

### Infectious & other Environmental Phenotypes in GEM

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Regardless of the method of generation of mutation(s) and mutants, phenotypes are impacted by:

1. Genetic influences of background strains.
2. Infectious agents and other environmental factors.

Examples of Phenotypes: coat color, size, sex, enzyme levels, fecundity, social behaviors ...

Also Phenotype = Lesion = Pathology:

Dt drug or treatment (focus of industry, pharma)

Dt infectious or other environmental factors (important focus in diagnostic path (+ phenotyping))

Dt genetic background, manipulation or spontaneous mutation (also important in diagnostic path (+ phenotyping))

In Functional Genomics initiatives & other translational research:

What pathology/phenotype is not something to be concerned (or excited) about  
*e.g. related to background strain.*

What pathology /phenotype is something to be concerned about  
*e.g. related to pathogens or environment.*

What pathology /phenotype is something to get excited about  
*i.e. really a phenotype, attributable to the mutation(s)*

When evaluating mutant mice, consider:

1. **Genetic principles + genetic manipulations** used to develop mutant animals.
2. **Molecular mechanism(s) and pathology of the human conditions** that the mutant mice are intended to model.
3. **Mouse strain peculiarities** + genetic influences of background strains.
4. **Intercurrent infections and other environmental influences.**

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**Differences in susceptibility to infectious diseases** should be expected in addition to phenotypes such as:

**C57BL/6:** microphthalmia, hydrocephalus, ulcerative dermatitis, osteoporosis, presbycusis, amyloidosis, acidophilic crystalline/macrophage pneumonia; lymphoma or histiocytic sarcoma

**129:** +/- corpus callosum; teratomas (Ter); lung tumors, nephropathy, acidophilic crystalline/macrophage pneumonia

**FVB:** retinal degeneration; seizures and 'Space Cadet' syndrome; lung tumors; acidophilic crystalline/macrophage pneumonia

**BALB/c :** +/- corpus callosum; dystrophic cardiac calcinosis (epicardial)

**C3H/ rd1/rd1;** dystrophic cardiac calcinosis, mammary tumors, liver tumors, +/- Tlr4

**C3H, CBA, SJL, SWR, FVB, some Swiss stocks: rd1/rd1** retinal degeneration

**BALB/c, C3H, DBA:** dystrophic cardiac calcinosis

**AKR:** thymic lymphoma

**A/J:** lung tumors, teratogen sensitivity

**SJL/J:** rd1/rd1; lymphoproliferative dz – lymphoma

**Some recognized genotype variations associated with immune functions**

Gene symbol	Gene /Locus name	Chrom	Allele Symbol	Allele name	Mutation	Strains
<i>Hc</i>	Hemolytic complement ( <i>c5</i> )	2	<i>O</i> ( <i>Hc<sup>O</sup></i> )	deficient	2 base "TA" deletion	A/HeJ, AKR/J, DBA/2J, FVB/N; NZB/B1NJ, SWR/J, B10.D2/oSnJ
<i>Tlr4</i>	Toll like receptor 4	4	<i>Lps-d</i> ( <i>Tlr4<sup>LPS-</sup></i> ) <sup>d</sup>	defective lipopolysaccharide response	C to A substitution in 3 <sup>rd</sup> exon	C3H/HeJ
<i>Rmcf</i>	MCF sensitive	5	<i>S</i> ( <i>Rmcf<sup>S</sup></i> )	sensitive to mcf forming leukemia viruses	recessive	AKR/J, C57BL/6, BALB/c, CBA/J, NFS, NZB, 129/J.
<i>Rmcf</i>	MCF sensitive	5	<i>R</i> ( <i>Rmcf<sup>R</sup></i> )	Resistant to mcf forming leukemia viruses	Dominant allele	DBA/1, DBA/2, and CBA/Ca
<i>Ceacam1</i>	carcinoembryonic antigen-related cell adhesion molecule 1	7	<i>Hc2-r</i> ( <i>Ceacam1<sup>Hv2-r</sup></i> )	Mouse hepatitis virus (MHV-4) resistance	Deletion → 23 aa substitution	SJL/J

Search for gene/locus/allele updates at <http://www.informatics.jax.org/>

Search for mice at <http://www.findmice.org/index.jsp>

**NON infectious Environmental Factors** that may impact (cause, increase or diminish) 'phenotypes':

**Cage Population (single/group, same sex/breeding)** → behavior, bioburden, body wt, longevity, tumors ...

**Cage Change Intervals** (bioburden, NH3) → respiratory function, abscesses etc

NH3 levels vary with strain, enteric flora, bedding, caging

Dust/aerosols vary with bedding, caging

**Phytoestrogens** in feed, bedding, plastics → ♀ production, cancer, cardiovasc dz etc

**Diet** – e.g. caloric restriction → ♂ cancer, ♀ longevity, etc.

- **Fat** - %? Source? animal ? vegetable?
- **Protein** - %? Source ? soy ? alfalfa ? casein ?

**Light** levels, light/dark cycles → ♀ production, activity/metabolism, vision etc

**Noise** – construction, HVAC, computer etc → hearing loss, fertility etc [1, 2]

**Temperature/Humidity** → ♀ activity/metabolism, production? Dermatitis? Tumor growth?

**Water:** Acid, chlorine, antibiotics → ♂ infection; ♀ dental/periodontal dz?

**TREATMENTS!?:** Fenbendazole, Ivermectin, TMZ, enrofloxacin (Baytril) [3-8]

**What is the Optimal Environment?** Is the 'Cleanest Barrier' best for your studies?

**Exclusion list** = everything you can test for? (\$\$\$)

**Practices/equipment** = Autoclaved Feed, Bedding, Caging/Isolator/Glove box; PPE....?

**Health/Pathogen Status of GEM**

Mice to be evaluated should be of **known microbial status**, preferably 'clean', but consider: *Microbial challenge might 'expose' a phenotype that would not be apparent in perfectly clean mice in a perfectly clean environment.*

**SPF** = Specific Pathogen Free' -- absent (excluded) pathogens must be defined.

'Clean' is a moving target, as new pathogens emerge or are rediscovered

'Barrier' defined by exclusion list and practices (e.g. PPE, autoclaved feed, water, equipment etc.)

Scientific collegiality and collaborations can involve sharing of mice, with their infectious agents within and between institutions and continents.

Mutant phenotypes, especially immune compromise or dysfunction can complicate maintenance of the animals, and design and performance of health surveillance and diagnostic programs.

**Immune Function/Status** involves more than just humoral and cell-mediated immunity:

- E.g. pneumocystis pneumonia in an 'immunologically normal' mouse
- Is there abnormal surfactant? defective mucociliary escalator?

Genetically Engineered Mice (& Spontaneous Mutants) may manifest

1. overt disease due to organisms that are considered to be non-pathogenic or opportunistic (e.g. *Pneumocystis murina*),
2. unusual clinicopathologic manifestations of infections,
3. persistence of infectious agents that are cleared by 'normal' mice,
4. prolonged shedding of infectious agents, or
5. failure to seroconvert.

**What is 'normal' immune function/status?**

**What is 'normal (microbial) flora' in research mice?**

What we're used to seeing and does not cause a problem?

- ▶ be careful – what DID NOT cause a problem may cause problems in some GEM's
- ▶ WE HAVE THE TECHNOLOGY to make them susceptible (or resistant) to anything ...
- ▶ 'normal' or 'control' flora can vary with strain, environment and goals of the study

### Infectious Agents

**Pathogens** → morbidity, mortality – host/situation dependent?

**Confounders** – host/project-dependent?

**Commensals/Opportunists** – host/situation dependent?

### Viral agents in mice – why they are of concern

Likely to be or was Pathogenic	Usually inapparent infections - &/or unlikely unless inoculated (e.g. biological contaminant)		Zoonotic
<b>MHV (corona)</b> <b>EDIM (rota)</b> Sendai (para) Ectromelia (pox)	<b><i>MNV Norovirus</i></b> <b>MPV, MVM (parvo)</b> <b>TMEV (Cardiovirus)</b> Retroviruses (retroelements)	MCMV, MTV (herpes) Mad 1,2 (adeno) MPtV MPyV (poly) LDHeV (Arterivirus) Reo3 (Reo)	<b>Han (Bunya)</b> <b>LCMV (Arena)</b>

**Agents estimated to be most PREVALENT in US and EU are bolded [9-15] - most recent refs:**

- Mahler & Kohl, 2009. A serological survey to evaluate contemporary prevalence of viral agents and *Mycoplasma pulmonis* in laboratory mice and rats in western Europe. *Lab Anim (NY)*, 38(5): p. 161-5.
- Pritchett-Corning, Cosentino, & Clifford, 2009. Contemporary prevalence of infectious agents in laboratory mice and rats. *Lab Anim*, 43(2): p. 165-173.

### Prevalence and incidence

**Prevalence** ~ how widespread the disease is.

Total number of cases of a disease in a given population at a specific **time point**.

- Estimated or calculated, based on testing a **relevant sample of appropriate size**.

**Incidence** ~ **risk of contracting the disease**.

Number of new cases during a given **time interval**, usually one year. expressed as a proportion or rate.

**Incidence proportion (aka risk)** = number of new cases divided by the size of population at risk

**Incidence rate** = number of new cases per unit of time

**Sentinel Surveillance for viral agents in mice**

Test for agents based on their importance or likelihood in a given situation (facility).

Are the agents:

Prevalent ?

Pathogenic ?

Zoonotic ?

Do you need to document 'negative' status

For export ?

For publication ?

What's the point of testing for an agent that is not excluded?

- ▶ Less testing of positive areas (→ fewer positive results in 'seroprevalence' studies)
- ▶ More testing to confirm negative status (→ more negative results in 'seroprevalence' studies)

Is there a good (available, reliable) test for the agent?

PCR & RtPCR for almost anything, requires appropriate sample selection & handling

- ▶ Fecal PCR – is the infected host shedding? (often can pool samples)
- ▶ Tissue PCR – does the agent persist? Is it cleared already?

Serology tests detect Antibodies, not agents.

