Fifty shades of mouse inflammation: usefulness and caveats of the existing model systems

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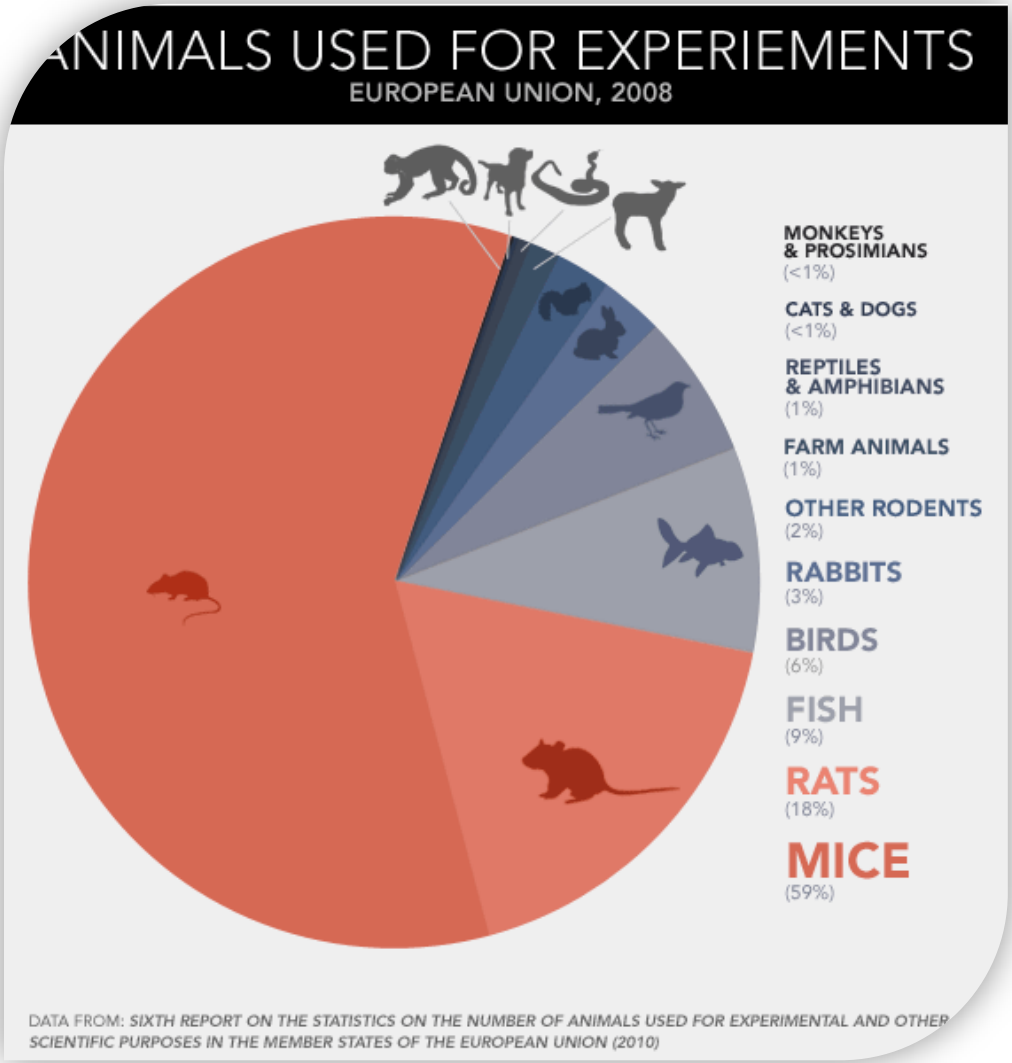
Inflammation Research Center (IRC)

VIB - Ghent University, BELGIUM

Cologne, September 26th 2015

Introduction

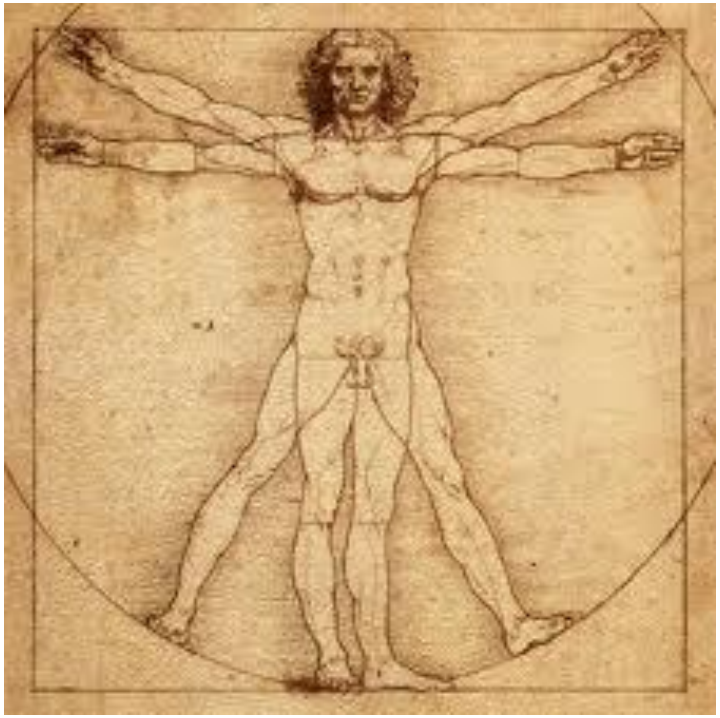
Experimental animals



Source http://www.slate.com/articles/health_and_science/the_mouse_trap/2011/11/the_mouse_trap.html

Introduction

Human vs mouse



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Is mouse research to study inflammation still useful?

Possible caveats…

Choose your models wisely

- **Caecal ligation and puncture = gold standard for sepsis?**

Review

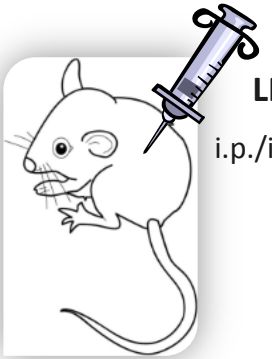
Cell PRESS

Cecal ligation and puncture: the gold standard model for polymicrobial sepsis?

Lien Dejager[1,2], Iris Pinheiro[1,2], Eline Dejonckheere[1,2] and Claude Libert[1,2]

[1] Department for Molecular Biomedical Research, Flanders Institute for Biotechnology (VIB), B9052 Ghent, Belgium
[2] Department of Biomedical Molecular Biology, Ghent University, B9052 Ghent, Belgium

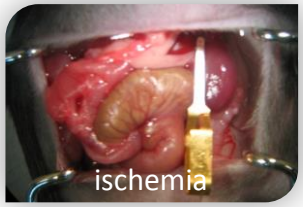
- **Endotoxemia or TNF-induced shock**

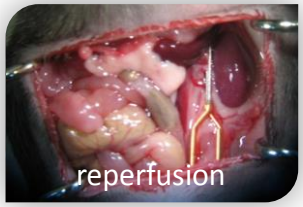


LPS/TNF

i.p./i.v. injection

kidney ischemia/reperfusion





Possible caveats…

Choose your models wisely

- **Endotoxemia**

LPS ≠ LPS!

