

Mouse colony management in a nutshell: Getting the most from your colonies and ensuring reproducibility



Sarah Hart-Johnson

Head of Colony Management Services

Francis Crick Institute

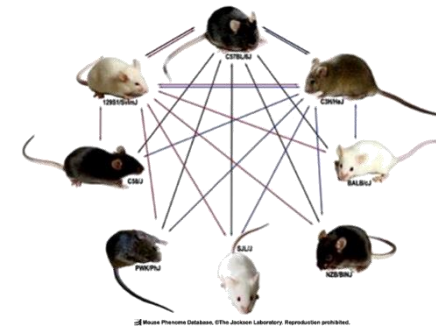
Know your strain!

- Highly inbred = a genetically uniform experimentation group

IF PROPERLY MAINTAINED



Choosing a strain



- Inbreds, outbreds, hybrids...
- Factors to consider will include;

Reproduction, Life-span and Spontaneous disease, cancer predisposition, drug response, immunology, specific phenotypes (e.g. pigmentation, susceptibility to disease) & availability of genomic data, what others have used.

Strain	Average weaning age (wks)	Average breeding lifespan (wks)	Average litter size (born)	Average # litters (born)	Overall tumour incidence	Specific phenotype
BALB/cJ	3	30	4.9	4.5	43%	Generation of monoclonal AB, used to study infectious disease
C57BL/6J	4	30	4.9	5.5	1-7%	Disease resistant “standard” strain
FVBN/J	4	26	5.3	8.4	50-60%	Retina degeneration, aggression in cage

Which wildtypes do you use?... What's normal for them?

Mouse Search Q

Jax Employees



POPULAR

C57BL/6j

Stock No: 000664 | Common Name: B6
Also Known As: B6j, B6/J

C57BL/6j is the most widely used inbred strain and the first to have its genome sequenced. Although this strain is refractory to many tumors, it is a permissive background for maximal expression of most mutations. C57BL/6j mice are resistant to audiogenic seizures, have a relatively low bone density, and develop age related hearing loss. They are also susceptible to diet-induced obesity, type 2 diabetes, and atherosclerosis. Macrophages from this strain ar...

Read More S

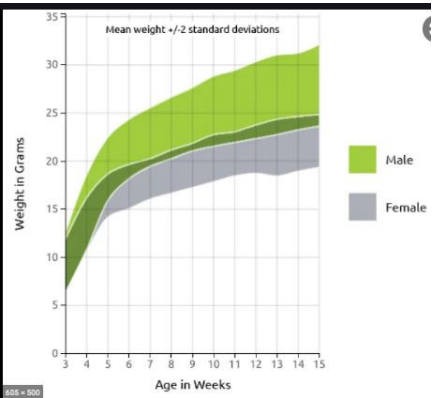
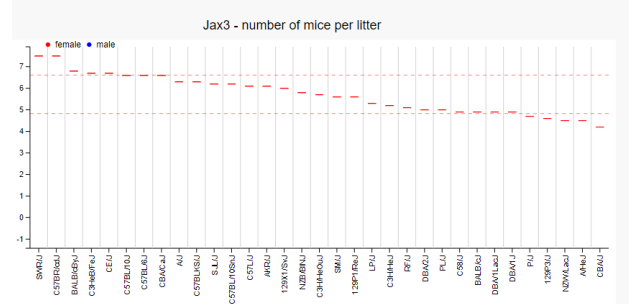
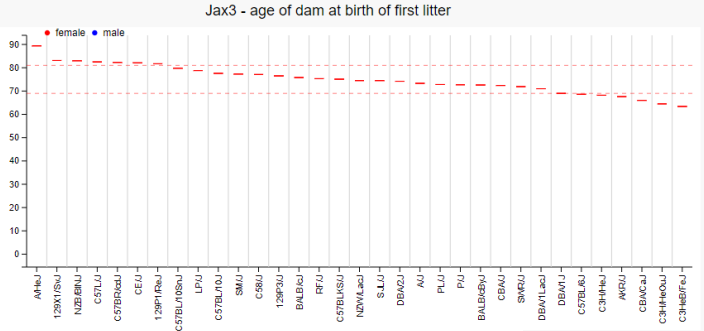


Table 1. Reproductive information for the most widely used JAX® Mice strains, readily available in large quantities.