- ▶ New multiplex microsphere based options [16]

**What do sentinel results mean?****'Positive sentinel'**

- Received dirty bedding from 1-1000's infected, shedding mice >2 weeks prior
- Made sufficient antibodies to be detected by a serologic test
- False positive ?

**'Negative sentinel'**

- Did not receive any dirty bedding – *is the sentinel cage dirty?*
- Did not receive dirty bedding from a cage when the mice were shedding
- Infected mice don't shed much
- Old sentinel did not mount much immune response
- False Negative ?

**(Mouse) Viral agents of interest or concern**

In approximate order of seroprevalence & testing recommendations in US & EU

Frequent testing		Less frequent testing	
1. MNV <i>Norovirus</i> *	7. <u>Ect</u>	13. <u>LDV</u>	
2. <u>MHV</u>	8. <u>MAD1,2</u>	14. <u>MCMV</u>	
3. <u>Parvoviruses</u>	9. <u>PVM</u>	15. <u>MTLV</u>	
4. <u>MRV</u>	10. <u>LCMV</u>	16. <u>(MPyV)</u>	
5. <u>TMEV</u>	11. <u>HTN</u>	17. <u>(MPTV)</u>	
6. <u>Sen</u>	12. <u>Reo</u>		

*Agents recognized to be potential contaminants of biological materials are underlined.*

**Viral Agents in Biologicals** (tissues, cell culture, tumor cell lines, harvested or commercial serum, antibodies, virus stocks) [17-31]: **ATCC does NOT test for viruses.**

- ▶ Dx/Detection: MAP (mouse antibody production test); **PCR, RtPCR**

**Mouse serology: agents and methods** from Pritchett-Corning, Cosentino, Clifford (2009) (Charles River Laboratories) [10] see also [16]

Agent (abbreviation)	Primary	Confirmation	
Cilia-associated respiratory bacillus (CARB)	MFIA/ELISA	IFA	BACTERIA
Ectromelia virus (ECTRO)	MFIA/ELISA	IFA	
<i>Encephalitozoon cuniculi</i> (ECUN)	MFIA/ELISA	IFA	Microsporidian
Epizootic diarrhea of infant mice virus (EDIM)	MFIA/ELISA	IFA	
Hantavirus (HNT)	MFIA/ELISA	IFA	
Lactate dehydrogenase-elevating virus (LDHV)	Enzyme*	PCR	*Chem test not serum AB
Lymphocytic choriomeningitis virus (LCMV)	MFIA/ELISA	IFA	
Minute virus of mice (MVM, MMV)	MFIA/ELISA	IFA, HAI	
Mouse adenovirus FL/K87 (MAV, MAV 1 and 2)	MFIA/ELISA	IFA	
Mouse cytomegalovirus (MCMV)	MFIA/ELISA	IFA	
Mouse hepatitis virus (MHV)	MFIA/ELISA	IFA	
Mouse parvovirus (MPV 1 and 2)	MFIA/ELISA	IFA	
Mouse pneumonitis virus (K)	MFIA/ELISA	IFA	
Mouse thymic virus (MTV, MTLV)	IFA	PCR	
Murine norovirus (MNV)	MFIA/ELISA	IFA	
<i>Mycoplasma pulmonis</i> (MPUL)	MFIA/ELISA	IFA, PCR	BACTERIA
Pneumonia virus of mice (PVM)	MFIA/ELISA	IFA, HAI	
Polyoma virus (POLY)	MFIA/ELISA	IFA	
Reovirus (REO, REO-3)	MFIA/ELISA	IFA, HAI	
Sendai virus (SEND)	MFIA/ELISA	IFA, HAI	
Theiler's murine encephalomyelitis virus (TMEV, GD-VII)	MFIA/ELISA	IFA	

**Mouse serology: Results** – from Pritchett-Corning, Cosentino, Clifford (2009) (Charles River Laboratories) [10] and Mahler & Kohl (2009) [Western Europe] [9]; Liang & al, (2009) [Taiwan c 2007 estimate of positive colonies]

Agent (assay abbreviation)	N	Prevalence %			Mahler	Liang
		NA	Europe	Total	W EU	Taiwan
Ectromelia (ECTRO)	246,857	0.02	0.00	0.02		
<b>Hantavirus (HANT)</b>	<b>144,946</b>	<b>0.00</b>	<b>0.00</b>	<b>0.00</b>		
K virus (K)	225,353	0.00	0.00	0.00		
<b>Lymphocytic choriomeningitis virus (LCMV)</b>	<b>241,453</b>	<b>0.01</b>	<b>0.02</b>	<b>0.01</b>		
Mouse adenovirus 1 and 2 (MAV)	230,351	0.02	0.22	0.02		
Mouse cytomegalovirus (MCMV)	146,511	0.04	0.00	0.04		
<b>Mouse hepatitis virus (MHV)</b>	<b>558,673</b>	<b>1.57</b>	<b>3.25</b>	<b>1.59</b>	<b>5.5</b>	<b>&gt;20%</b>
<b>Mouse norovirus (MNV)</b>	<b>44,876</b>	<b>32.64</b>	<b>24.03</b>	<b>32.37</b>	<b>31.8</b>	
<b>Parvovirus generic assay (NS-1)</b>	<b>578,464</b>	<b>1.65</b>	<b>1.92</b>	<b>1.65</b>	<b>1.0</b>	<b>&gt;20%</b>
<b>- Mouse parvovirus 1 and 2 (MPV)</b>	<b>594,539</b>	<b>1.83</b>	<b>3.64</b>	<b>1.86</b>		
- Mouse minute virus (MMV, MVM)	595,903	0.33	0.46	0.33		
Pneumonia virus of mice (PVM)	447,656	0.01	0.01	0.01		~8%
Polyoma virus (POLY)	225,868	0.02	0.20	0.02		
Reovirus 3 (REO, REO-3)	428,821	0.01	0.05	0.01		
<b>Rotavirus (EDIM)</b>	<b>466,[32]572</b>	<b>0.56</b>	<b>0.35</b>	<b>0.56</b>	<b>1.7</b>	
Sendai virus (SEND)	462,209	0.00	0.00	0.00		
<b>TMEV, GD-VII</b>	<b>435,772</b>	<b>0.26</b>	<b>0.27</b>	<b>0.26</b>		<b>&gt;20%</b>

Top few VIRAL agents of concern

<http://www.felasa.eu/recommendations.htm> --> <http://www.lal.org.uk/pdf/LAfel2.PDF>

	2001 FELASA	2003 Livingston & al	2009 Pritchett Corning	2009 Mahler
1	MHV	MHV	MNV	MNV
2	MRV (EDIM)	Parvoviruses	MHV	MHV
3	Parvoviruses	MRV (EDIM)	Parvoviruses	Parvoviruses
4	PVM	SEN	MRV (EDIM)	MRV (EDIM)
5	SEN	TMEV	TMEV	TMEV
6	TMEV			

**Agents of interest or concern, in mice.** In (approximate) order of discussion here.

Viruses (by prevalence/concern)	P 4-	Bacteria general (by likely Phenotype)	P19-	Fungi & larger (Eukaryota) (by taxon)	pp
<b>MORE PREVALENT</b>		<b>ENTEROHEPATIC</b>	<b>21</b>	<b>Fungi</b>	<b>25</b>
Norovirus (MNV)	8	<i>Helicobacters (~16%)</i>		<i>Pneumocystis murina</i>	
Coronavirus (MHV)	9	<i>Citrobacter rodentium</i>		<i>Trichophyton mentagrophytes</i>	
Parvoviruses (MPV > MMV)	10	( <i>Escherichia coli</i> )		<i>Kazachstania (Torulopsis)</i>	
Rotavirus (MRV, Reo)	11	<i>Clostridium piliforme</i>			
PicoRNAvirus (TMEV etc)	12	( <i>C difficile, perfringens</i> )		<b>EUKARYOTA</b>	<b>26</b>
Paramyxovirus (Sen, MPV)	13	<i>Salmonella enterica</i>		<b>Protozoa</b>	<b>27</b>
		<i>Ssp typhimurium</i>		<i>Giardia muris</i>	
<b>LESS LIKELY</b>				<i>Spironucleus muris</i>	
Ectromelia virus	14	<b>RESPIRATORY</b>	<b>22</b>	<b>LI Flagellates</b>	
Adenovirus (MAV1,2)	15	<i>Pasteurella pneumotropica</i>		<i>Entamoeba muris</i>	
Herpesvirus (MTV, MCMV)	15	<i>Mycoplasma pulmonis etc</i>		<i>Cryptosporidium muris</i>	
Papova (K, MPyV)	16	CAR bacillus		<i>Cryptosporidium parvum</i>	
Arterivirus (LDV)	16	<i>Bordetella (hinzii, avium etc)</i>		<i>Eimeria species</i>	
		<i>Klebsiella oxytoca</i>		<i>Klossiella muris</i>	
<b>ZOONOSES</b>		<i>K pneumoniae</i>		<i>Sarcocystis muris</i>	
LCM virus	17				
Hantaviruses	17	<b>SKIN (+ abscesses)</b>	<b>23</b>	<b>Helminths</b>	<b>28</b>
		<i>Staphylococcus aureus etc</i>		<i>Aspicularis tetraptera</i>	
		<i>Corynebacterium bovis</i>		<i>Syphacia obvelata, muris</i>	
<b>VIRUS ⇔ GENE</b>		( <i>C kutscheri</i> )		<i>Cysticercus fasciolaris</i>	
Retroviruses Retroelements	18			<i>Rodentolepis diminuta</i>	
		<b>SEPSIS</b>	<b>23</b>	<i>Rodentolepis nana</i>	
		<i>Streptococcus pneumoniae etc</i>			
		<i>Pseudomonas aeruginosa</i>		<b>Arthropods</b>	<b>28</b>
		<i>Streptobacillus moniliformis</i>		<i>Myobia musculi</i>	
		<i>Proteus mirabilis</i>		<i>Myocoptes musculinus</i>	
		<i>Klebsiella spp</i>		<i>Radfordia affinis</i>	
				<i>Psorergates simplex</i>	
		<b>HISTORICAL</b>	<b>24</b>	<i>Demodex musculi</i>	
		<i>Mycoplasma (E) coccoides</i>		<i>Ornithonyssus bacoti</i>	
		<i>Chlamydia muridarum</i>		<i>Laelaps echidnina</i>	
		<i>Mycobacterium avium etc</i>		<i>Polyplax serrata</i>	
				NON parasitic arthropods	
		<b>INTERESTING</b>	<b>24</b>		
		Segmented Filamentous Bacteria (SFB)		<b>Immunodeficient info</b>	<b>30</b>
		Defined Flora		<b>Resources/references</b>	<b>32</b>

**Agents in boldface** are estimated to be more prevalent, based on Pritchett-Corning, Cosentino, Clifford (2009) (Charles River Laboratories) [10] and Mahler & Kohl (2009) [Western Europe] [9], also Livingston & al. 2003, Nicklas & al 2002, Perdue & al 2007; Schoondermark & al 2006.