…nilized Powders

…ame	Cat. No.
Lipopolysaccharides from *Escherichia coli* 0111:B4 purified by gel-filtration chromatography	L3012-5MG L3012-10MG L3012-25MG
Lipopolysaccharides from *Escherichia coli* 0111:B4 purified by ion-exchange chromatography	L3024-5MG L3024-10MG L3024-25MG
Lipopolysaccharides from *Escherichia coli* 0127:B8 purified by gel-filtration chromatography	L3137-5MG L3137-10MG L3137-25MG
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Lipopolysaccharides from *Escherichia coli* 0128:B12 purified by gel-filtration chromatography	L2887-5MG L2887-10MG
Lipopolysaccharides from *Escherichia coli* 026:B6 purified by gel-filtration chromatography	L2762-5MG L2762-10MG L2762-25MG
Lipopolysaccharides from *Escherichia coli* 055:B5 purified by gel-filtration chromatography	L2637-5MG L2637-10MG L2637-25MG
Lipopolysaccharides from *Escherichia coli* 055:B5 purified by ion-exchange chromatography	L4524-5MG L4524-10MG L4524-25MG
Lipopolysaccharides from *Escherichia coli* K-235 purified by gel-filtration chromatography	L2018-5MG L2018-25MG
Lipopolysaccharides from *Klebsiella pneumoniae* purified by phenol extraction	L4268-10MG L4268-100MG
Lipopolysaccharides from *Klebsiella pneumoniae* purified by trichloroacetic acid extraction	L1519-100MG
Lipopolysaccharides from *Pseudomonas aeruginosa* 10 purified by phenol extraction	L9143-10MG L9143-25MG L9143-100MG
Lipopolysaccharides from *Pseudomonas aeruginosa* 10 purified by trichloroacetic acid extraction	L7018-10MG L7018-100MG
Lipopolysaccharides from *Salmonella enterica* serotype abortus equi purified by gel-filtration chromatography	L1887-5MG L1887-25MG
Lipopolysaccharides from *Salmonella enterica* serotype enteritidis purified by gel-filtration chromatography	L2012-10MG L2012-25MG
Lipopolysaccharides from *Salmonella enterica* serotype enteritidis purified by ion-exchange chromatography	L4774-10MG L4774-25MG
Lipopolysaccharides from *Salmonella enterica* serotype minnesota purified by gel-filtration chromatography	L2137-5MG L2137-10MG
Lipopolysaccharides from *Salmonella enterica* serotype typhimurium purified by gel-filtration chromatography	L2262-5MG L2262-25MG
Lipopolysaccharides from *Salmonella typhosa* purified by gel-filtration chromatography	L2387-10MG L2387-25MG
Lipopolysaccharides from *Serratia marcescens* purified by phenol extraction	L6136-25MG L6136-100MG

Detoxified Lipopolysaccharides

Detoxified lipopolysaccharides are prepared by removal of the fatty acid portions of lipid A. The LPS is delipidized by alkaline hydrolysis and chromatographically purified. The resulting detoxified LPS has an endotoxin level ~10,000× lower than that of the parent LPS.

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Lipopolysaccharides from *Salmonella enterica* serotype typhimurium	L2525-25MG

Ready Made Solutions

Lipopolysaccharides Ready Made solutions are convenient reagents provided as 0.2 µm filtered aqueous solutions at a concentration of 1 mg lipopolysaccharides per ml. The LPS used to prepare the solutions have been phenol-extracted and chromatographically purified by gel filtration.

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Lipopolysaccharides from *Escherichia coli* 026:B6 Ready Made solution	NEW	L5543-2ML
Lipopolysaccharides from *Escherichia coli* 055:B5 Ready Made solution	NEW	L5418-2ML

Sigma

Possible caveats…

Choose your models wisely

- **Endotoxemia**
  - Purity!

…nilized Powders

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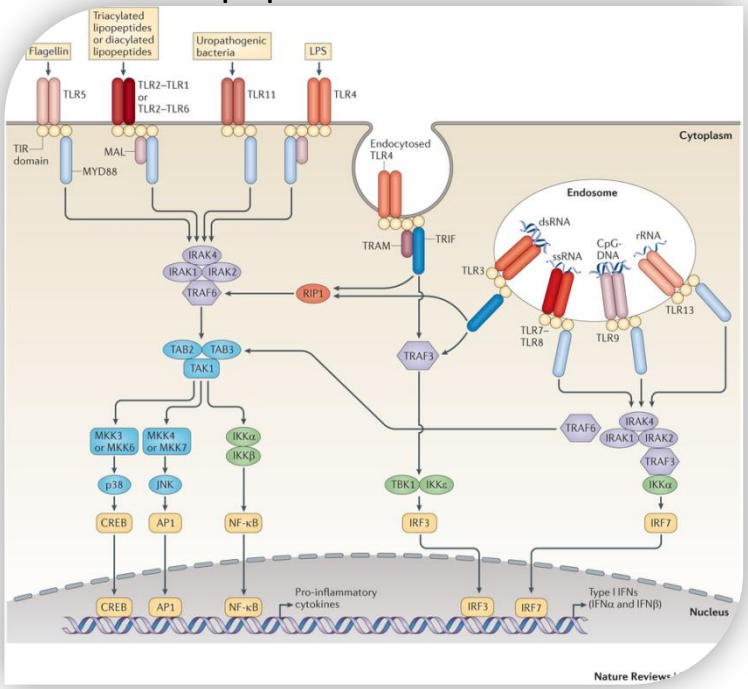
Lipopolysaccharides from *Escherichia coli* 055:B5 Ready Made solution	NEW	L5418-2ML

Sigma

Possible caveats…

Choose your models wisely

- **Endotoxemia**
  - Purity!
    - TCA (~2% RNA and ~10% denatured proteins)
    - Phenol (60% RNA and <1% proteins)
    - phenol-chloroform-petroleum ether (for rough strains)
    - gel filtration chromatography (10-20% nucleic acids & no proteins)
    - ion exchange chromatography (<1% RNA and <1% proteins)
    - + enzymatic removal of lipoproteins



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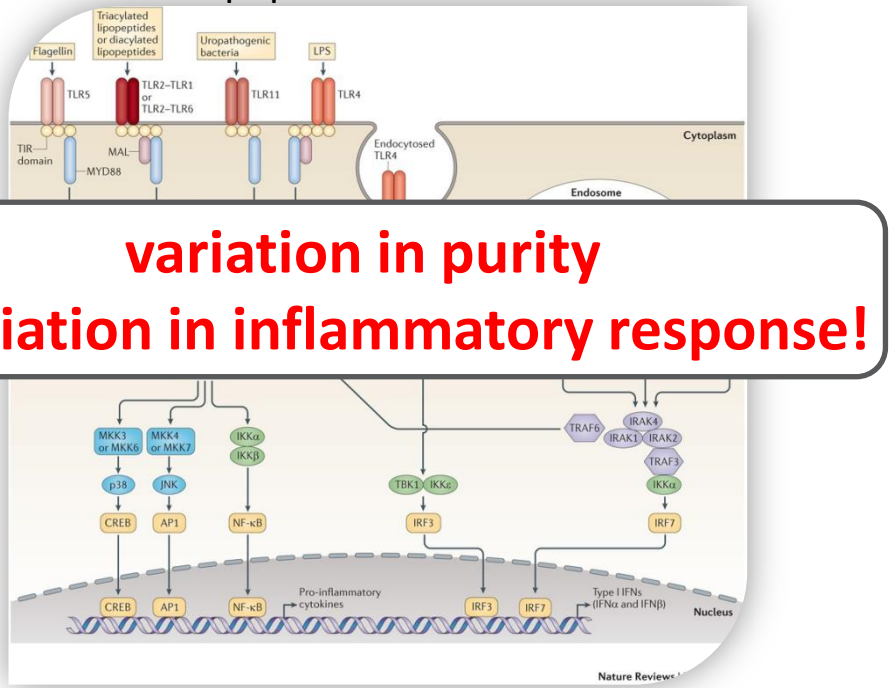

variation in purity
= variation in inflammatory response!