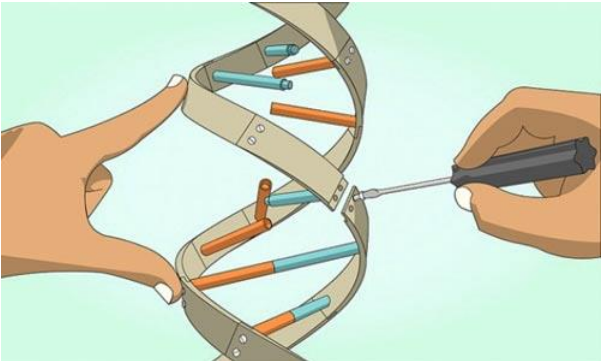
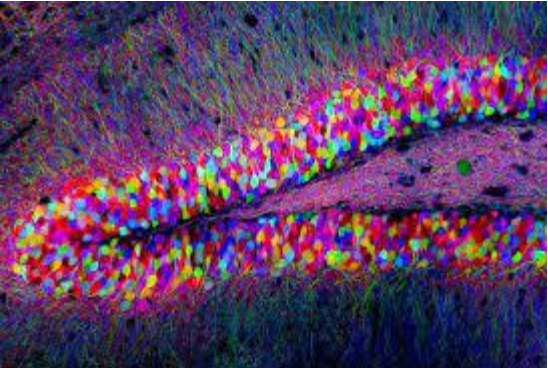
Strain	Mean weaning age (wks)	Rotation Length ¹ (wks)	Mean litter size (weaned)	Mean number of litters (born)	Wean:born ratio	Percent females (weaned)
BALB/cj [000651]	3	30	5.4	4.1	0.99	50%
BALB/cByj [001026]	3	30	5.2	3.8	0.96	56%
B6.129P2-ApoE ^{tm1b} /j [002052]	4	26	4.5	3.9	0.83	44%
C3H/Hej [000659]	3	22	5.0	3.5	0.92	44%
C57BL/6j [000664]	4	30	5.6	5.4	0.92	47%
CBA/j [000656]	3	26	4.0	5.4	0.93	48%

Detailed Description

C57BL/6j is the most widely used inbred strain. It is commonly used as a general purpose strain and background strain for the generation of congenics carrying both spontaneous and induced mutations. Although this strain is refractory to many tumors, it is a permissive background for maximal expression of most mutations. C57BL/6j mice are used in a wide variety of research areas including cardiovascular biology, developmental biology, diabetes and obesity, genetics, immunology, neurobiology, and sensorineural research. C57BL/6j mice are also commonly used in the production of transgenic mice. Overall, C57BL/6j mice breed well, are long-lived, and have a low susceptibility to tumors. Primitive hematopoietic stem cells from C57BL/6j mice show greatly delayed senescence relative to BALB/c and DBA/2J. This is a dominant trait. Other characteristics include: 1) a high susceptibility to diet-induced obesity, type 2 diabetes, and atherosclerosis; 2) a high incidence of microphthalmia and other associated eye abnormalities; 3) resistance to audiogenic seizures, 4) low bone density; 5) hereditary hydrocephalus (early reports indicate 1 - 4 %); 6) portosystemic shunts (~5%); 7) hairloss associated with overgrooming; 8) a preference for alcohol and morphine; 9) late-onset hearing loss; 10) increased incidence of hydrocephalus and malocclusion and 11) spontaneous calcaneal luxation in 1% of aged males beginning at 6-8 months of age, resulting in ankylosing enthesopathy of that tarsal joint.



Genetically Altered (GA) animals



Getting the right mutation & finding out more...