**MNV Murine Norovirus [9, 11, 15, 33-44]**

Calicivirus(es) - ss RNA non enveloped

MNV 1-4 + possibly many genetic variants (like human noroviruses)

**Most prevalent viral pathogen** in contemporary laboratory mice

▶ **30-60% in research colonies** – vendor colonies still Negative ....

Dx/Detection: Serology by microsphere based serologic multiplex fluorescent immunoassay (not commercially available yet) MNV 1-4 are cross reactive on serology

▶ RtPCR – mesenteric Lymph nodes

Susceptibility: Innate immunity (e.g. signal transducer and activator of transcription 1 (Stat1) -dependent), but *not T and B cell-dependent adaptive immunity*, is essential for Norovirus resistance.

Transmission: Fecal oral with massive shedding early in infection, persistent in environment (non-enveloped – *hard to get out of cruise ships too...*)

Rx/Control: REDERIVE (foster)

Research impact: immunomodulation (innate immunity), ???

<i>Phenotypes (pathology) in competent mice</i>
Subclinical in seropositive SW sentinels; Few inflammatory foci in liver, some immunoreactive (IHC) to MNV. MNV antigens in mesenteric lymph nodes Perdue & al 2007 Mild Intestine inflammation & mild spleen red pulp hypertrophy & white pulp activation) – Mumphrey & al 2007
<i>Experimental phenotypes (pathology)</i>
Seroconversion in competent Swiss mice; See immune deficient ↗
<i>Phenotypes (pathology) in Immune deficient mice</i>
Subclinical in some; or → Encephalitis, cerebral vasculitis, pneumonia, meningitis, hepatitis in stat deficient mice Ward, et al. 2006

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**MHV (Mouse Hepatitis Virus)** [17, 30, 45-53]

Hi seroprevalence ~ US + EU lab mice (was > 50%), common in wild mice too

**Coronavirus** ss RNA, enveloped

- ▶ mutate & recombine (cf SARS, SDAV) → new 'strains'
- ▶ wimpy (enveloped) but highly infectious (cf FIP in cats, TGE in swine)

**Enterotropic** strains (gut only) e.g. LIVIM (lethal intestinal virus of infant mice)

**Polytropic** strains (nasal infection → disseminate) e.g. laboratory strains used to model demyelinating diseases

**Epizootic Dz** – dt enterotropic strains (e.g. historical presentation of LIVIM)

- ▶ hi mortality + diarrhea in sucklings →
  - ✓ prox colon/cecum (+ ileum) for inflammation, syncytia
- ▶ possible ♀ pups, or ♂ pup death/disappearance/cannibalism, without other signs

**Enzootic dz** → sucklings passively protected → most survive, +/- diarrhea, +/- runting,

Transmission: direct contact, aerosol, fomites (dirty bedding sentinels should detect)

- ▶ contaminated biologicals hybridoma, ES cells etc

Susceptibility varies with virus strain; also

- ▶ mouse **strain**: BALB/c susceptible;
  - SJL/J** have mutant allele of Ceacam1 → resistant dt lack functional receptor
- ▶ mouse **age** (all ages susceptible to infection, but Age related susceptibility to Dz)
  - Neonates susceptible (LIVIM die)
  - ♀ Morbidity/mortality with ♂ age

Immunocompetent mice > 1 wo clear virus in 3-4 w (T cells etc required)

Dx/Detection: ELISA, IFA, RtPCR (VI, IHC etc)

Rx/Control: Rederive (foster, breeding moratorium??)

Research impact: Immunomodulation; liver, gut, CNS phenotypes

<i>Phenotypes (pathology) in competent mice</i>
Spectrum of disease depends on virus strain, mouse strain & age <ul style="list-style-type: none"> <li>▶ No Clin Dz; Transient syncytia</li> <li>▶ Suckling diarrhea/death → 100% with Necrotizing enterocolitis</li> <li>▶ Necrosis/<b>syncytia</b> liver, spleen, enterocytes, lymph nodes, GALT, marrow, vascular endothelium, brain; cytoplasmic inclusions/enterocytes</li> </ul>
Experimental Phenotypes
Necrotizing M-Encephalitis + Demyelination (neonatal infection)
<i>Phenotypes (pathology) in Immune deficient mice</i>
Adult wasting with necrosis/syncytia liver, spleen, lymph nodes, GALT, marrow, brain Don't clear virus i.e. persistent infection (granulomatous peritonitis/ pleuritis in Ifn Ko – similar to Feline Infectious Peritonitis? )

**MPV (Mouse Parvovirus) MMV (Mouse minute virus, formerly MVM)** [23, 53-59]

Hi seroprevalence ~ US + EU lab mice (MPV > MMV)

**Parvoviruses** ss DNA, NON-enveloped (tough, persistent), small ('parvo')

Require **S phase** for infection / cytolysis

**NS1, 2** proteins non structural (functional); non specific (highly conserved)

**VP1, 2, 3** proteins: structural, capsid proteins,

▶ VP2 is strain specific, binds host receptors (transferrin in carnivores)

Transmission: fecal oral, fomites/environment (Mighty Persistent Virus – *W White*)

▶ contaminated biologicals

Dx/Detection: CHALLENGING: **ELISA, MFIA, IFA, PCR** (VI, IHC etc)

**NS1** useful for screening dt cross reactivity BUT

- seroconversion may be slow
- shedding may be low → 0-slow seroconversion in sentinels
- C57BL/6 and DBA/2 strains may seroconvert later or may NOT seroconvert

**Vp2** – for detecting different strains (e.g. with microsphere techniques MFIA)

**PCR: mesenteric nodes**, some MMV may not persist

**Feces** + when/if shedding

Rx/Control: Rederive (foster?)

Research impact: Immunomodulation (many are lymphotropic); oncotropic/oncolytic; Developmental?

Phenotypes; infects cell lines, sometimes lytic

<b>MMV (MVM)</b> (c, i, m, p strains)	<b>MPV (MPV1-4)</b>
<i>Phenotypes (pathology) in competent mice</i>	
Subclinical, Immunomodulation May not persist (Sero+/PCR-) MVMm → most prevalent, persistent MVMi → disrupt hematopoiesis in C3H	Subclinical, Immunomodulation (T tropic) Persistent/latent in mesenteric nodes
<i>Experimental phenotypes (pathology)</i>	
Neonate → multisystem infection → cerebellar hypoplasia, renal infarct anemia	NO gross or histo lesions(?)
<i>Phenotypes (pathology) in Immune deficient mice (scid, nude)</i>	
MVMi exp → Lethal leucopenia in scid	

**MRV (Murine Rotavirus A)** [aka Epizootic Diarrhea of Infant Mice (EDIM) virus] [60-65]

Mod seroprevalence (was ~30%)

**Type A Rotavirus** ds RNA, enveloped, Reovirus family (cf MRV3, Mouse Reovirus 3)

Type A rotaviruses cause **neonatal diarrhea in many species**

Rotaviruses **target terminally differentiated epithelium (villus tips)**

Transmission: Hily contagious fecal oral, fomites/environment (enveloped ~ fragile)

- ▶ Shedding by adults is variable, usually low (C57BL/6 < BALB/c)
- ▶ Beware of experimentally infected mice (used to model human rotavirus)  
(*not a 'biohazard'*, so where to do these studies? Are there sentinels in biohazard?)

Susceptibility: 4-14 do naïve pups

Dx/Detection: ELISA, IFA, RtPCR, Also

- ▶ rotazyme (ELISA for fecal antigen); fecal EM → wheel like rotavirus 60-80nm

Rx/Control: Rederive (foster?) - depopulation should not be necessary

- ▶ should be pretty easy to detect, decontaminate & cull

Research impact: immunomodulation, runting

MRV (EDIM)	Reo (MRV3)
<i>Phenotypes (pathology) in competent mice</i>	
Subclinical or Suckling diarrhea yellow, watery (+ milk in stomach), usually survive Malabsorption + E coli overgrowth Transient hydropic swelling of villus TIP epithelium (~ nursing ...) Acidophilic cytoplasmic inclusions ?? Dry skin, fecal impaction, runting ...	Subclinical or suckling diarrhea, Steatorrhea dt pancreatitis, maldigestion biliary atresia (→ jaundice) → OHE = oily hair effect Runting dt pituitary lesion (⬇ GH)
<i>Experimental phenotypes (pathology)</i>	
	Multisystem inflammation/necrosis: liver, pancreas, heart, adrenals, CNS Lymphoid depletion thymus spleen nodes Biliary atresia, hepatic fibrosis
<i>Phenotypes (pathology) in Immune deficient mice (scid, nude)</i>	
Suckling neonatal diarrhea (milk/stomach) Adult → no lesions (like competent mice) Nudes clear it SCID, Rag etc → persistent infection + shedding	Scid exp dz = lethal (black foot) Nu exp dz → subclinical +/-liver lesions

**MRV 3 (Mouse Reovirus 3)** [66-71]

Low seroprevalence (rare)

Historical reports of hepatic etc pathology may have had MHV also

**TMEV Theiler's Mouse Encephalitis Virus (GDVII, FA, TO, DA strains) [72-75]**

**Picornavirus**, ss RNA, non enveloped (**cardiovirus** group) cf EMCV

enterotropic, but no enteric lesions)

