


The laboratory mouse
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What we'll cover


Board oriented! (I hope; it's been a while. . .)

Mouse biology, reproductive biology, and behavior

Nomenclature


Immunodeficient mice

Mouse history, the top 5 inbred mice, and their characteristics




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**MOUSE BIOLOGY,
REPRODUCTIVE BIOLOGY, AND
BEHAVIOR**



Why mice?


- Mammalian system
- Small and easy to handle
- Litter-bearing
- Easy to house
- Relatively inexpensive
- Embryos readily accept manipulation and culture conditions
- Don't live forever
- Breed often
- Share many of the same genes as humans



Laboratory mice are rodents and retain many wild-derived behaviors



But!

Laboratory mice are not WILD mice! They are domesticated animals.

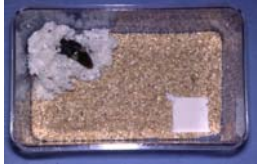



What does this mean?

- Mice: monophyodont hypsodonts
- Mice: poor thermoregulatory capabilities
- Mice: poor eyesight (comparatively)



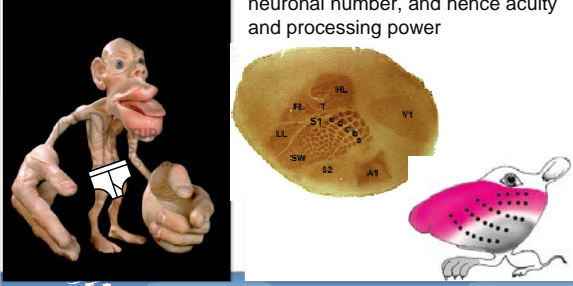
Normal behavior

- Gnawing 
- Nest-building and burrowing 
- Thigmotropism

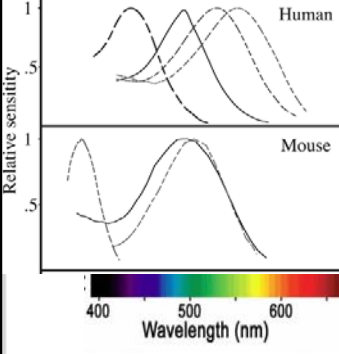
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Sensory homunculi: Mouse whiskers, human fingers

Sensory maps in the cortex reflect neuronal number, and hence acuity and processing power



London Natural History Museum, Vanderhaeghen et al 2000, Blakemore, 1977, Moskowitz, AMG




Human

Mouse

Relative sensitivity

Wavelength (nm)


Mice are dichromats that see into the UV but lack cones that are sensitive above ~600 nm



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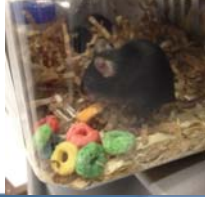
What does this mean?

- Mice: nocturnal
- Mice: herbivores, shading to omnivores
- Mice: ultrasonic hearing



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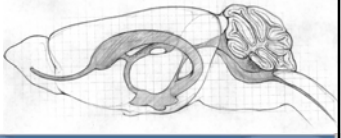
Normal behavior

- Active at night 
- Diet usually controlled
 - Cannibalism is normal
- Disturbed by noises we can't hear 

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What does this mean?


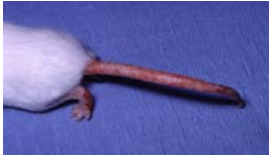
- Mice: hindgut fermenters
- Mice: dominance hierarchies
- Mice: excellent sense of smell



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Normal behavior


- Coprophagic
- Fighting /social interactions
- Scent marking



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Abnormal behavior

- Sluggish
- Hunched
- Piloerection
- Ungroomed
- Stereotypies



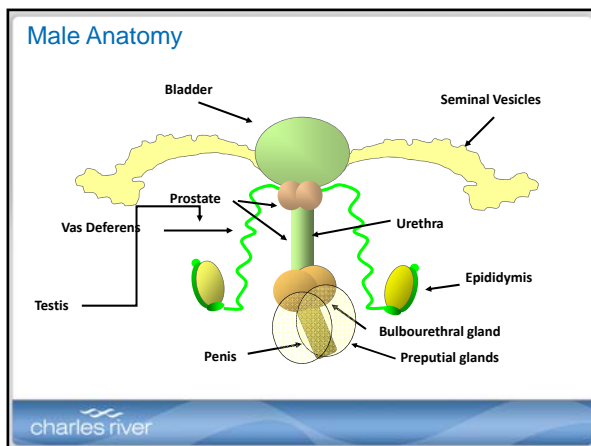
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Males