Strain Name	Synonyms	States	Repository	Mutation Types	Alleles	Genes
B6.JGpt-Lif ^{em1Cd} /Gpt		sperm	GPT		Lif ^{em1Cd} /Gpt	Lifr
B6.JGpt-Lif ^{em1Cloxy} /Gpt		sperm	GPT		Lif ^{em1Cloxy} /Gpt	Lifr
Lif ^{tm1a} /EUCOMM/Hmgu		ES Cell	EUMMCR	targeted mutation	Lif ^{tm1a} /EUCOMM/Hmgu	Lifr
Lif ^{tm1e} /EUCOMM/Hmgu		ES Cell	EUMMCR	targeted mutation	Lif ^{tm1e} /EUCOMM/Hmgu	Lifr
B6NTac.B6N-Lif ^{tm1a} /EUCOMM/Hmgu/H	C57BL/6N-Lif ^{tm1a} /EUCOMM/Hmgu/H	embryo sperm	HAR	targeted mutation	Lif ^{tm1a} /EUCOMM/Hmgu	Lifr
C57BL/6N-Lif ^{tm1a} /EUCOMM/Hmgu/H	B6NTac.B6N-Lif ^{tm1a} /EUCOMM/Hmgu/H	sperm	EMMA	targeted mutation	Lif ^{tm1a} /EUCOMM/Hmgu	Lifr
C57BL/6N-Lif ^{tm1c} /EUCOMM/Hmgu/H	B6NTac.B6N-Lif ^{tm1c} /EUCOMM/Hmgu/H	sperm	EMMA	targeted mutation	Lif ^{tm1c} /EUCOMM/Hmgu	Lifr
B6NTac.B6N-Lif ^{tm1a} /EUCOMM/Hmgu/HTacAnuApb		sperm	APB	targeted mutation	Lif ^{tm1a} /EUCOMM/Hmgu	Lifr
B6.129S7-Lif ^{tm1mx} /J		embryo	JAX	targeted mutation	Lif ^{tm1mx} /J	Lifr
KOMP ES cell line Lif ^{tm1} (KOMP)/Vc9		ES Cell	MMRRC	deletion	Lif ^{tm1} (KOMP)/Vc9	Lifr
C57BL/6N-A ^{tm1Brd} Lif ^{tm1a} /EUCOMM/Hmgu/HMmucd	C57BL/6N-A ^{tm1Brd} / Lif ^{tm1a} /EUCOMM/Hmgu/HMmucd	archived sperm	MMRRC	targeted mutation	Lif ^{tm1a} /EUCOMM/Hmgu	Lifr
B6NTac.B6N-Lif ^{tm1c} /EUCOMM/Hmgu/H		embryo sperm	HAR	targeted mutation	Lif ^{tm1c} /EUCOMM/Hmgu	Lifr

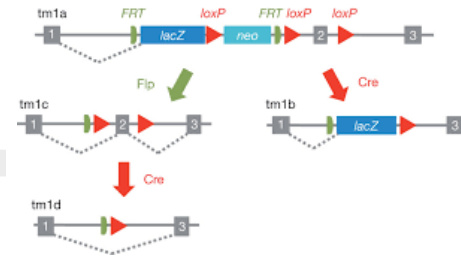
Gene: Lifr MG1:96788

Gene Summary
 Name: Lifr receptor alpha
 Synonyms: soluble differentiation-stimulating factor receptor, A230075M04Rk
 Order Alleles

IMPC Phenotype Summary
 Body Weight Measurements
 Embryo Imaging Data
 Viability Data

Phenotypes
 The IMPC applies a panel of phenotyping screens to characterise single-gene knockout mice by comparison to wild types. Click on the different tabs to visualise significant phenotypes identified by the IMPC, as well as all data that was measured.

Phenotype	System	Allele	Zyg	Sex	Life Stage	P Value
preweaning lethality, complete penetrance		Lif ^{tm1b} /EUCOMM/Hmgu	HOM	♀♂	Early adult	0.00
abnormal brain morphology		Lif ^{tm1b} /EUCOMM/Hmgu	HET	♂	Early adult	0.00



MGI Gene Detail: Lifr

Summary
 Symbol: Lifr
 Name: Lifr receptor alpha
 Synonyms: A230075M04Rk, soluble differentiation-stimulating factor receptor
 Feature Type: protein coding gene
 IDs: MG1:96788, NCBI Gene: 16880
 Alliance: gene page
 Transcription Start Sites: 8 TSS

Location & Maps
 Sequence Map: Chr15:7120095-7226970 bp, + strand
 Genetic Map: Chromosome 15, 3.46 cM

Strain Comparison
 SNPs within 2kb: 749 from dbSNP Build 142
 Strain Annotations: 18

Homology
 Human Ortholog: LIFR, LIF receptor subunit alpha
 Vertebrate Orthologs: 4

Human Diseases
 Diseases: 1 with Lifr mouse models

Mutations, Alleles, and Phenotypes
 Phenotype Summary: 32 phenotypes from 3 alleles in 4 genetic backgrounds
 All Mutations and Alleles: 36
 Gene trapped: 28
 Targeted: 7
 Transposon induced: 1
 Genomic Mutations: 1 involving Lifr
 Incidental Mutations: Mutagenetix, APF
 Find Mice (IMSR): 45 strains or lines available
 Comparison Matrix: Gene Expression + Phenotype

Phenotype Overview
 Click cells to view annotations.