(*Coxsackieviruses and human polio virus are Enteroviruses*)

Mod seroprevalence < 1% (used to be pretty common)

Transmission: fecal oral, not extremely infectious contagious (intermittent shedding)

► contaminated biologicals

Susceptibility: varies with virus strain, mouse strain, age, etc

Resistant mouse strains → T cell mediated clearance (before demyelination)

SJL, SWR, DBA/2 >> CBA, C3H >> A, B6, B10, DBA/1 (resistant)

Dx/Detection: ELISA, IFA, RtPCR

Rx/Control: Rederive, test & cull Sero+ animals

Research impact: immunomodulation, CNS phenotypes

<i>Phenotypes (pathology) in competent mice</i>
Usually subclinical, persistent infection, intermittent shedding RARE clinical dz, posterior paresis with poliomyelitis
<i>Experimental phenotypes (pathology)</i>
Clinical: Convulsions, posterior paresis, flaccid paralysis (tail OK), spastic, trembling Acute encephalitis with neuronolysis (virulent strains e.g. GD7, FA) - 'Early Dz' (less virulent strains e.g. TO DA) Encephalomyelitis, neuronolysis, meningitis, perivasculitis, poliomyelitis with neuronolysis, neuronophagia → paralysis 'Late Dz' (less virulent strains e.g. TO DA) Demyelination (immune mediated) – spastic
<i>Phenotypes (pathology) in Immune deficient mice</i>
Nu exp dz Early Encephalomyelitis (neuronolytic) → demyelination (oligo-lytic)

**EMCV encephalomyocarditis virus [76-80]**

PicoRNAvirus Also a cardiovirus but does not cross react with TMEV

Model for autoimmune diabetes ? with Ljungan virus in Biobreeding rat?

Myocarditis esp in DBA2 mice

**Ljungan virus [81-84]**

PicoRNAvirus, Parechovirus – no commercial test (yet)

Associated with glucose intolerance and diabetes in some rodent models

► BioBreeding rats, voles,

**SEN (Sendai)** [85-93]

**Paramyxovirus** ss RNA enveloped, (respirovirus genus cf human parainfluenza 1)

Low 'seroprevalence' <1% (was ~20%)

Transmission: Direct contact, contaminated fomites, aerosol

- ▶ contaminated biologicals

Susceptibility:

- ▶ DBA, 129 (may die) > A, BALB, SWR > B6, SJL resistant
- ▶ 3 phases of disease in **competent** mice that survive

**Acute Phase 8-12 d (T cell mediated destruction of infected resp epithelium)**

Syncytia & cytoplasmic inclusions occur early

Necrotizing rhinitis, tracheitis, bronchitis

Alveolar exudates: sloughed necrotic cells fibrin, PMN, mononuclear

Atelectasis, bronchiectasis, emphysema

**Repair phase 10d-3w:** regeneration of airway lining epithelium

Adenomatous hyperplasia, Squamous metaplasia in bronchioles

Mixed interstitial infiltrates (not alveolar)

**Resolution** ~ 4w → minimal lesions or

Bronchiolitis obliterans, fibrosis, collagen, foamy macrophages, lymphoid infiltrates, cholesterol crystals etc debris

- ▶ Nu, scid (T cell deficient) → different disease, wasting with proliferative bronchiolitis  
– *NOT necrotizing in these*

Dx/Detection: ELISA, IFA, RtPCR,

- ▶ Hily Infectious -- But NOT reliably detected by dirty bedding sentinels

Rx/Control: Rederive (foster?)

- ▶ IVC (individually ventilated caging) isolates well

Research impact: immunomodulation (T cell mediated dz & clearance), respiratory compromise, pathology

Sendai	MPV / PVM (Pneumonia virus of Mice)
<i>Phenotypes (pathology) in competent mice</i>	
Chattering, Resp distress, Hunched, runting Neonate/suckling death, Lungs Discolored (plum), heavy, consolidated Splenomegaly, Lymphadenopathy Lung Histology <b>Syncytia, cytoplasmic inclusions</b> → necrotizing bronchiolitis → hyperplasia (sq metaplasia) → min dz - bronchiolitis obliterans	Subclinical upper resp dz
<i>Experimental phenotypes (pathology)</i>	
Similar to natural dz ↗	Rhinitis, bronchiolitis, interstitial pneumonia
<i>Phenotypes (pathology) in Immune deficient mice (scid, nude)</i>	
Proliferative instead of necrotizing lesions	Wasting dz dt progressive interstitial pneumonia

**MPV murine pneumonia virus (= PVM pneumonia virus of mice)** [92-96]

Low seroprevalence (i.e. rare) now

Pneumovirus group, similar to and used to model HRSV

**Ectromelia virus ECTV → mousepox** (= disease) [18, 97-104]**Orthopoxviridae cf Vaccinia** = BIG ds DNA virus

Ectromelia means short limbs (due to necrotic amputation)

Very low seroprevalence (was pretty common – probably in plenty of freezers...)

Transmission: direct contact + fomites -- scratch bite cannibalism – not hily contagious

Dirty bedding sentinels are not reliably infected → do not reliably seroconvert

**Contaminated biologicals** e.g. lymphoma/hybridoma cell lines

▶ contaminated mouse serum → recent outbreaks

Susceptibility: varies with mouse strain, age, etc

DBA/1,2, BALB, C3H, immune deficient → acute lethal dz &gt;&gt; B6, AKR (resistant)

Dx/Detection: Death or clinical signs in experimentally inoculated mice → histo &amp; PCR

Sentinel serology is slow (experimental mice are dead already) or not very reliable

▶ Vaccinia vectors (e.g. in gene therapy studies) can cause seroconversion

**Characteristic intracytoplasmic inclusions** may be uncommon in natural outbreaks▶ **Cowdry A** cytoplasmic inclusions in skin mucosa▶ **Cowdry B** basophilic cytoplasmic inclusions in liver etc tissues

Rx/Control: TEST BIOLOGICALS, Depopulate or Rederive, test &amp; cull Seropositive animals

▶ difficult to detect by sentinels

Research Impact: kills susceptible animals; immunomodulation etc phenotypes in survivors

<i>Phenotypes (pathology) in competent mice</i>
Subclinical rapid resolution, minimal shedding → hi mortality Susceptible: Disseminated Dz, facial edema, conjunctivitis, multisystem necrosis: liver, spleen, lymphoid tissue, gut, skin → death Semisuscept: rash, ectromelia, long term shedding; splenic fibrosis <b>Cytoplasmic inclusions</b> – skin + mucosa
<i>Experimental phenotypes (pathology)</i>
Vaccinia gene therapy vectors → ECTV seroconversion
<i>Phenotypes (pathology) in Immune deficient mice</i>
Hily susceptible → acute lethal dz

Esteban, D.J. and R.M.L. Buller, Ectromelia virus: the causative agent of mousepox. J Gen Virol, 2005. 86(10): p. 2645-2659.

**Mad 1,2 – Mouse adenovirus 1, 2 [105-112]**

Adenoviruses BIG ds DNA viruses

0-rare true positives ? – seropositives dt gene therapy vectors?

<b>Mad1</b> – FL (Friend Leukemia agent)	<b>Mad2</b> – K87 = Strictly enterotropic
<i>Phenotypes (pathology) in competent mice</i>	
Subclinical, persistent → viruria 2 y+ <b>Nuclear inclusions renal tubules</b>	Subclinical, +/- runting, clear/2w <b>Nuclear inclusions/ enterocytes</b>
<i>Experimental phenotypes (pathology)</i>	
Lethal/suckling → <b>Multiorgan necrosis + basophilic nuclear inclusions</b> (liver, adrenal, heart, kidney, salivary glands, spleen, brain, pancreas, brown fat) Hemorrhagic encephalomyelitis	Subclinical, +/- runting <b>Nuclear inclusions/ enterocytes</b> esp ileum, cecum
<i>Phenotypes (pathology) in Immune deficient mice (scid, nude)</i>	
Lethal / scid; Subclinical / nu Enteritis	Persistent shedding/feces

**MuHV1,2 (MCMV); MuHv3 (MTV); MuHV4-6 (Mhv68, 72 etc)****Herpesviruses** – dsDNA, enveloped, big

Rare/unlikely in lab mice unless exposed to wild mice or old contaminated biologicals

**MuHV1,2 Murid Herpesvirus 1,2** formerly Mouse Cytomegalovirus (MCMV) [113-122]Currently classified as **Muromegalovirus** genus (in betaherpesvirus subfamily)

Salivary tropism – MTV contaminated MCV stocks

Typical cytomegaly, karyomegaly, nuclear + cytoplasmic inclusions

**MuHV1,3 Murid Herpesvirus 3** formerly Mouse thymic virus (MTV) [123-128]

Currently an unclassified herpesvirus

Salivary tropism – MTV contaminated MCMV stocks

Discovered by thymic necrosis/loss, after experimental inoculation of MCMV ....