Possible caveats…

Choose your models wisely

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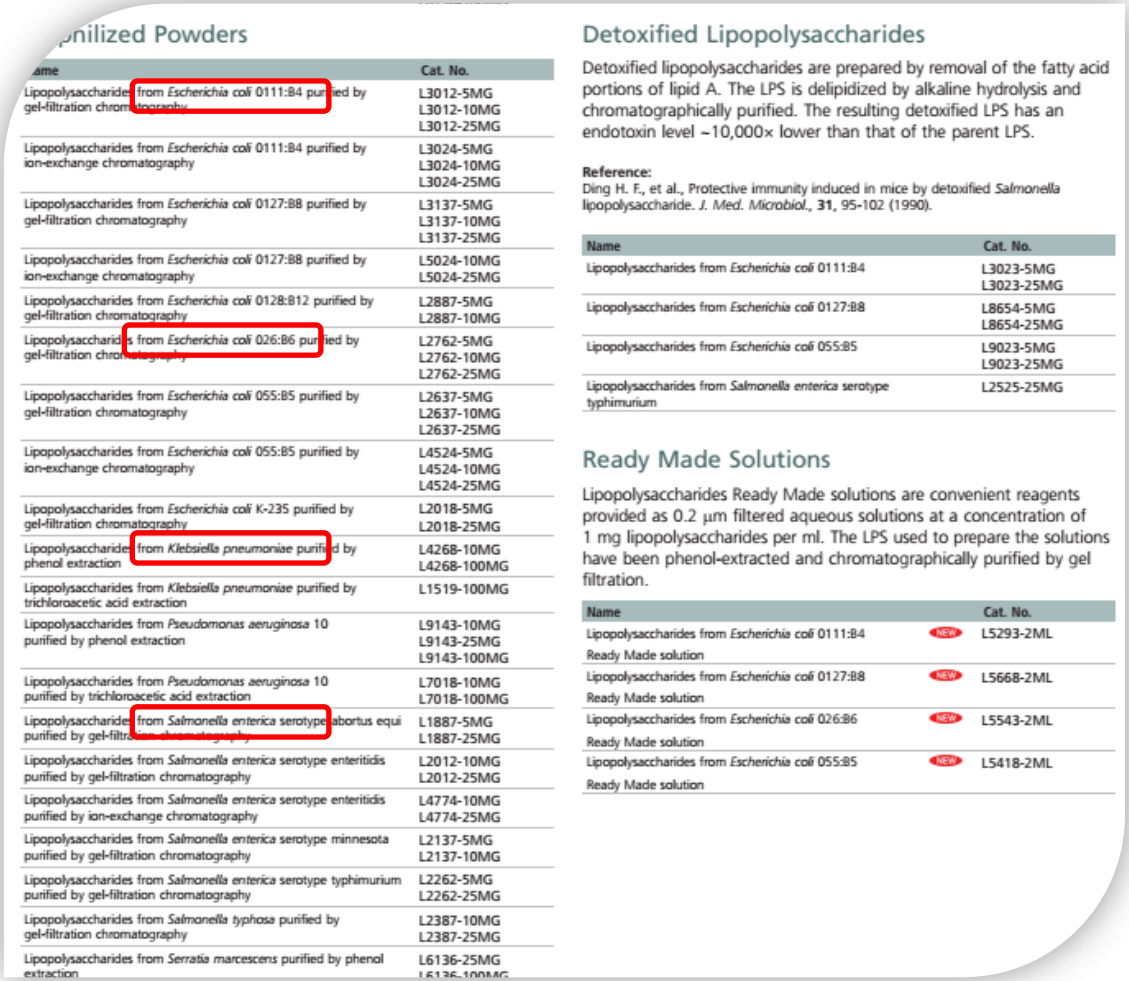
  - Source!



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Possible caveats…

Choose your models wisely

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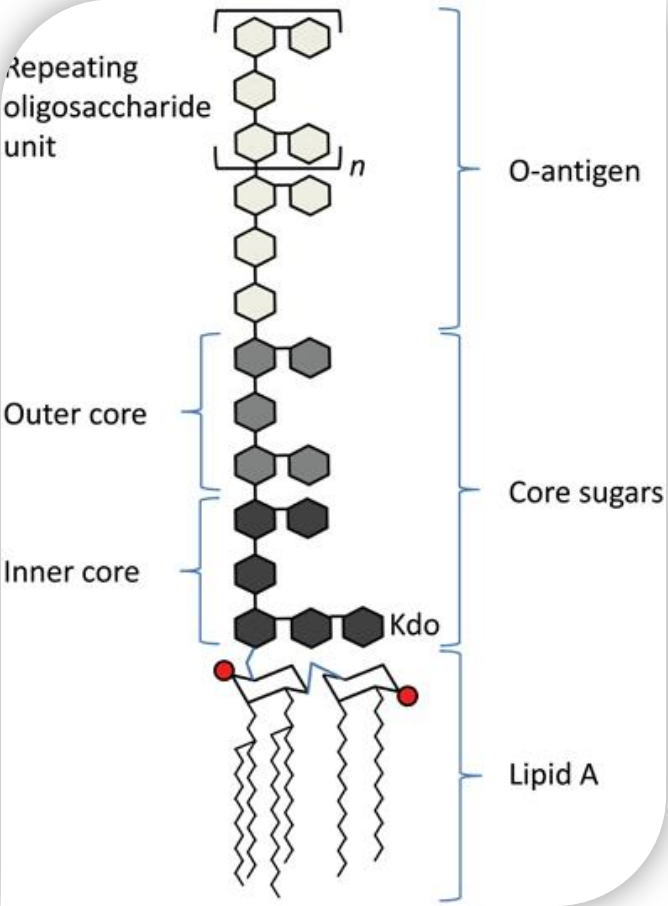
  - Source!



- Conical (highly active) vs cylindrical shape (poor TLR4 activation)

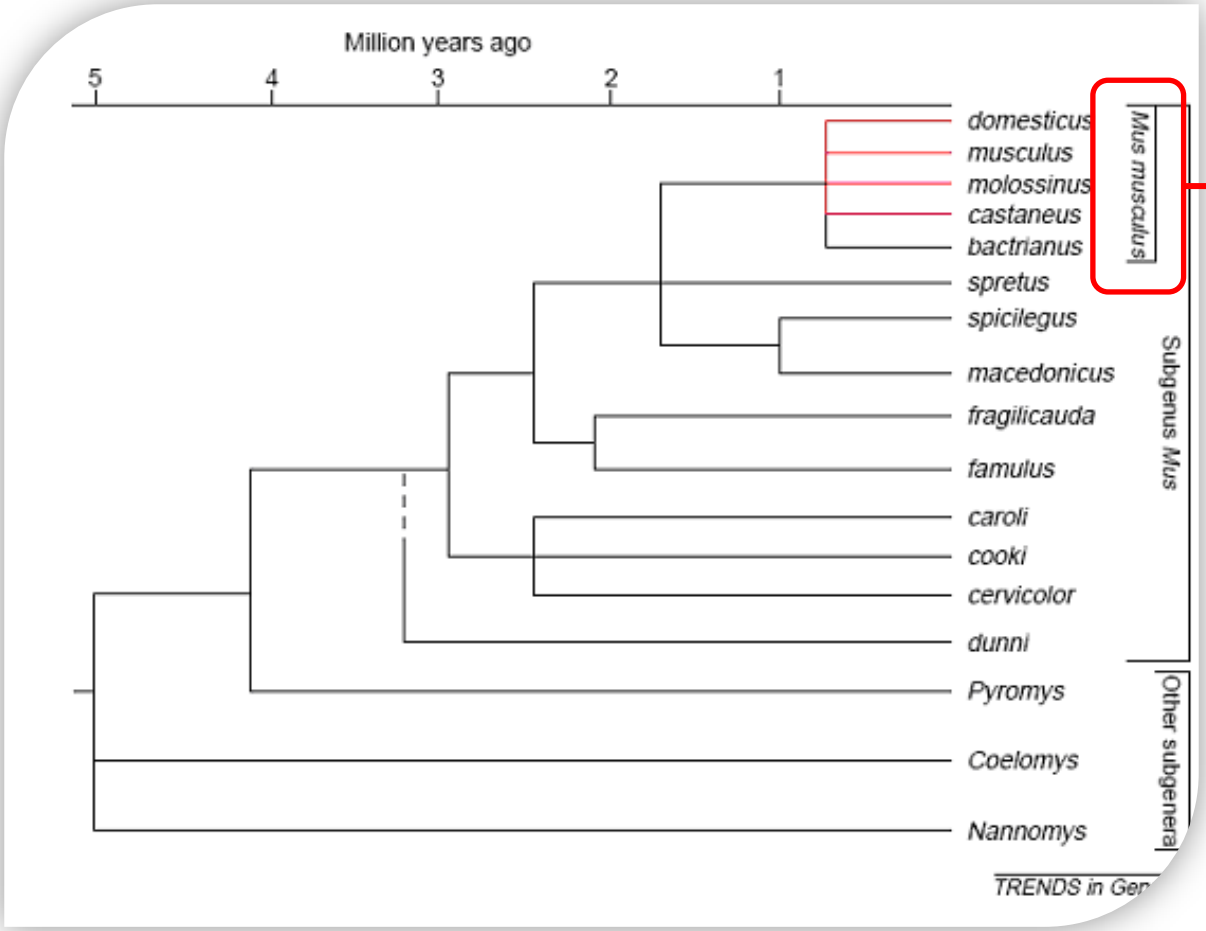
- Differential modifications (e.g. phosphorylation, glucosamine modification,…)

> Different biological effects!