Homozygotes for targeted null mutations die as neonates with reduced numbers of facial and spinal motor neurons, neurons of the nucleus ambiguus, and astrocytes. Mutants also show impaired placentation, severe osteopenia, and low hepatic glycogen stores.

Laboratory
B6.129S7-Lifr^{tm1mx}/J
 Stock No: 002402
 Targeted Mutation

Typically mice are recovered in 10-14 weeks. Contact Customer Service to place an order or for more information.

Detailed Description
 These leukemia inhibitory factor receptor (*Lifr*) deficient mice exhibit placental, skeletal, neural and metabolic defects resulting in perinatal death.

Development
 A lacZ/neomycin cassette replaced the ATG start codon of the leukemia inhibitory factor receptor (*Lifr*) gene. The construct was electroporated into 129S7/SvEvBrd-Hprt⁻-derived AB1 embryonic stem cells (ES cells). Correctly targeted ES cells were injected into blastocysts and the resulting mice were bred to C57BL/6 mice. The Lifr-deficient strain was developed in the laboratory of Dr. Jacques Peschon at ImmuneX Corporation.

Nomenclature

Understanding mouse strain nomenclature is critical to understand the complex strains, sub-strains, transgenics, knockouts, etc. in your care

To anticipate phenotypes and understand the importance of maintaining genetic background and good breeding records.

Common names - B6

Official Nomenclature - C57BL/6J



Nomenclature basics

Guidelines are set by the International Committee on Standardised Genetic Nomenclature for Mice.

Inbred lines - normally named for appearance and origin or occasionally phenotype

C57BL/6J

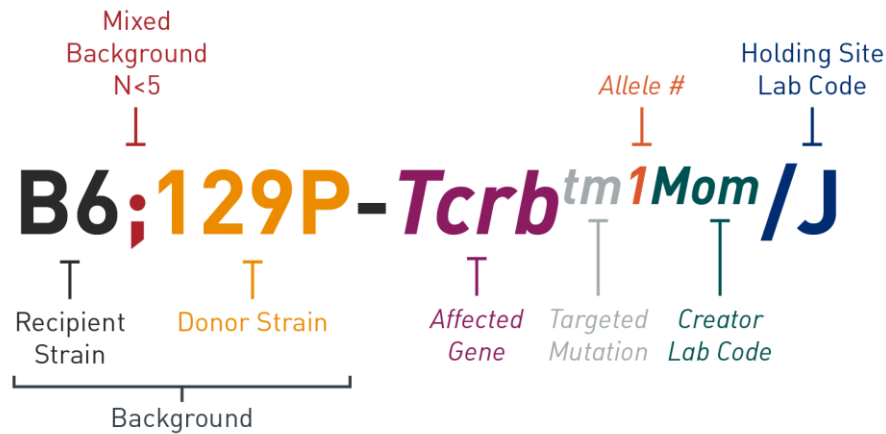
- C57BL parent strain designation after 20 generations of brother sister mating (from CC Little, 57th female, black)
- / separates parental strain from the sub-strain
- 6 line number
- J laboratory code

Labcode	Status	Investigator	Organization
J	active	The Jackson Laboratory	The Jackson Laboratory
Crick	active	Jan-Bas Prins	The Francis Crick Institute

Nomenclature can also tell us about how a strain has been made and bred....

And help us decide on the way forward!

- Guide to Nomenclature & tutorial/webinars...



QUICK GUIDE TO MOUSE NOMENCLATURE

This infographic provides a comprehensive overview of mouse nomenclature, categorized by strain type and genetic modification:

- Inbred and Hybrid**:
 - Inbred***: C57BL/6J = B6, 129S1/SvImJ = 129S
 - F1Hybrid***: B6129SF1/J
- Spontaneous or Induced Mutation**: C57BL/6J-Apc^{Mh}/J
- Knock-out, Knock-in or Floxed**: B6;129P-Tcrb^{tm1}Mom/J
- Transgenic (Tg)**: B6.Cg-Tg(PDGFB-APP)5Lms/J
- Endonuclease-mediated**: C57BL/6J-Ngly1^{am9}Lutzy/J