**MuHV 4-6 Murid Herpesvirus 4-6** formerly MHV 68, 72 etc [129-135]

Currently unclassified Herpesviruses, similar to gammaherpesviruses

found in wild mice (field mice, microtus, sand rats

vasculitis &amp; lymphoma in experimentally infected BALB/c

<b>MuHV1 (MCMV)</b>	<b>MuHv3 (MTV)</b>	<b>MuHV4-6 (MHV68, 72 etc)</b>
<i>Phenotypes (pathology) in competent mice</i>		
Subclinical, persistent Salivary (esp submaxillary) gland infection, Adenitis Nuclear & Cytoplasmic inclusions	Subclinical, persistent infection Infects salivary glands	Subclinical in Seropositive wild mice (Microtus, etc )
<i>Experimental phenotypes (pathology)</i>		
Disseminated infection, Death Multiorgan necrosis (spleen, liver, adrenal) Inclusions + syncytia	Indiscernible (NO) thymus Thymic (T cell) necrosis (cf stress) Necrosis in Lymph nodes, spleen Nuclear inclusions	Vasculitis, lymphoma in BALB/c
<i>Phenotypes (pathology) in Immune deficient mice (scid, nude)</i>		
Disseminated infection, Death Multiorgan necrosis (spleen, liver, adrenal) Inclusions + syncytia		

**MPtV (K virus), MPyV**

Both in polyomavirus genus of Polyomaviridae family (Cf SV40)– ds DNA, not enveloped

Rare - historical – in freezers somewhere, and in wild mice

Transmitted in urine, efficient in wild mice, unlikely in lab setting

**MPtV (mouse Pneumotropic or K virus) [136-139]**

CAN cause severe disease (experimental neonatal infection)

virus replicates in vascular endothelial cells of the lung, liver, and spleen

→ Intracellular inclusion bodies, intestine, kidneys

*Not pneumotropic*

**MPyV (Mouse Polyomavirus 1) [140-146]**

Experimental neonatal infection → multiple tumors (poly oma)

MPyV induced salivary myoepitheliomas reported to have significant inflammation

MPtV (K virus)	MPyV
<i>Phenotypes (pathology) in competent mice</i>	
Subclinical, persistent Intranuclear inclusions in Endothelium of intestine villus endothelium	Subclinical, Mild renal necrosis, nuclear inclusions, interstitial nephritis→ viruria
<i>Experimental phenotypes (pathology)</i>	
Neonatal infection → Interstitial pneumonia + Hi mortality Endothelial infection	Multisystem infection → hyperplasia, neoplasia (poly oma) esp salivary gland
<i>Phenotypes (pathology) in Immune deficient mice (scid, nude)</i>	
Subclinical, persistent in nu	Exp dz – paraplegia dt vertebral TT , PML- like dz ~ primates

**LDV (LDHeV) Lactate dehydrogenase elevating virus [21, 23, 147-149]**

Arterivirus – ss RNA, enveloped (Arteriviridae)

now classified in Nidovirales order (with Coronaviridae)

Transmission: usually by inoculation

**NOTORIOUS Tumor cell line contaminant**

- ▶ Infects MOUSE monocyte/macrophages only

Dx/ Detect: serology tests don't work

**In mice by serum chemistry Tests – LDH > 2500? ⚠with hemolysis etc**

- ▶ Persistent enzyme elevation dt infection & destruction of macrophages that normally clear them (hemolysis also elevates LDH etc)
- ▶ Confirm with PCR on serum

**In cell lines by PCR**

Rx/ Control: 'clean' cell lines by passage in rats

<i>Phenotypes (pathology) in competent mice</i>	
Subclinical, persistent viremia; Persistent ⚠LDH etc enzymes Mild splenomegaly, mild glomerulopathy	
<i>Experimental phenotypes (pathology)</i>	
Immunosuppressed C58, AKR (with ecotropic retrovirus) → late demyelination	
<i>Phenotypes (pathology) in Immune deficient mice</i>	

**ZOONOSES****LCMV Lymphocytic Choriomeningitis virus**[150, 151]

**Arenavirus** – ss RNA, enveloped; Virulent (cytolytic), avirulent (non-cytolytic) strains

**ZOONOTIC** → **depopulate** [23, 152-155]

- ▶ Aseptic meningitis or meningoencephalitis; teratogen
- ▶ Hamsters, nude mice implicated in human infections
- ▶ Agent of Callitrichid hepatitis [156]

Disease (phenotypes, lesions) requires T cell immunity

Transmission: vertical, horizontal, biologicals[24, 30, 157]

DX/ Detection: Diagnosis: serology; PCR

▶ **PCR (biologicals)**

Research Interference: immunomodulator, autoimmunity; endocrine effects e.g. diabetes, pituitary dwarfism

<i>Phenotypes (pathology) in competent mice</i>
Subclinical, with chronic persistent shedding/urine Intrauterine/neonatal infection → late onset multi-organ lymphocyte infiltration GN – late dz
<i>Experimental phenotypes (pathology)</i>
Lymphocytic choriomeningitis, endocrinopathy
<i>Phenotypes (pathology) in Immune deficient mice</i>
Subclinical infection/nude (inoculated biologicals)

**Hantaviruses – zoonotic concern** → **depopulate** [158-163]

**Bunyaviridae** ss RNA, enveloped

**ZOONOTIC** → **depopulate**

Laboratory mice can be infected → no dz or

IP infection of C57BL/6, BALB/c, AKR/J, and SJL/J → fatal neurologic disease

Serology for KHF, Han – required for import/export for some countries institutions

Peromyscus, Sigmodon, etc wild rodent hosts reservoirs

<i>Phenotypes (pathology) in competent mice</i>
Subclinical Hanta-like viruses → interstitial pneumonia, perivasculitis in rats, mice?
<i>Experimental phenotypes (pathology)</i>
IP infection of C57BL/6, BALB/c, AKR/J, and SJL/J → fatal neurologic disease
<i>Phenotypes (pathology) in Immune deficient mice</i>

**MMTV's, MuLV's** [164-175]

Retroviruses &amp; retro elements

**Exogenous** – salivary, milk, semen transmission – wild mice still have them**MMTV** intentionally eliminated from most/all commercial strains including C3H  
intentionally maintained in a few strains – strain name should include 'mtv'**Endogenous** – proviruses, IAP, transposons → named genes (Mtv1...; Mlv1...; Emv1...)

▶ ~ 10 % of mouse genome (endogenous retrovirus elements or pieces ~ 8% of human genome)

▶ Vary with strain so useful for mapping etc &amp; contribute to phenotypes e.g

*Myo5a<sup>d</sup>* → Dilute color in DBA, etc*Hr<sup>hr</sup>* → 'Hairless' phenotype (cf *Hr<sup>rh</sup>*)*Pde6b<sup>rd1</sup>* → rd blindness in C3H, SJL, FVB etc.

○ Viral insertion (Xmv-28) in intron 1

○ + nonsense mutation (C → A) that truncates the protein

**Types of retroelements****IAP** = intracisternal A particle**VL30** = virus like 30 ss RNA sequence**MuRVY** = murine repeated virus sequence on Y chromosome**ETn's** early transposons

MTV's used in targeted mutagenesis (e.g. promoters) → gene/construct name should include 'mtv'

Many MuLV's are not oncogenic

Dx/Detection: Mapping ? if interesting/important to your studies

Rx/Control: ??

MMTV Bittner agent	MuLV – Murine Leukemia viruses
<i>Phenotypes (pathology) in competent mice</i>	
Mammary tumors Early onset in C3H dt vert transmission of Bittner – eliminated by rederivation Thymic lymphoma in GR mice B Cell lymphoproliferative dz in SJL	e.g. AKR thymic lymphoma, Moloney sarcoma, Friend Leukemia Etc. Lymphoma Sarcoma Dilute color in DBA Hairlessness in HR Ecotropic
<i>Experimental phenotypes (pathology)</i>	
Mammary & other tumors	Tumors & genetic manipulation
<i>Phenotypes (pathology) in Immune deficient mice (scid, nude)</i>	
	Scid etc lymphomas

Morse, H.C., Retroelements in the Mouse, in The M[175]ouse in Biomedical Research, J.G. Fox, et al., Editors. 2006, Elsevier: Amsterdam, NL. p. 269-279

Stocking, C. and C. Kozak, Endogenous retroviruses. Cellular and Molecular Life Sciences, 2008. 65(21): p. 3383.

Zhang, Y., et al., Genome-wide assessments reveal extremely high levels of polymorphism of two active families of mouse endogenous retroviral elements. PLoS Genet, 2008. 4(2): p

**BACTERIA****Dx/Detection:**

In contrast to virus detection in mice, often by sentinel serology testing, testing for bacteria often is 'for cause', only when a disease phenotype is identified.

This section is organized (as much as possible) by the site of a typical or likely disease phenotype, according to the table below.

**Microbial culture / isolation** of bacteria,

identification by testing largely replaced by computerized automated methods  
do the results make sense?

**PCR** also requires appropriate selection and handling of suitable specimens.

Especially useful for intracellular agents that are difficult to cultivate in vitro

Replacing culture methods because more cost effective, automate-able

**Serology testing is (widely) used for *M pulmonis*, *CAR bacillus*, *C piliforme***

**Mouse Bacteriology Results** – from Pritchett-Corning, Cosentino, Clifford (2009) (Charles River Laboratories) [10]

Gram positive agents are shaded; **boldface agents detected in > 1% of specimens**

Bacterium	Method	N	PREVALENCE %		
			NA	Europe	Total
<i>Bordetella bronchiseptica</i>	Culture	109,802	0.00	0.00	0.00
Cilia-associated respiratory bacillus	Serology	158,741	0.01	0.00	0.01
<i>Citrobacter rodentium</i>	Culture	82,337	0.00	0.00	0.00
<i>Corynebacterium kutscheri</i>	Culture	109,804	0.00	0.00	0.00
<b><i>Helicobacter</i> genus (any sp.)*</b>	<b>PCR</b>	<b>91,119</b>	<b>15.88</b>	<b>21.28</b>	<b>16.08</b>
- <i>Helicobacter hepaticus</i>	PCR	91,463	12.45	10.23	12.37
- <i>Helicobacter bilis</i>	PCR	91,386	2.20	1.49	2.17
<b><i>Klebsiella oxytoca</i></b>	<b>Culture</b>	<b>185,937</b>	<b>0.38</b>	<b>1.32</b>	<b>0.38</b>
<i>Klebsiella pneumoniae</i>	Culture	186,667	0.10	0.85	0.10
<i>Mycoplasma pulmonis</i>	Culture	61,592	0.00	nt	0.00
	Serology	455,102	0.01	0.16	0.01
	PCR	43,777	0.00	nt	0.00
<i>Pasteurella multocida</i>	Culture	109,376	0.00	0.00	0.00
<b><i>Pasteurella pneumotropica</i></b>	<b>Culture</b>	<b>109,403</b>	<b>13.20</b>	<b>4.00</b>	<b>12.90</b>
Other <i>Pasteurella</i> species	Culture	106,232	0.31	0.00	0.31
Any <i>Salmonella</i> species	Culture	109,655	0.00	0.00	0.00
<b><i>Staphylococcus aureus</i></b>	<b>Culture</b>	<b>107,002</b>	<b>6.03</b>	<b>11.56</b>	<b>6.07</b>
<i>Streptobacillus moniliformis</i>	Culture	2842	0.00	0.00	0.00
<i>Streptococcus pneumoniae</i>	Culture	109,804	0.00	0.00	0.00
<i>Streptococcus</i> sp. – $\beta$ -haemolytic, Group B	Culture	106,971	0.24	0.00	0.24
<i>Streptococcus</i> sp. – $\beta$ -haemolytic, Group G	Culture	109,733	0.00	0.11	0.00

**Rx/Control:**

In most situations antimicrobial therapy does not eliminate the agent from the mice or environment and is not a practical approach, for experimental animals.