- Start breeding at 8 weeks
- Up to one year as breeders or studs
- Retire at one year*
- Retire if infertile with young females
- Rotational vs. same cage stable matings

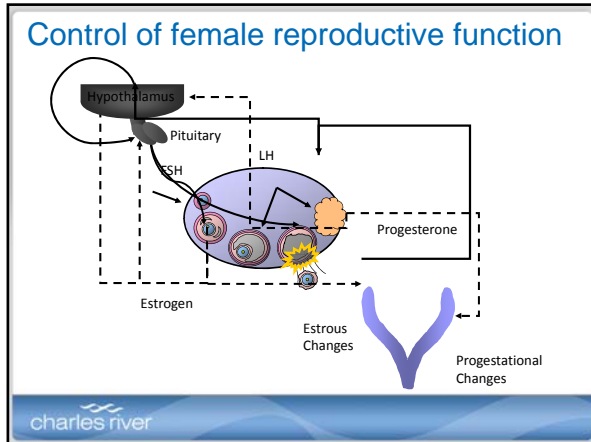
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Females

- Polyestrous
- Spontaneous ovulators
- Estrous cycle = 4 days
- Pseudopregnancy
- Pregnancy length 19-21 days
- Fertile post-partum estrus
- Delayed implantation

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Control of the estrous cycle

- Exogenous hormones
- Individual housing
- Group housing/overcrowding (Lee-Boot effect)
- Whitten effect
- Bruce effect
- Pseudopregnancy

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NOMENCLATURE

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Outbred rodent/rabbit nomenclature

Breeder code	CrI
Producer stock designation	CrI:CD
Origin of stock	CrI:CD(SD)

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Outbred mice

Producer, ":", producer designation, (origin of stock)

CrI:CD1(lcr)	CrI:WTF
CrI:PDQ	CrI:SKH2- <i>H^{hr}</i>
CrI:CF1	CrI:CFW(SW)

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Inbred rodent/rabbit nomenclature

Inbred strains named with numbers and capital letters	C57BL
Substrains identified by parent strain followed by slash	C57BL/6
First letter of lab code capitalized, rest lowercase	C57BL/6 CrI

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Spontaneous mutations

(we're naming genes now)

Novel mutation, phenotypic descriptor assigned
(**bs** = blind sterile)

Allelic to previous mutation? New symbol becomes superscript.

- **rh** = rhino, discovered to be allele of
- **hr** = hairless
- rhino symbol now **Hr^{rh}**

gene → allele

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Spontaneous mutations

Once gene is cloned, new function-based symbol assigned, and old descriptor superscripted to gene symbol to indicate that it's an allele of that gene

ob = descriptive symbol
Lep^{ob} = function-based symbol

nu to
Hfh11^{nu} to
Foxn1^{nu}

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Transgenics

Colloquially, animals overexpressing genes from another species.

This genetic material is randomly integrated into the genome.

DNA is injected into the one-celled embryo.

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Transgenic nomenclature

**Genetic background-
Tg(YYYYYY)#####Zzz**

Tg: Denoting transgene was inserted

(YYYYYY): The official gene symbol of the inserted DNA
Promoter designations encouraged

#####: Laboratory assigned number (1-99,999)

Zzz: Laboratory code (ILAR-assigned)

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Transgenic nomenclature

Genetic background-Tg(YYYYYY)#####Zzz

Example:

C57BL/6-Tg(ACTb-EGFP)1Okb

BL/6 mouse containing the b actin promoter and the enhanced green fluorescent protein gene and the 1st germline transmission (founder) from the lab of Dr. Masaru Okabe

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Targeted mutations

Colloquially, "knockouts".

Complicated process to produce these animals—involves donor animals, genetic manipulation of embryonic stem cells from other animals, and multiple crosses before you're sure you have an animal of interest.

Homologous recombination in embryonic stem cells to knockout/knockin genes.