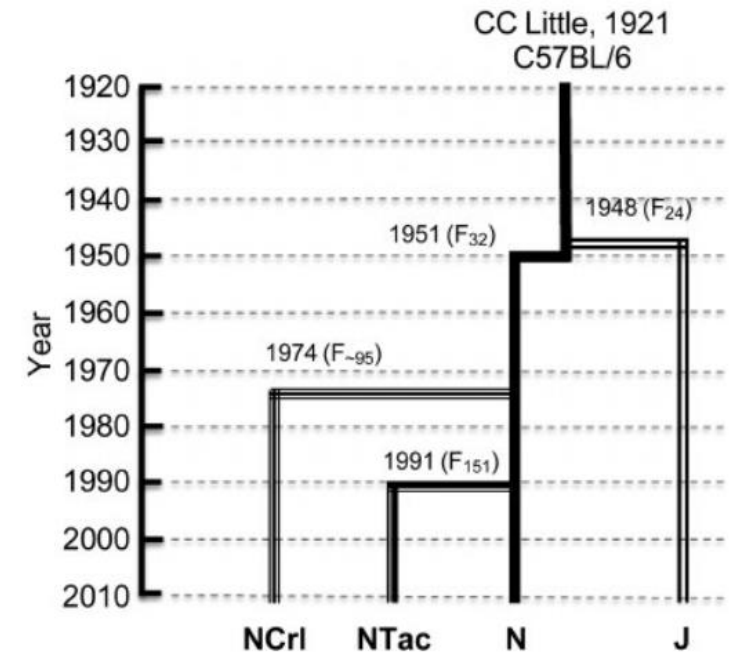
Additional information includes contact details for The Jackson Laboratory and a legend for mixed strain backgrounds and congenic/incipient congenic strains.

Genetic drift & Sub-strains

Once a colony has been separated from its parent colony by 20 generations it should be considered a new sub-strain, and named as such i.e. C57BL/6J or C57BL/6NTac

This is because of Genetic contamination & drift:

- Residual heterozygosity (Inbreds are only 99.9% similar)
- Spontaneous mutation (100 bases mutate/generation)



Genetic drift describes random fluctuations in the numbers of gene variants (alleles) in a population, and the constant tendency of genes to evolve through spontaneous mutations.

Phenotypes change on different background!!

Differing

- susceptibilities to infection
- mortality rates
- rates of tumour growth
- breeding performance
- behavioural responses

Reported phenotypes disappear...



Examples..

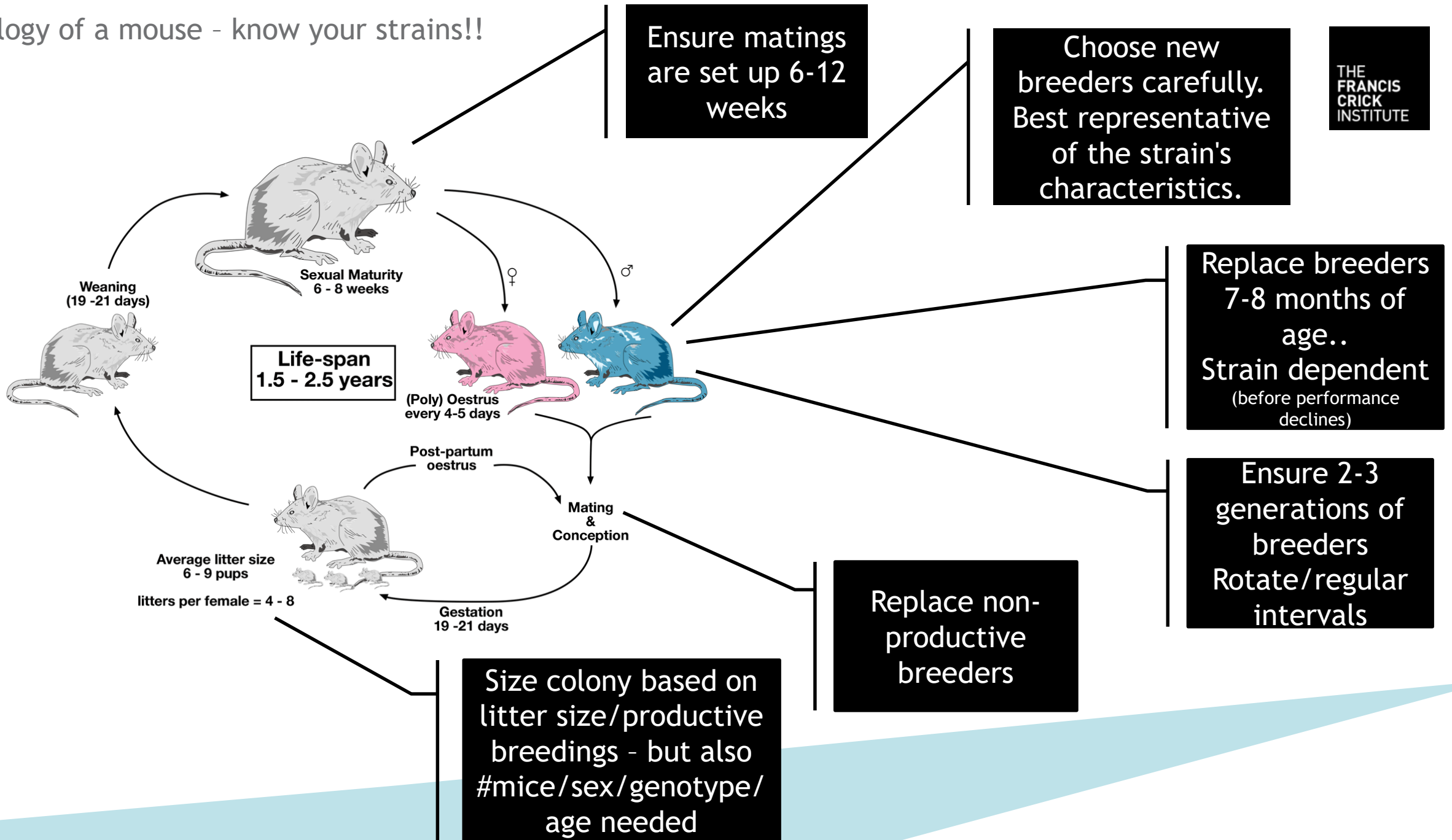
- IL10KO & IBD on C57BL/6J 😊 v 129Sv/Ev, BALB/c or C3H/He ☹️
- APC min & intestinal polyps on C57BL/6J ☹️ v AKR/J, MA/MyJ or CAST/Eij 😊😊
- C57BL/6J &N - difference in fear responses, cardiac function, retinal degeneration, response to high fat diet...