Mashima & Fernandez, 2013

Possible caveats…

Mouse background!



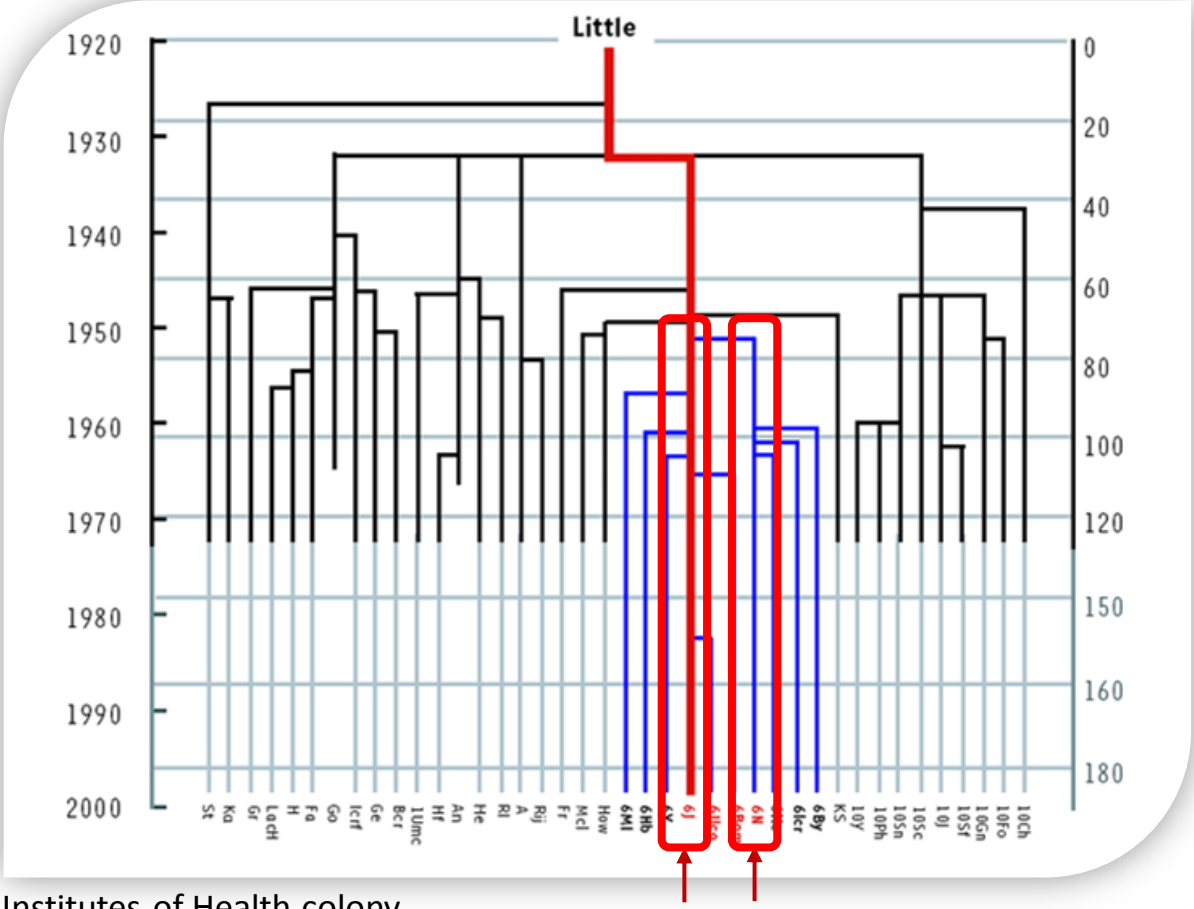
129
C57BL6
DBA/2
DBA/1
BALB/c
FVB
CBA
…

Possible caveats…

Mouse background!

- **Sensitivity to inflammation depends on background!**

C57BL/6 **N** and **J** substrains originated in 1951



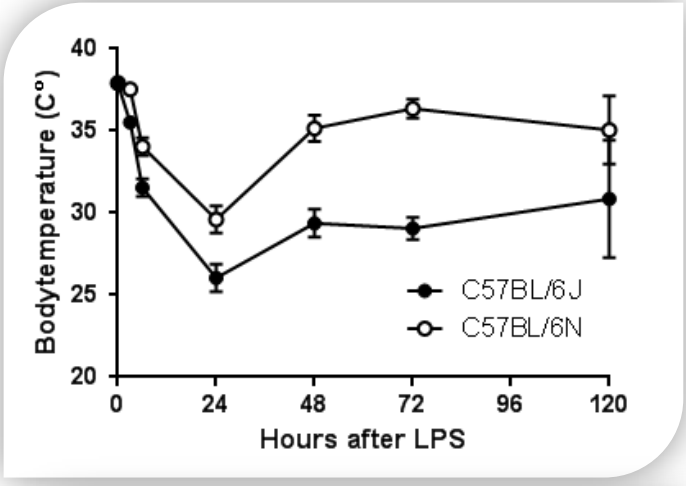
"N" = National Institutes of Health colony

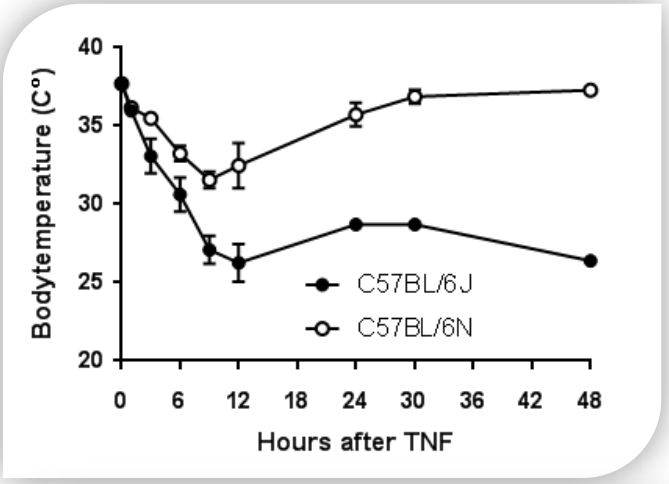
"J" = The Jackson Laboratory's substrain