- ▶ antimicrobial therapy may be useful to control disease in incompetent or compromised animals, to permit survival and rederivation of valuable animals.

**Sentinel testing for bacteria:**

What agents are excluded and why ?

What to test for and how ?

Acceptable agents in competent mice, may be opportunist or pathogenic in immunocompromised or immunodeficient animals.

Vendor health surveillance information for known immunodeficient animals can be helpful in determining what agents may be affecting your mice from that colony, and in designing husbandry and surveillance programs for immunodeficient areas.

ENTERIC/HEPATIC	SKIN	HISTORICAL?
<b>Helicobacters (15-20%)</b> <b><i>H hepaticus</i> (10-12%)</b> <i>(H bilis, rodentium, typhlonius, etc.)</i> <i>Citrobacter rodentium</i> <i>(Escherichia coli)</i> <i>Clostridium piliforme</i> <i>(C difficile, perfringens)</i> <i>Salmonella enterica typhimurium</i>	<b><i>Staphylococcus aureus</i> (6-12%)</b> <b>(etc <i>Staph</i> spp)</b> <i>Corynebacterium bovis</i> <i>(C kutscheri)</i>  SEPSIS (in immuno ?) <i>Streptococcus pneumoniae</i> <i>(etc. Strep spp)</i> <i>Pseudomonas aeruginosa</i> <i>Proteus mirabilis</i> <i>Klebsiella oxytoca, pneumoniae</i>	<i>Eperythrozoon coccoides</i> <i>Chlamydia muridarum</i> <i>Mycobacterium avium</i> <i>(M chelonae etc atypicals)</i>  ZOOZOSES <i>Streptobacillus moniliformis</i> <i>(S. Typhimurium)</i>  INTERESTING Segmented Filamentous Bacteria Defined Flora
RESPIRATORY <b><i>P pneumotropica</i> (4-14%)</b> <i>(P multocida)</i> <i>Mycoplasma pulmonis</i> <i>(M arthritis, collis, neurolyticum)</i> CAR bacillus <i>Bordetella (hinzii, avium etc. ?)</i> <i>Klebsiella oxytoca, pneumoniae</i>		

\* % positive results from Pritchett-Corning, Cosentino, Clifford (2009)

FYI Goto, K., et al., First trial in the developmental phase of the "performance evaluation program" based on the ICLAS animal quality network program: self-assessment of microbiological monitoring methods using test samples supplied by ICLAS. Exp Anim, 2009. 58(1): p. 47-52 [176]

**ENTERIC and/or HEPATIC DISEASE primarily*****Helicobacters* [177-186]**

Hi prevalence ~16% + of 81,000 PCR samples submitted to CRL 2006

- ▶ Most (12% = *H hepaticus*)

Suspect helicobacters with rectal prolapse, esp in females ...

Research impact: immunomodulation, cancer, gallstones, enterohepatic phenotypes

***H hepaticus* → strain/sex dependent dz:**

necrotizing – chronic hepatitis A/J, > B6, M>F;

typhlocolitis in immunodeficient + competent mice, F> M

☛susceptibility to neoplasia

***H bilis* → chronic typhlocolitis in immunodeficient mice**

Hepatobiliary dz in human

***H muridarum* – chronic gastritis*****H rodentium*, *typhlonius*, (*Flexispira*) *rappini*, *ganmani*, etc sp...*****H heilmani*, *pylori* in stomach – strain dependent dz/pathology– experimental only?**

Dx/ Detect: fecal PCR = currently most practical

***Lawsonia intracellularis***

→ Proliferative ileitis/enteritis in hamsters, ferrets, swine etc  
potential mouse pathogen ?

***Citrobacter rodentium* (*C freundii* 4280) [187-191]**

Unlikely, difficult to detect, dt transient infection, prompt clearance

Proliferative colitis: transmissible murine colonic hyperplasia

Model for human EPEC

***Escherichia coli***

Overgrow in mice with viral enteritis

Hyperplastic typhlocolitis in scid etc immune deficient, not nude

DDx *Citrobacter* , *Helicobacter*

***Clostridium piliforme* (*Bacillus piliformis*) → Tyzzer's dz [192-195]**

UNUSUAL-RARE Sudden death +/- diarrhea

Colitis/ typhlitis → multifocal hepatitis → myocarditis

Necrosis + intracytoplasmic argyrophilic fascicles of slender bacilli (filamentous)

Hamsters are MUCH more susceptible than mice

Dx/ Detect: Histo, Serology, PCR – Intracellular agent, culture is impractical

***Clostridium perfringens*, *Clostridium difficile***

Unlikely but possible causes of clostridial overgrowth and enteropathy, especially in a situation of antibiotic induced dysbiosis

***Salmonella enterica* serovar *Typhimurium* (*S. typhimurium*) [196-201]**

- ▶ **Zoonotic → depopulate**

Subclinical or enteritis, mesenteric lymphadenopathy, ☛ Peyer's patches, splenomegaly, hepatic granulomas

Historically important disease of mice causing population losses (mouse typhoid)

Also consider Enterococcus (*E faecalis*) in (weanling) diarrhea outbreak

→ **gram positive** cocci covering villi in SI (in rats)

**RESPIRATORY phenotypes primarily*****Pasteurella pneumotropica* [202-211]**

**HIGH prevalence** (14% + by PCR from 94,898 submitted samples to CRL 2006)

'Normal' gut microflora?? isolate from nasopharynx → opportunist

Conjunctivitis, otitis, pneumonia, cystitis, preputial adenitis

Bronchopneumonia with PcP

Vaginitis → metritis → subfertility/infertility ?

**Gram neg** – pure cultures, can't see it with tissue gram or silver stains

Dx/Detection: somewhat fastidious, but culture or PCR

Rx/Control: Antibiotic (enrofloxacin) reported → Depopulate, rederive into barrier

***Mycoplasma pulmonis* [23, 211-217]**

Agent of murine respiratory mycoplasmosis (rats + mice)

**Historically important** cause of morbidity/mortality, research interference

Low prevalence now (0-2% by PCR or serology)

Chronic respiratory dz: Chronic suppurative, rhinitis, otitis, bronchopneumonia

Peribronchiolar / perivascular lymphoplasmacytic infiltrates (B cell mitogen)

Significant strain (+ sex) variations in susceptibility

Reported as a biological contaminant although many other non-pathogenic mycoplasmas are more likely.

Dx/Detection: ELISA serology is more common than culture which is difficult

Rx/Control: Depopulate, rederive into barrier

***M arthritidis, neurolyticum, collis***

**CARbacillus – Cilia associated respiratory bacillus [213, 218]**

Related to Flexibacter Flavobacterium

Mice more susceptible than rats, hier prevalence in rats

Historically important copathogens in rodent respiratory disease complex

Subclinical – chronic suppurative pneumonia – argyrophilic bacilli among cilia

Peribronchiolar lymphoplasmacytic infiltrates (B cell mitogen) ~ Mycoplasma

Dx/Detection: by histo, serology

***Bordetella (e.g. B. avium, B. hinzii)* [219, 220]**

Gram neg, small – silver stain may detect among cilia ? (smaller than CARbacillus)

Possible cause / opportunist of pneumonia etc in immunodeficient

Recent reports of rhinitis, tracheitis, and bronchopneumonia due to *B hinzii*

***Klebsiella (e.g. K oxytoca, K pneumoniae)*[204, 221, 222]**

Gram neg, small - May see gram negative colonies, pale halo due thick capsule

*K oxytoca* - Another possible cause or opportunist in pneumonia, otitis etc

- Suppurative otitis media, pneumonia, urogenital tract infections
- Especially in C3H/HeJ (Lack Tlr4) and immunodeficient
- Also sepsis in immunodeficient

*K pneumoniae* - pneumonia, abscesses, sepsis – historical & experimental [197, 223-226]

- Experimental infections → Leptin, ApoE, myeloperoxidase, lysozyme, surfactants, TNF, TLR4, IL12, IFNG, etc play roles in susceptibility/resistance to sepsis etc
- CBA more susceptible to chronic pneumonia: lobar consolidation, esp anterior-middle lobes

**SKIN (&/or abscess) phenotypes primarily*****Staphylococcus*** [227-235]***Staphylococcus aureus* = 1 of few coagulase positive species**

- Also *S intermedius*, *S. pseudintermedius*, *S delphinii*, *S hyicus* [236, 237]

**Common** (~6% of bacterial cultures to Criver ) [10]

Cervical lymph node etc abscesses, **botryomycosis** in competent mice

Furunculosis, abscesses, **botryomycosis** in immunodeficient

Ulcerative dermatitis with 'burn-like' lesions dt epidermolytic toxins

- ▶ Look for large Gram positive cocci in colonies/clusters
- ▶ sugar + povidone-iodine stimulates healing of MRSA-infected skin ulcers in db/db mice.. [238]
- ▶ Role *S aureus* toxins in glomerulonephritis ? (→ model human post MRSA GN) [239]

***S xylosum*, *sciureus*, *hominis* etc 'commensal' (coagulase NEG) spp.** isolated from abscesses + Botryomycosis lesions in immunodeficient & GEM

**'Coagulase negative *Staphylococcus sp*'** may NOT be sufficient or useful identification for a disease problem in immunodeficient /immunoweird.