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Targeted mutation nomenclature

Name the mouse:

Genetic background of **recipient mouse**
; (semicolon)
genetic background of **ES cells**
- (dash)

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Targeted mutation nomenclature

Then, name the gene:

XXXXtm###Zzz

XXXX = gene **tm** = targeted mutation
= number Zzz = lab code

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Targeted mutation nomenclature ("knockouts")

B6;129P2-Apoa1^{tm1}Unc

- Recipient: C57BL/6
- Donor: 129P2/OlaHsd
- Targeted gene: Apoa1
- Founder info: tm1
- Lab code: Unc

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Congenic

The transfer of a gene* from one background to another.

An animal is not congenic until it has been backcrossed 10 times
- (there are ways to get around this now)

*Any gene may be transferred!

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Punctuation junction

(strain abbreviation)	Small contribution from 3 rd strain
STOCK or Cg	Mixed genetic background, more than two strains
Semicolon ;	Genetic background is some mixture of the strains separated by the semicolon
Period .	N5-N9 or N10 Incipient congenic or congenic

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Nomenclature for spontaneous mutation congenics

BKS.Cg-Dock7^m +/+ Lepr^{db}/J

Background strain: C57BLKS/J

Donor strain: Lepr^{db}, C57BLKS;
Dock7^m, DBA/2J


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Nomenclature for targeted mutation congenics

C.129P2(B6) – *Il2^{tm1Hor}*


Background strain: BALB/c

Donor Strain: **129P2 ES cell line injected into a B6**
(then the tm was transferred from B6;129 onto BALB/c by mating)



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IMMUNODEFICIENT MICE

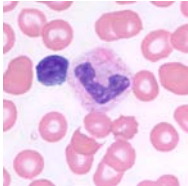



Immunodeficient?

Which part of the immune system?

Innate
Immediate response
Non-specific

Acquired (or adaptive)
Response takes time to develop
Lasts lifetime* of host
Specific response





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Mice

Nude
Scid
Beige
Xid (*Btk* gene)
Rag-1, *Rag-2*
Stat-1, *Stat-2*
Deficiencies in cytokines
Deficiencies in antigen presentation
Background strain characteristics (polygenic)

Combinations of the above through breeding or transgenesis





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The most immunodeficient mouse currently known

NOG (or NSG or NOD-scid-gamma)

A natural severe combined immunodeficiency mutation (*Prkdc^{scid}*) on a NOD (non-obese diabetic) background with the further knockout of the interleukin 2 receptor gamma chain gene (*Il2rg^{tm1Wjl}*)

Scid = no adaptive immunity
NOD = innate immunity very impaired (strain characteristic)
Il2rg = no NK cell function

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Immunodeficient mice: nude

Chromosome: 11

Gene: *Foxn1* (forkhead box N1)

Effects: Homozygotes for different mutations have in genetically determined absence or loss of hair and failed hair keratinization, premature lethality (differing by genetic background) and absence of thymus, resulting in multiple immune abnormalities

Uses: Oncology studies, xenografted tumors



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Immunodeficient: scid

Chromosome: 16

Gene: Prkdc (protein kinase, DNA activated, catalytic polypeptide)

Effects: Mutations at this locus affect genome stability, radiation sensitivity and DNA repair. Nonsense (scid) and null homozygotes have severe combined immunodeficiency.

Uses: oncology studies, xenografted tumors

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Immunodeficient: beige

Chromosome: 13

Gene: Lyst (lysosomal trafficking regulator)

Effects: Homozygous mice have a phenotype similar to human Chediak-Higashi syndrome patients, exhibiting lysosomal dysfunction with resultant protein storage; diluted coat color; abnormal melanogenesis; immune cell dysfunction resulting in increased susceptibility to bacterial, viral, and parasitic infections and decreased cytotoxic activity against tumor cells

Uses: Knocking down NK cells for increased tumor take in immunodeficient models

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Immunodeficient: xid

Chromosome: X

Gene: Btk (Bruton's agammaglobulinemia tyrosine kinase)

Effects: Mutants have immune defects including reduced B cell numbers, serum immunoglobulin deficiencies, and defective responses to B cell activators and thymus-independent antigens. B-1 B cells are absent in these mice.