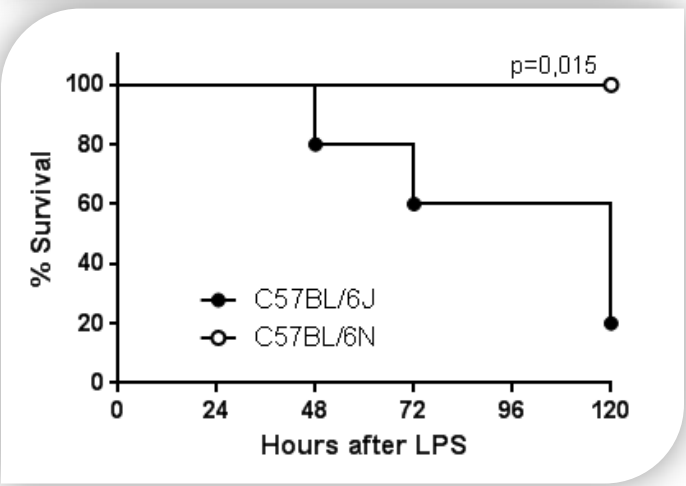
Possible caveats…

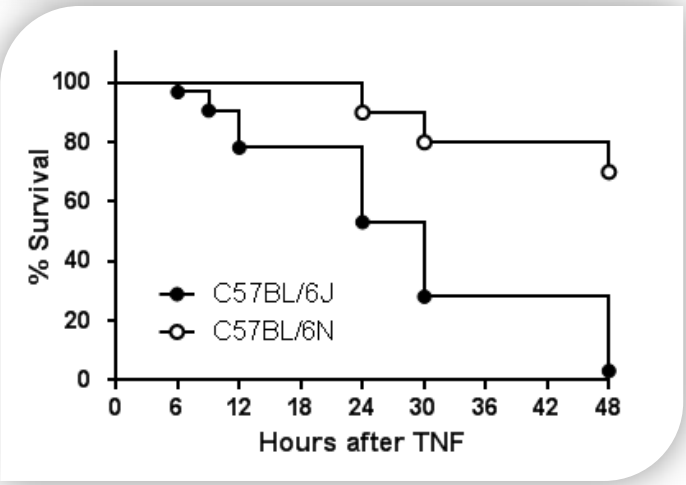
Mouse background!

- **C57BL/6N strain is significantly more resistant to lethal dose of LPS and TNF**





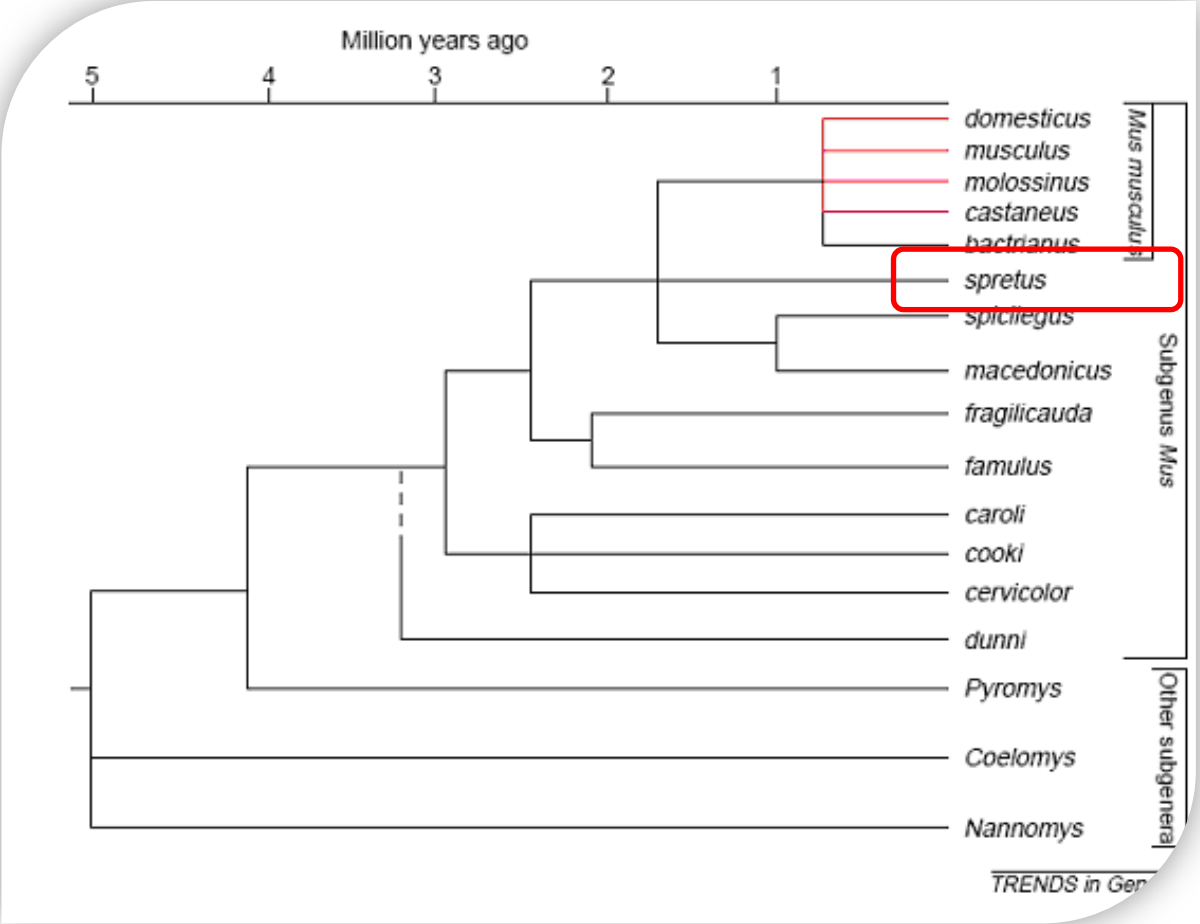




Vanden Berghe et al, Immunity, 2015

Possible caveats…

Differences in genetic background can also be useful…



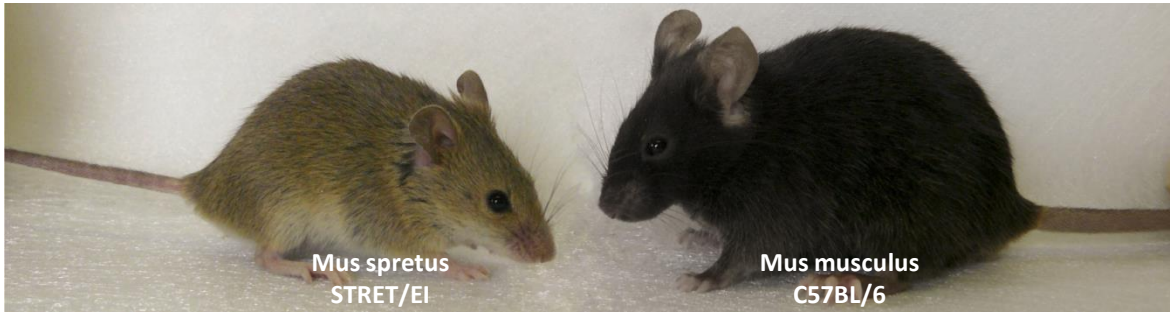
Mus spretus diverged from Mus musculus about 1.5 million years ago

⇒ high degree of genetic polymorphisms

Possible caveats…

Differences in genetic background can also be useful…

- **Mus spretus (SPRET/EI) vs Mus musculus (C57BL/6)**
  - SPRET/EI mice = inbred strain of Mus spretus Dejager et al, Trends Genetics, 2009