***Corynebacterium bovis*** (hyperkeratosis associated coryneform bacteria) [240-243]

Orthokeratitic epidermitis, dermatitis in nude & hairless mice, immunodeficient (& competent?) haired mice

- ▶ → 'dusty' colonies of small gram positive rods in follicles & stratum corneum

Mortality in suckling mice

***Corynebacterium kutscheri*** (→ 'pseudotuberculosis') [244-246]

Cervical lymphadenopathy (not abscessed)

Also abscesses in liver, kidney, lung etc – Gram + bacilli (Chinese letters)

**SEPSIS (etc problems especially in immunodeficient mice)*****Streptococcus*** [247-252]

***S pneumoniae*** (beta hemolytic, non A, non B)

- ▶ Mice considered more resistant (than rats) to *S pneumoniae*, but ...
- ▶ → otitis / meningoencephalitis / mortality in integrin deficient GEM
- ▶ Pneumonia/mortality in C3H/HeJ (Tlr4 deficient)

Group B (e.g. ***S agalactiae***) → rhinitis, meningitis, encephalomyelitis in nude

***S zooepidemicus*** dermatitis

*Streptococcus* spp. Alpha hemolytic, non hemolytic species → septicemia in scid ?

- ▶ Look for small gram positive cocci in pairs (diplococci) and chains (streptococci)

Cariogenic species in/around teeth ?

Enterococcus ? May → weanling diarrheal disease with gram positive cocci on mucosal surfaces

***Streptobacillus moniliformis*** [253-258]

**Zoonosis → rat bite fever**

Septicemia, diarrhea, conjunctivitis, hepatitis, suppurative **arthritis**

***Pseudomonas aeruginosa*** [259-264]

Opportunist → bacteremia, mortality in **neutropenic** (esp irradiated, cytoxin) mice

Tap water – control with acidification, hyperchlorination

(widespread use of acidified water, largely related to controlling this agent)

***Proteus mirabilis*** [87, 207, 265]

Immunodeficient mice → septicemia, fibrinosuppurative peritonitis, hepatitis, pneumonitis, mortality

Overgrows fecal cultures, especially if you let them sit...

**HISTORICAL**

***Mycoplasma (Eperythrozoon) coccoides*** (now Mycoplasmatales) [266-268]

Blood transmission, Polyplax serrata etc vectors (O bacoti?)  
 Subclinical, or anemia, splenomegaly (RE👁)  
 Potentiates viral dz

***Mycobacterium avium-intracellulare***, etc atypicals [269-271]

Possible in immunocompromised mice  
 Granulomas with AFB  
 Mice have interesting strain and sex related susceptibilities to mycobacteria  
 Generally quite resistant to tuberculous form of M tuberculosis infection

***Chlamydia muridarum*** – closely related to C trachomatis

Exp interstitial pneumonia

***Chlamydophila (Chlamydia) psittaci*** –

Associated with serial passaging of persistently infected tissues  
 → Pulmonary dz, hepatosplenomegaly, peritonitis

**INTERESTING**

**Segmented Filamentous Bacteria (SFB) of the Small Bowel of mammals and birds**

[272-274]; RP Orcutt *personal communication*  
 Cannot be grown in pure culture  
 Gram Positive, Spore former, Attach to brush border  
 Distal SI – esp in ID (immunodeficient) out of isolators

**DEFINED FLORA** [178, 275, 276]

**Schaedler's Flora** (many modifications, alterations, recipes)

<p><b>8 bacterial spp</b>                  Gram Neg                  Rods, spiral or fusiform                  Aerobic (proximal) → EOS (extremely Oxygen Sensitive) distal</p>	<p>2 lactobacilli                  2 clostridia                  1 Bacteroides                  1 Eubacterium                  2 ASF#'s</p>	<p><b>No gram POS</b>  <b>No fungi</b>  <b>No protozoa</b>  <b>No SFB</b></p>
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**FUNGI*****Pneumocystis murina (P carinii)*** [206, 277-279]

No dz in immunocompetent mice?

Interstitial pneumonia with intralveolar, extracellular, eosinophilic, foamy material, with argyrophilic cysts → mortality in nu, scid, etc

+/- ***P pneumotropica***, acidophilic macrophage pneumonia

Dx/Detect: Histo (cysts may be rare), PCR (prob most practical/useful in immunodeficient where these are concern; IHC is challenging

Rx/Control: Rederive → clean barrier

- ▶ Antibiotics (TMZ or Baytril (enrofloxacin)) still widely used for control

**Gastric Yeasts *Kazachstania (Torulopsis)*** [280-283]

On surface of gastric mucosa

usually on glandular mucosa, may colonize forestomach after antibiotics

***Kazachstania*** sp in various species, rodents (***T pintolopesii***), livestock etc

Commensal

***Trichophyton mentagrophytes***

Wide host range → ringworm

Usually subclinical – alopecia, crusts

***Aspergillus, Paecilomyces***

***A terreus, P variotti*** pulmonary granulomas – immunodeficient mice / corn cob bedding

Opportunist → immunodeficient hu also

***Blastomyces, Histoplasma, Cryptococcus, etc***

Variable mouse strain susceptibilities to typical dz

Experimental respiratory infections complicated by acidophilic macrophage pneumonia in susceptible strains

**Mouse EUKARYOTA Results** – from Pritchett-Corning, Cosentino, Clifford (2009) (Charles River Laboratories) [10]

Agent	Method	N	PREVALENCE %		
			NA	Europe	Total
<i>Encephalitozoon cuniculi</i>	Serology	145,053	0.00	0.00	0.00
<b>Metazoa</b>					
Lice	Direct	126,482	0.00	nr	0.00
Mites	Direct	130,976	0.11	0.43	0.12
<b>Oxyurids*</b>					
<i>Aspicularis tetraptera</i>	Direct	135,860	0.19		
<b><i>Syphacia muris</i></b>	<b>Direct</b>	<b>128,657</b>	<b>0.01</b>	<b>1.31</b>	<b>0.25</b>
<i>Syphacia obvelata</i>	Direct	128,657	0.11		
<b>Protozoa</b>					
<b><i>Chilomastix sp.</i></b>	<b>Wet mount</b>	<b>94,890</b>	<b>3.74</b>	<b>nr</b>	<b>3.74</b>
<b><i>Entamoeba sp.</i></b>	<b>Wet mount</b>	<b>94,890</b>	<b>8.08</b>	<b>nr</b>	<b>8.08</b>
<b><i>Giardia sp.</i></b>	<b>Wet mount</b>	<b>102,093</b>	<b>0.00</b>	<b>0.00</b>	<b>0.00</b>
<i>Hexamastix sp.</i>	Wet mount	94,890	4.45	nr	4.45
<i>Monocercomonoides sp.</i>	Wet mount	94,890	0.04	nr	0.04
<i>Retortamonas sp.</i>	Wet mount	94,890	0.03	nr	0.03
<b><i>Spironucleus sp.</i></b>	<b>Wet mount</b>	<b>102,093</b>	<b>0.08</b>	<b>0.00</b>	<b>0.08</b>
<b>Trichomonads</b>	<b>Wet mount</b>	<b>94,890</b>	<b>8.88</b>	<b>nr</b>	<b>8.88</b>

**PROTOZOA****Small Intestine Flagellates*****Giardia muris***

Chronic enteritis ?? in nu/nu mice; nu/+, competent clear it

Dx/Detect: **HISTO ☺ Trophozoite (flying saucers) on duodenum brush border**

Direct smear intestine contents; Fecal cysts may be rare; PCR

Rx/Control: Eliminate source; Depopulate, Rederive → clean barrier

***Spiroucleus (Hexamita) muris***

Hyperplastic enteritis ?? in nu/nu ??

Dx/Detect: **HISTO ☺ Trophozoites (tiny binucleate torpedoes) in crypts**

Direct smear intestine contents; Fecal cysts may be rare; PCR

Rx/Control: Eliminate source; Depopulate, Rederive → clean barrier

▶ *Where's the hamster ?*

**Large intestine flagellates**

Common (?) All Commensal ?

Significance: these are not in Schaedler's flora

**e.g. *Chilomastix, Hexamastix, Tritrichomonas,***

Dx/Detect: **HISTO ☺** Pyriform-rounded trophozoites, usually 4-10 u;

can fill lumen of cecum, prox colon

characteristic movements on direct smear → cool videos at RADIL site

Rx/Control: ???

***Entamoeba muris***

Common (?) in lumen of cecum, prox colon

Commensal (?)

Dx/Detect: Histo ☺ amoebae up to ~ 12 u diam; direct smear

Rx/Control: ???

***Cryptosporidium***

Rare

Opportunist – pathogen ?

Brush border, intracellular extracytoplasmic

***C muris*** – stomach

***C parvum*** – SI, Bile duct

***Eimeria muris***

Intestinal coccidia

***Klossiella muris***

Renal coccidia

Still around in wild mouse populations

***Encephalitozoon cuniculi***

Microsporidial cysts in kidney → nephritis, granuloma, shed in urine

Still around in wild mouse populations, pet stores, hamsters!

***Sarcocystis muris* – where's the cat?**

Cysts in skeletal + cardiac muscle

**NEMATODES****Pinworms [5, 284-288]**

- ▶ Adults, larvae in cecum + colon (check both in direct exam)

***Aspicularis tetraptera*** → colon → symmetric eggs /feces

***Syphacia obvelata*** > ***muris*** → cecum → asymmetric eggs / perineal (tape test)

Dx/Detect: **Histo** ☺ ; Tape test, fecal float; Direct evaluation of cecum, colon is terminal

Sentinels seem NOT to be very sensitive presumably dt Intermittent shedding with low burdens in competent mice

Rx/Control: Eliminate eggs in environment, on equipment ☺

Ivermectin etc avermectins, topically, in water – beware of genetic susceptibilities; Fenbendazole feed

**Research Impacts of Worms ? Treatments?**

**CESTODES**

***Cysticercus fasciolaris*** ← ***Taenia taeniaeformis***

- ▶ Asymptomatic → liver cysts noted at necropsy
- ▶ **Where's the cat?**

Rx/Control: Eliminate the source; Praziquantel, depopulate

***Rodentolepis nana*** (smallest) 'dwarf tapeworm' - Small intestine Adults (lumen) + Larvae

Dx/Detect: Histo: birefringent hooks (armed rostellum) in lamina propria

Fecal float: Hexacanth ova

- ▶ Requires no intermediate host → autoinfect
- ▶ Zoonotic ?