Uses: Oncology, immunology

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Immunodeficient: Rag1 and Rag2

Chromosome: 2

Gene: Rag1 and Rag2 (recombination activating gene)

Effects: Inability to undergo V(D)J recombination prevents B and T cells from maturing beyond certain stage. Functionally a severe immunodeficiency.

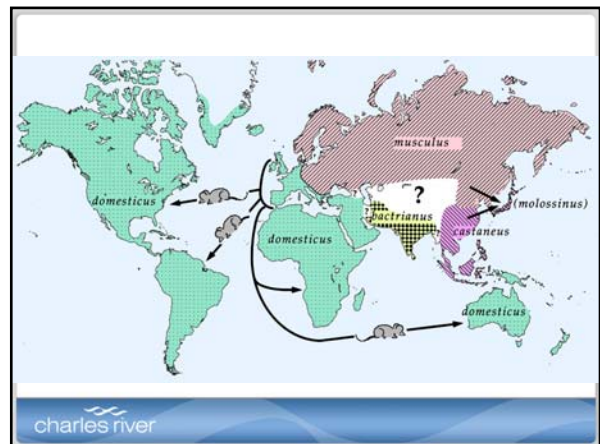
Uses: Immunology studies

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MOUSE HISTORY AND THE ORIGINS OF THE TOP 5 INBRED STRAINS

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Laboratory mice. . .

Fancy mice and deviants


- Ancient Romans and Greeks
- Japanese and Chinese
- Thanks to Miss Abigail Lathrop who collected them and...

William Castle and Clarence Cook Little



Quick coat color tutorial


Old name	New name	Chr.	Effect	Coat color	Epistatic?
A	A	2	Banded hair	Agouti	No
a	A ^a		Solid hair	Non-agouti	No
B	Tyrp1	4	Black pigment	Black	No
b	Tyrp1 ^b		Brown pigment	Brown	No
C	Tyr	7	Has pigment	Pigmented	No
c	Tyr ^c		Albino	Albino	Yes (some)
D	Myo5a	9	Has pigment	Pigmented	No
d	Myo5a ^d		Diluted pigment with pigmented eyes	Dilute	No
P	Oca2	7	Has pigment	Pigmented	No
p	Oca2 ^p		Diluted pigment with pink eyes	Dilute	No




C57BL/6

Coat color : a/a B/B C/C D/D P/P
H2^b

Micro- , anophthalmia
Hydrocephalus
Malocclusion
Age-related hearing loss
Barbering/ulcerative dermatitis
Methylates DNA
Nnt (J) and *Snca* (JOLAhsd) and *rd8* (B6N)
Defect in melatonin production
Vaginal septa




"B6" or "Black 6"
NOT "C57"



BALB/c

Coat color: a/a b/b c/c D/D P/P
H2^d


Vaginal septa
Imperforate vagina
Spontaneous corneal opacities
Age-related hearing loss
Ulcerative blepharitis
Cardiac calcinosis



DBA

Coat color: a/a b/b C/C d/d P/P
DBA/1 and DBA/2 are different STRAINS, not substrains.
DBA/1 H2^a DBA/2 H2^d

OLDEST INBRED STRAIN (1909)
Cardiac calcinosis
Age-related hearing loss
Audiogenic seizures
Glaucoma and corneal mineralization
Complement C5 deficiency




The 129 family of mice

Coat color: various, including white-bellied agouti, albino, and chinchilla
H2^b

Embryonic stem cells; match stem cell origin to parental strain

- 'P' indicates origin from the parental stock;
- 'S' indicates origin from a line that had carried *S*/
- 'T' indicates that the line carries/d *Ter*;
- 'X' indicates that the line was genetically contaminated.

Corpus callosum absent in 80% of some substrains
Hepatic portal systemic shunts
Testicular teratomas



C3H/He

Coat color: A/A B/B C/C D/D P/P
H2^k
Related to BALB/c and DBA
Originally selected for mammary tumor formation
Gone now; due to MMTV; hysterectomy rederived
C3H/HeJ mutation resistant to endotoxin (Tlr4)
Blind (rd1)
Hearing normal
Cardiac calcinosis
Barbering/alopecia areata?

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<http://www.hopkinsmedicine.org/mcp/PHENOCORE/CoursePDFs/09s1BraytonMouseDzOutline75p.pdf>
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