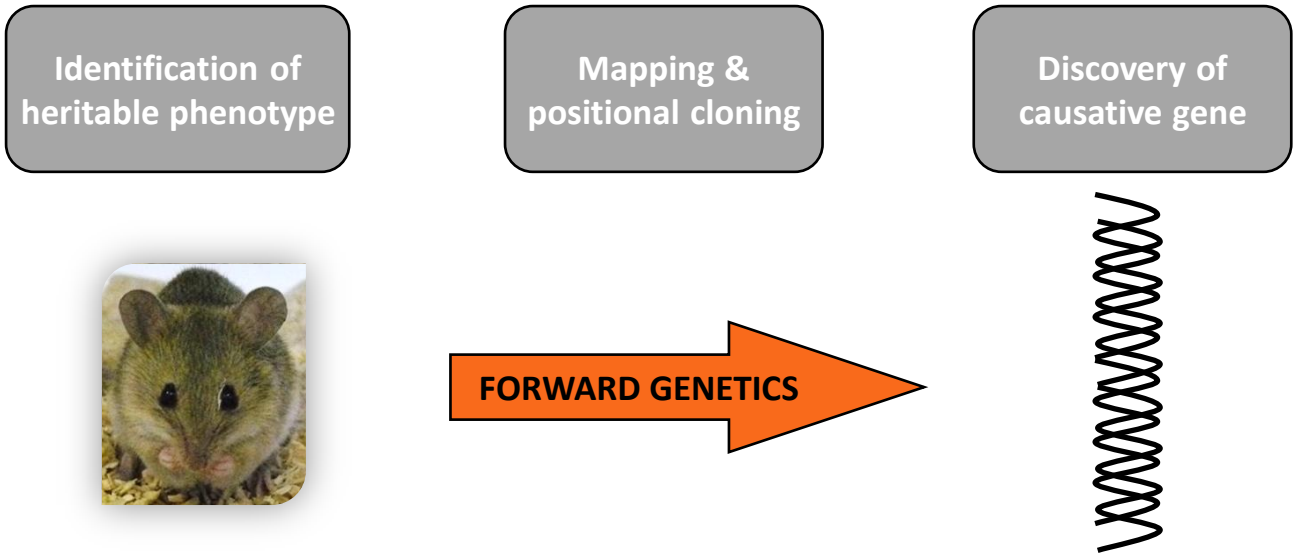


  - Many different phenotypes
    - Resistance to TNF Staelens et al, PNAS, 2002
    - Resistance to LPS Mahieu et al., PNAS, 2006
    - Resistance against influenza A Vanlaere et al., Cytokine, 2008
    - Resistance to Salmonella bacteria Dejager et al., Infect Immun, 2010
    - CLP?

Possible caveats…

Differences in genetic background can also be useful…

- **Forward genetics**



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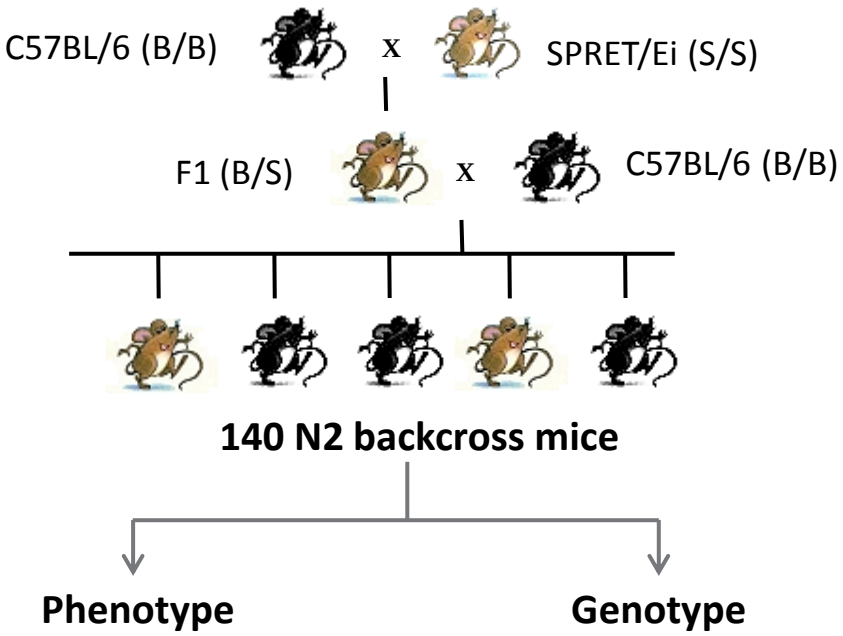

Possible caveats…

Differences in genetic background can also be useful…

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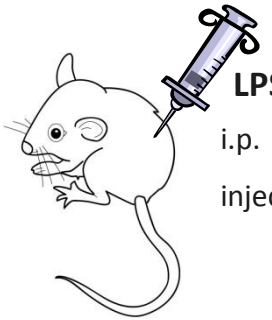
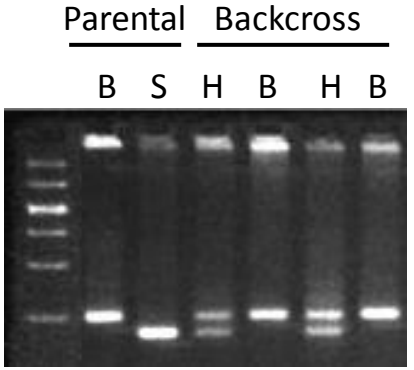
140 N2 backcross mice



LPS/TNF
i.p.
injection

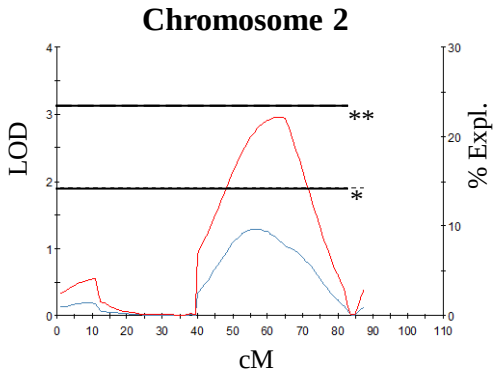
Phenotype?
LPS/TNF resistance

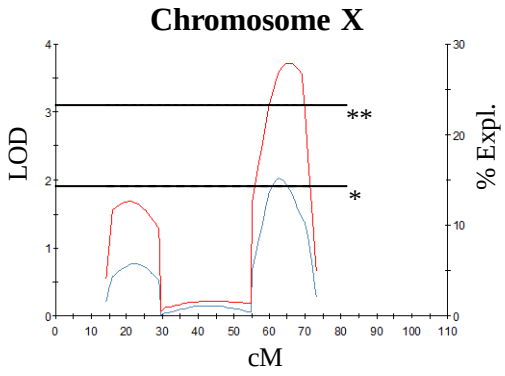
Genotype?
Microsatellite markers



B = C57BL/6
S = SPRET/Ei
H = heterozygous

Linkage analysis





Possible caveats…

Differences in genetic background can also be useful…

- **LPS resistance?**


EMBO Molecular Medicine

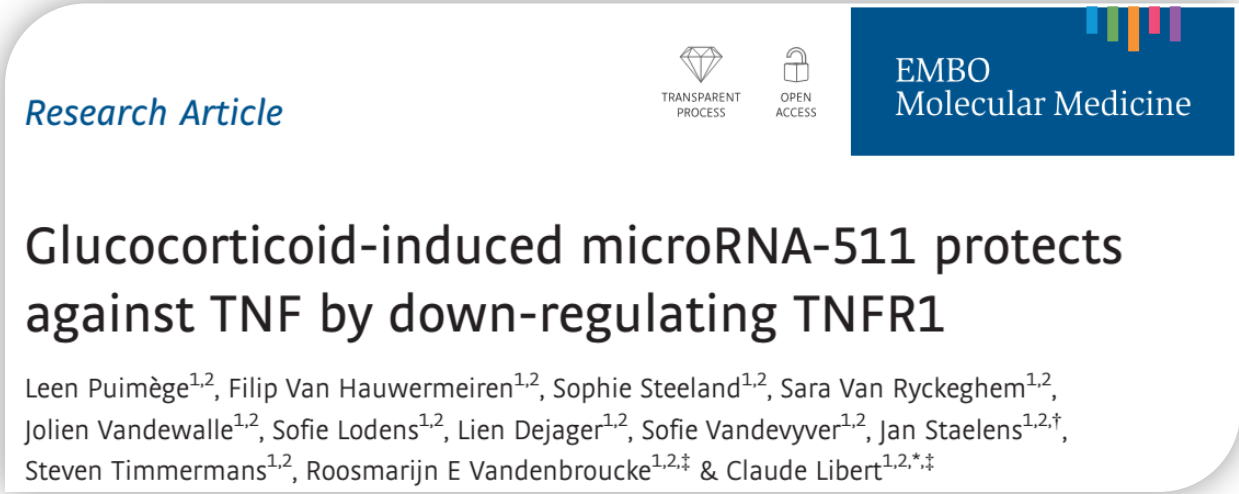
OPEN ACCESS TRANSPARENT PROCESS SOURCE DATA