***Hymenolepis diminuta*** 'Rat tapeworm' -- Small intestine

***Rodentolepis microstoma*** 'Bile duct tapeworm' -- bile pancreatic ducts, duodenum

- ▶ These 2 sp REQUIRE cockroach or other arthropod intermediate host

Rx/Control: Eliminate intermediate hosts; Praziquantel; depopulate

**ARTHROPODS**

**Mite** adults have 8 legs; Nymphs have 6 → acariasis

**Fur Mites** – identify spp by suckers, claws, etc. - does it matter to treatment/control? [289-295]

***Myobia musculi***, etc-- 1 empodial claw on 2<sup>nd</sup> pr legs

***Radfordia affinis***, ensifera etc—2 empodial claws on 2<sup>nd</sup> pr legs

***Myocoptes musculinus*** – esp on neck >

Dx/Detect: **Histo** ☺ ; Tape test, fecal float; Direct evaluation of cecum, colon is terminal

Rx/Control: Permethrins (Mite arrest ® cotton balls); OPS (Atgard)

Ivermectin etc avermectins, topically, in water – beware of genetic susceptibilities;

**Research Impacts of Mites ? Treatments?** Cotton ball problems ...

**Follicle Mites** – rare

***Demodex musculi*** – tiny -- dx by histo, skin scrape?

***Psorergates simplex*** – bigger – see nodules in removed pelt

**Blood Suckers** – Mesostigmatids NOT so rare

***Ornithonyssus bacoti*** – Tropical rat mite

***Laelaps echidnina***– Spiny rat mite

Dx/Detect: NOT on the mice **moving spots** → **blood spots on filter tops**

- ▶ **rash on investigators** ☺

Rx/Control: see fur mites + ENVIRONMENTAL Rx for feral mouse reservoirs ...

**Research Impacts of Mites ? Treatments?**

**Lice - 6 legs** → pediculosis = rare

***Polyplax serrata*** – fur -- nits

Rx/Control: Eliminate wild mice

**Fleas**

***Xenopsylla, Leptopsylla***

Rx/Control: Eliminate wild mice

**NON- parasitic arthropod pests** → allergenic ? → allergic dermatitis, conjunctivitis ? impact asthma studies?

**Psocids** = book (bark) lice in mouse rooms, not on mice

- ▶ 6 legs look like lice – can have wings
- ▶ environmental issue? Allergenic?

Rx/Control: hygiene; Reduce cellulose, humidity

**Dust mites** – not on mice

- ▶ *Dermatophagoides farinae* (American house dust mite)
- ▶ *Dermatophagoides pteronyssinus* (European house dust mite)
- ▶ environmental issue? Allergenic?

Rx/Control: hygiene

**QUIZ**

**What do you Know about your mouse’s environment?**

What **diet(s)** do your experimental mice receive? \_\_\_\_\_  
\_\_\_\_\_

What **water** do your experimental mice receive? \_\_\_\_\_

What is the **light cycle** in your mouse room(s)? **12/12** **10/14** Other: \_\_\_\_\_

What **agents** discussed here might impact your research or phenotypes of interest? \_\_\_\_\_  
\_\_\_\_\_

**What do you know about your surveillance program?**

**What (Who) is in your Mouse House ?**

What **microbial agents** are in your mouse facility? \_\_\_\_\_  
\_\_\_\_\_

What are **surveillance practices** for these agents? \_\_\_\_\_  
\_\_\_\_\_

If you use (inoculate) **biological agents** (cell lines, antibodies, virus stocks) in mice, when & how were they last tested for virus contaminants? \_\_\_\_\_  
\_\_\_\_\_

**IMMUNODEFICIENT MICE** adapted from Jaxnotes #501, 2006 [296]

Back ground	Innate NK etc	Leaky	H2	NAME	Characteristics (Phenotypes)
<b>BALB Substrains</b>	Normal	Yes T	d	CByJ.Cg- <i>Foxn1<sup>nu</sup></i> /J	Normal B cells etc → Extra thymic T cells with age POOR breeders, ♀ female fertility → nu/+ F x nu/nu M
	Normal	High	d	CBySmn.CB17- <i>Prkdc<sup>scid</sup></i> /J	NO functional B and T cells HIGH NK, complement activity (normal APC function) Thymic lymphomas but < NOD.CB17- <i>Prkdcscid</i> /SzJ RadioSensitive
<b>C57BL/6J</b>	Normal ♀	NO	b	B6.129S7- <i>Rag1<sup>tm1Mom</sup></i> /J	NO functional B and T cells HIGH NK activity (normal APC, complement)
	Normal ♀	High	b	B6.CB17- <i>Prkdc<sup>scid</sup></i> /SzJ	NO functional B and T cells HIGH NK, complement activity (normal APC function)
<b>NOD/LtSzJ</b>	Low	NO	g7	NOD.129S7(B6)- <i>Rag1<sup>tm1Mom</sup></i> /J	NO functional B and T cells Pre-B cell > Thymic lymphomas (→ 10.5mo) Somewhat RadioResistant
	Low	NO	g7	NOD.Cg- <i>Rag1<sup>tm1Mom</sup></i> <i>Prf1<sup>tm1Sdz</sup></i> /Sz	NO functional B and T cells NO NK cell activity Thymic lymphomas (short lifespan ~8.5mo) RadioResistant: survives up to 8 Gy
	Low	Low	g7	NOD.CB17- <i>Prkdc<sup>scid</sup></i> /SzJ	NO functional B and T cells NOD background → low NK activity, NO hemolytic complement activity, defects in myeloid development, poor APC functions Thymic lymphomas (short lifespan ~8.5mo) RadioSensitive: tolerates up to 4 Gy
	Low	Low	g7	NOD.Cg- <i>Prkdc<sup>scid</sup></i> <i>B2m<sup>tm1Unc</sup></i> /J	NO functional B and T cells No MHC 1 expression → ~NO NK activity Thymic lymphomas (short lifespan ~6.3mo) Hemochromatosis dt?
	Low	NO	g7	NOD.Cg- <i>Prkdc<sup>scid</sup></i> <i>Il2rg<sup>tm1Wjl</sup></i> /SzJ	NO functional B and T cells NO NK cell activity Lymphoma-resistant and long-lived > 16m
<b>NIH stock</b>	Normal	Yes T	q	NU/J ( <i>Foxn1nu</i> )	NIH outbred nude stock → inbred at TJL

<b>Gene</b>	<i>PROPERTIES of genes &amp; mutations leading to immune deficiency</i>
<b>B2m</b> beta-2 microglobulin	Required for normal <b>expression of major histocompatibility class I proteins</b> (displaying viral and self antigens to potentially responsive T cells) and for <b>CD8+ T cell maturation and NK cell development</b>  <b>Tm Deficiency</b> → <b>∅ NK cell development/activity, CD8+ T cell activity</b>
<b>Foxn1</b> forkhead box N1, formerly <i>Hfh11</i>	<i>nu</i> mutation known as nude. <i>nu/nu</i> lack a thymus → <i>T cell deficient; respond poorly to thymus-dependent antigens, are unable to reject allogeneic and xenogeneic grafts,</i> → <i>Greatly increased susceptibility to infection.</i>
<b>Il2rg</b> interleukin 2 receptor, gamma chain	Indispensable for IL2, IL4, IL7, IL9, IL15, IL21 high affinity binding & signaling. Role in mediating susceptibility to thymic lymphomas in mice  <b>Tm Deficiency</b> → <b>NO NK development +other defects in innate immunity.</b> → <b>NO thymic lymphomas on susceptible background</b>
<b>Prf1</b> perforin 1 (pore-forming protein)	Essential in lytic pathway by which NK and CD8+ lymphocytes kill targeted cells.  <b>Tm Deficiency</b> → <b>∅ NK cell activity, CD8+ T cell activity</b>
<b>Prkdc</b> protein kinase, DNA- activated, catalytic polypeptide	Involved in repairing double-stranded DNA breaks and in recombining the variable (V), diversity (D), and joining (J) segments of immunoglobulin and T-cell receptor genes. <b>scid</b> mutation stands for <b>severe combined immunodeficient</b> .  <i>scid/scid</i> → <b>no mature T and B cells, cannot mount cell mediated or humoral adaptive immune responses, do not reject allogeneic and xenogeneic grafts, → useful cancer research models.</b> <b>BUT leakiness</b> → <i>some functional B and T cells as they age.</i> 🕒 <i>leakiness in non-SPF conditions,</i> 🕒 <i>leakiness C57BL/6J, BALB/cByJ backgrounds &gt; C3H/HeSnJSmn &gt; NOD/LtSzJ background</i> <b>++ radiosensitive</b> → <i>cannot be as thoroughly irradiated as other immunodeficient models before being engrafted</i> <i>renders NOD mice diabetes-free → useful for adoptive transfer of diabetes by T cells.</i>
<b>Rag1</b> recombination activating gene 1	Essential for <b>V(D)J gene rearrangements</b> necessary → functional antigen receptors in T & B cells.  <i>Deficient tm1Mom mutants</i> → <b>no mature, functional T and B cells.</b> <i>Renders NOD mice diabetes-free.</i> <b>+ B cell lymphomas</b> in <i>NOD.129S7(B6)-Rag1tm1Mom/J</i>

Tm = targeted mutation (knockout)

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**Some useful Web Resources**

- <http://www.mh-hannover.de/institute/tierlabor/gv-solas/INF.HTML> Hannover infectious agents website
- <http://www.radil.missouri.edu/info/teaching/resources.asp> University of Missouri RADIL Diseases of Research Animals (DORA) teaching site
- [http://www.ncbi.nlm.nih.gov/ICTVdb/lctv/vf\\_fst-g.htm](http://www.ncbi.nlm.nih.gov/ICTVdb/lctv/vf_fst-g.htm) virus taxonomy
- <http://medic.med.uth.tmc.edu/path/00001458.htm> bacterial taxonomy
- <http://www.lal.org.uk/pdf/LAfel2.PDF> FELASA guidelines - health recommendations

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