (Stock# 025732)

↑

Background strain

Targeted Gene

Endonuclease-mediated mutation

Allele designation

Lab registration code

Lab maintaining strain
What does “em1.1” designate in B6.Cg-Vipr2^{em1.1(cre)Hze/J} name?

A. Variant in em1 template to make new strain

B. Backcrossed em1 allele to a different background

C. Made a second heritable change in existing em1

D. New and better version of em1
Nomenclature for Transgenics

C57BL/6-Tg(CAG-EGFP)1Osb/J (Stock# 003291)

Background Strain
Transgenic
Promoter
Gene expressed
Founder line number
Lab registration code
Lab Maintaining Strain

Transgene Founder Line Effects
B cell Leukemia/Lymphoma 2 Induced Mutations

Transgenic Overexpression

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

Original: STOCK Tg(BCL2)22Wehi
Transgene: When Integration Site Identified

**B6.Cg-Tg(Alb-cre)21Mgn/J**

- Sequencing of locus where transgene integrated

**B6.Cg-Speer6-ps1**

- Tg integration site identified

Tg integration site unknown

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**Nomenclature for Mouse Strains** | THE JACKSON LABORATORY
Compound Mutant/Transgenic Strains

NOD.Cg-Prkdc\textsuperscript{scid} Il2rg\textsuperscript{tm1Wjl} Tg(IL15)1Sz/SzJ

- Mutations/transgenes listed based on chromosomal location
  - Chr 1 listed first, then Chr 2, then Chr 3, \textit{etc.}
  - If multiple mutations on same chromosome…
    - Most proximal mutation listed first, then next most proximal, \textit{etc.}

- If location unknown, listed last
Summary

- Valuable information can be found in every strain name.
- Genetic background alters phenotype – know thy mouse!
- Use proper nomenclature in your publications:
  - C57BL/6J ≠ C57BL/6ByJ ≠ C57BL/6NJ
- Best practices allow you to generate (and publish) data that lasts and is relevant over time.
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- Neurobiology Models and Resources
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  - June 27, 2019, 1:00 PM USA Eastern Time

- **Sizing Experimental Mouse Colonies**
  - July 11, 2019, 1:00 PM USA Eastern Time

- **Efficient Mouse Colony Management**
  - July 18, 2019, 1:00 PM USA Eastern Time
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The Jackson Laboratory
Thank you!

We will now begin our live Q&A Session

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