Research Article
Gilz protects against LPS

LPS resistance of SPRET/Ei mice is mediated by Gilz, encoded by the *Tsc22d3* gene on the X chromosome

*Iris Pinheiro[1,2,3,4], Lien Dejager[1,2], Ioanna Petta[1,2], Sofie Vandevyver[1,2], Leen Puimège[1,2], Tina Mahieu[1,2], Marlies Ballegeer[1,2], Filip Van Hauwermeiren[1,2], Carlo Riccardi[5], Marnik Vuylsteke[3,4], Claude Libert[1,2]**

- **TNF resistance?**


Research Article

TRANSPARENT PROCESS OPEN ACCESS

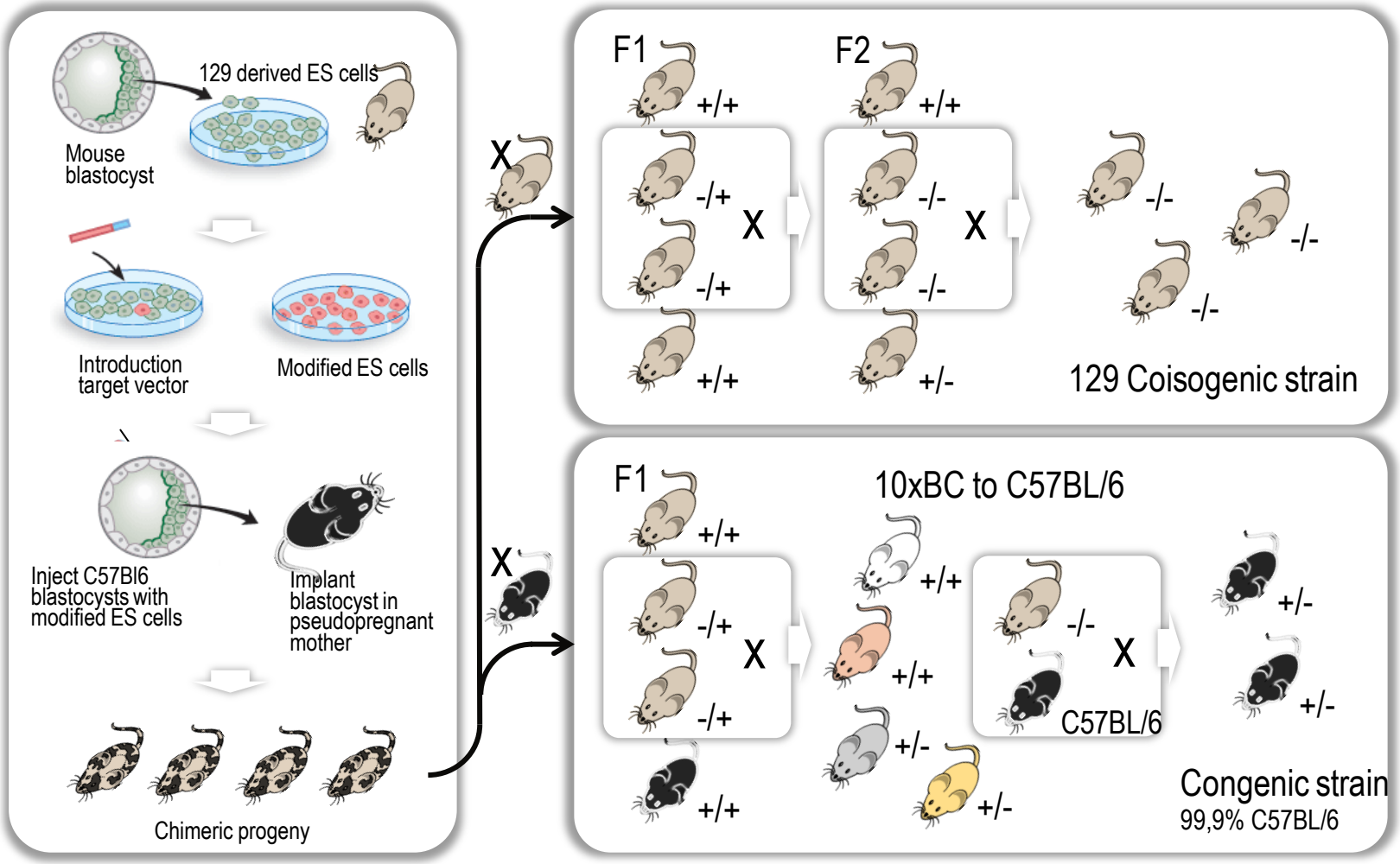
EMBO Molecular Medicine

Glucocorticoid-induced microRNA-511 protects against TNF by down-regulating TNFR1

Leen Puimège[1,2], Filip Van Hauwermeiren[1,2], Sophie Steeland[1,2], Sara Van Ryckeghem[1,2], Jolien Vandewalle[1,2], Sofie Lodens[1,2], Lien Dejager[1,2], Sofie Vandevyver[1,2], Jan Staelens[1,2,†], Steven Timmermans[1,2], Roosmarijn E Vandenbroucke[1,2,‡] & Claude Libert[1,2,*,‡]

Possible caveats…

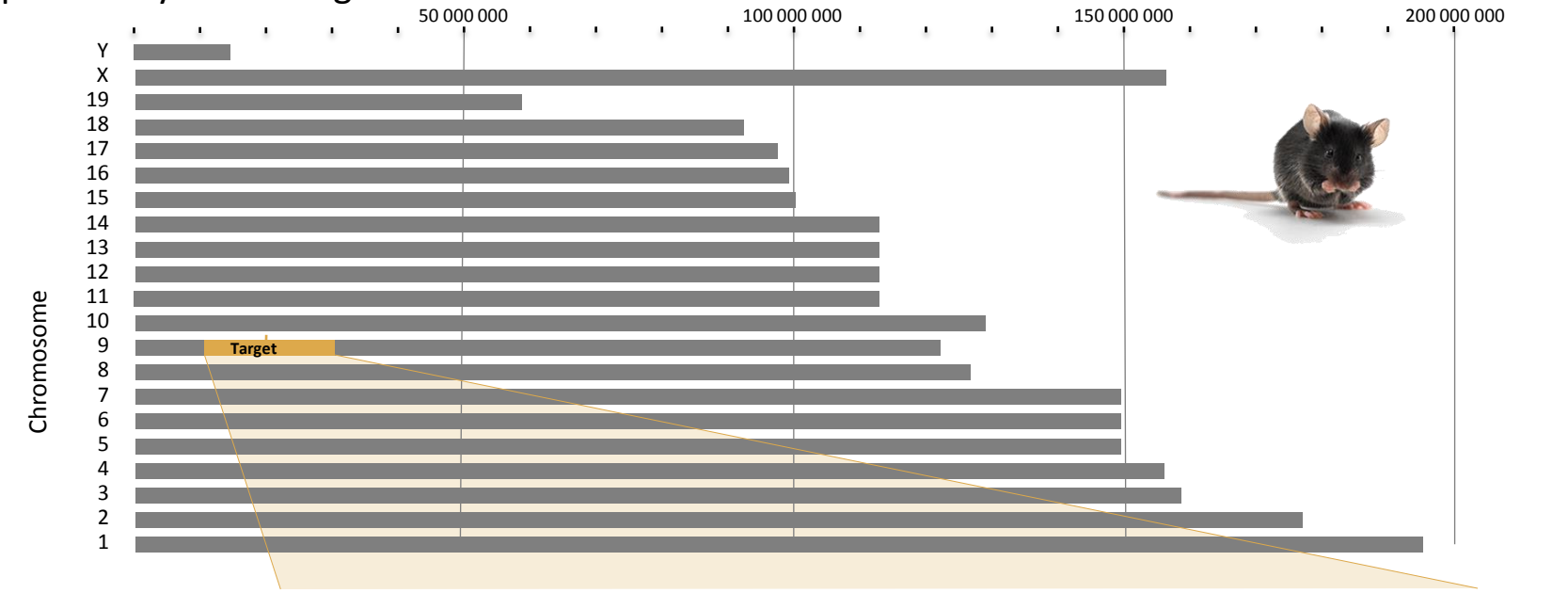
Be careful when using KO mice!