Slowing genetic drift & ensuring strains are on defined backgrounds



- Inbred colonies - Refresh/Replace regularly from a reliable commercial supplier every 5-10 generations.
- Genetically Altered colonies - Outcross to the wildtype (Refresh) every 5-10 generations.
- For complex GA lines (multiple alleles) - cryopreserve stock and return regularly to an earlier generation

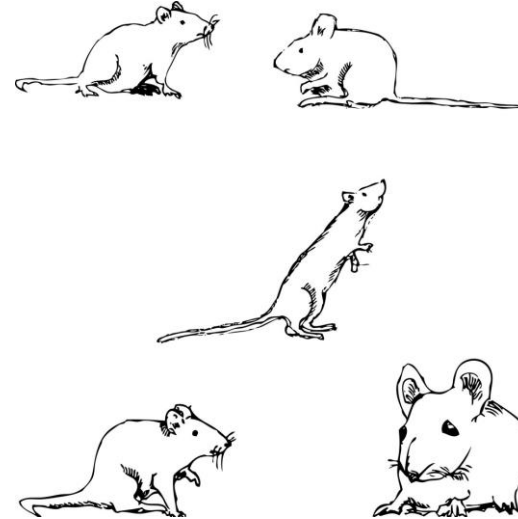
Biology of a mouse - know your strains!!



What's normal for your strain?

- Not all strains are the same
- If working with different strains or if backcrossing to another background expect changes in performance.
- The **Mouse Phenome database** or Jax resources can give you data on the averages for each background strain which can then be compared to your GA strain

1. **Average litter size**
(total pups/total litters)
2. **Average litter interval**
(# litters/breeding span(wks))
3. **Production Efficiency Index (PEI)**
(#weaned/female/week)
4. **Pre-weaning mortality**
(#born-#weaned / #born)
5. **% Productive matings**
6. **Total litter loss**



- **Know your mice!! - good records**

- Be informed - research your strains or other strains with similar alterations.
- Get a full history of any new strains or characterise fully
- Which allele are you using, how has it been made?
- Check genotype at each generation (& check for contamination) Is your assay specific
- Check your background - or backcross/refresh/replace from frozen stock regularly
- Know what's normal for your background strain to spot deviation

- **Reduce waste & optimise your colonies**

- Plan what is needed and size colony accordingly
- Regularly review demand & use & adjust
- Check the breeders, replace where TLL, unproductive
- Communicate with animal care staff
- Cryopreserve as back up/to use up spare/to remove a line
- Look at options like intermittent breeding (Ellen to elaborate!)

Thank you for listening