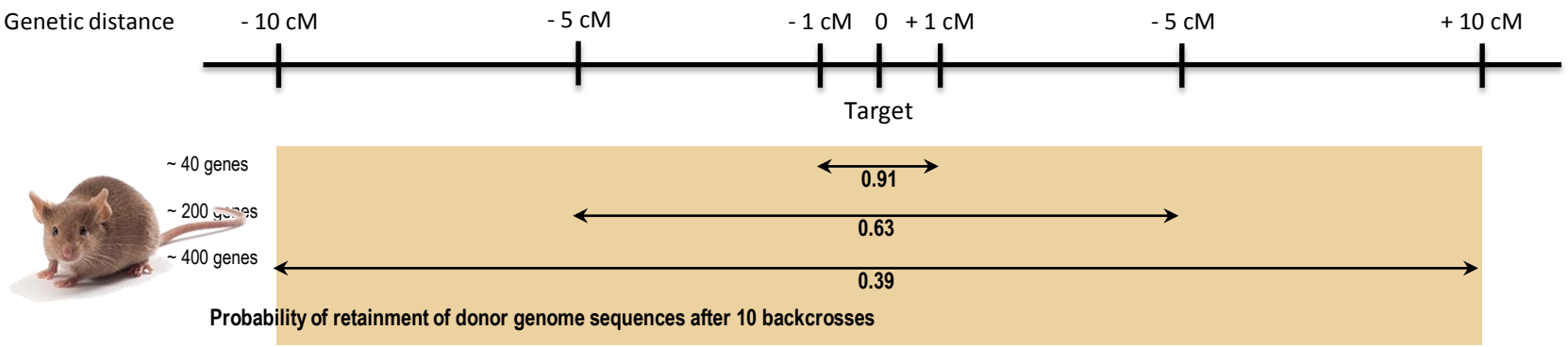


Possible caveats…

Be careful when using KO mice!

- **The passenger gene problem** = targeted gene is flanked by 129-derived passenger DNA potentially containing mutations





Possible caveats…

Be careful when using KO mice!

- **But what is the impact?**

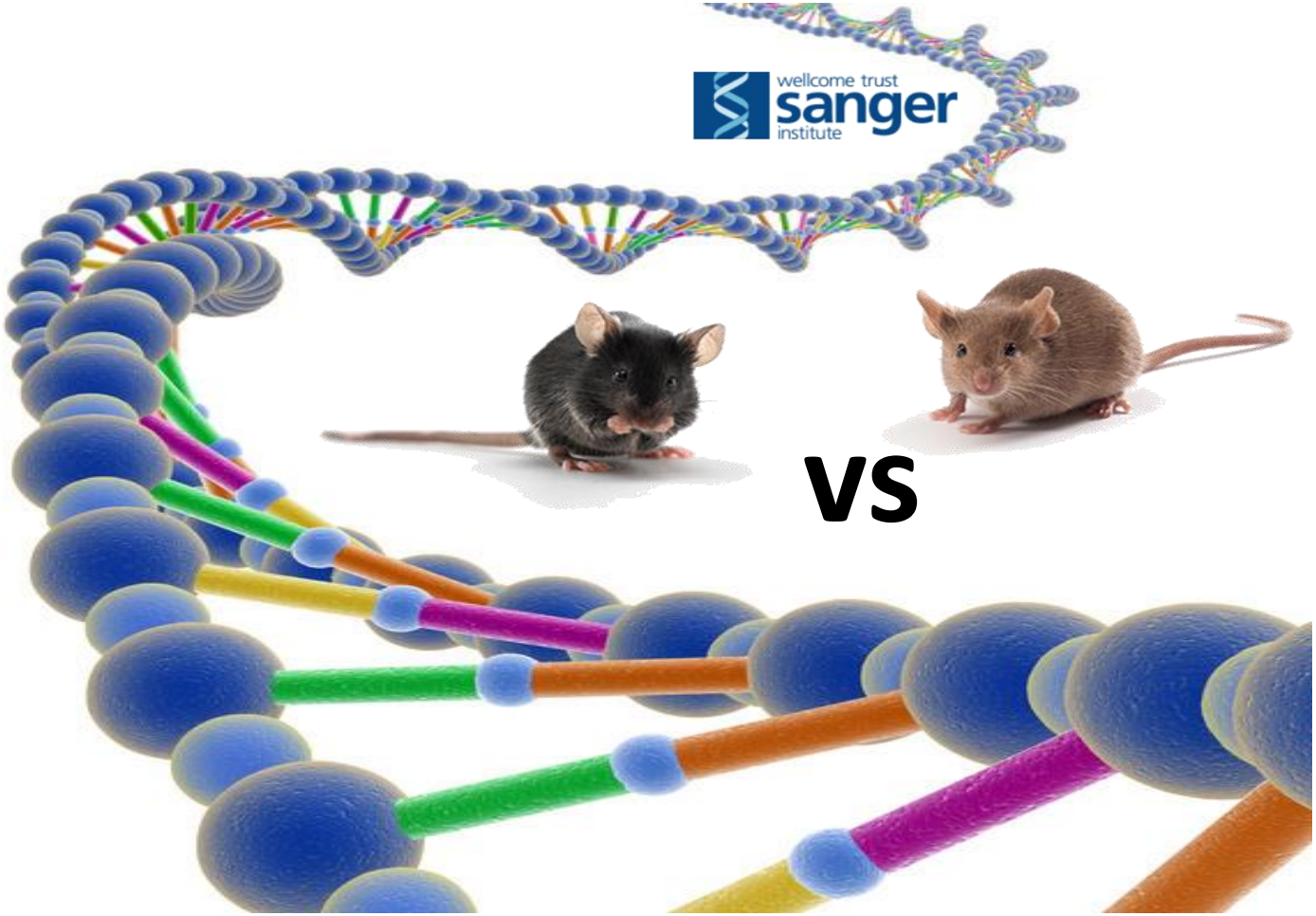
What is impact of 129-derived passenger mutations

on C57BL/6 congenic knockout mice?

Possible caveats…

Be careful when using KO mice!

- **Comparative Genomics**



Possible caveats…

Be careful when using KO mice!

- **Comparative Genomics**

Filtering on predicted

protein sequence alterations

yielded

949 indels

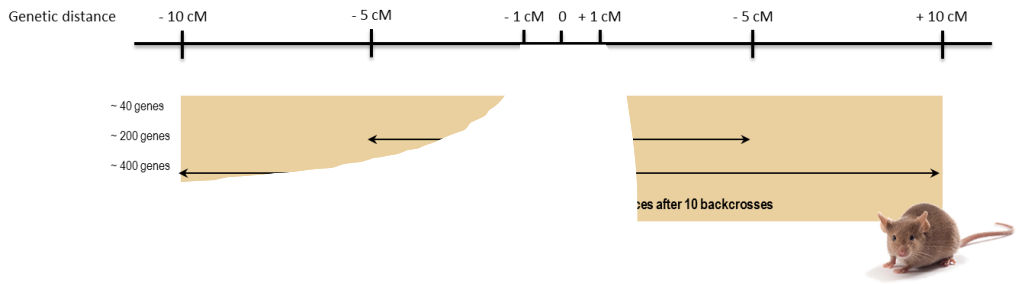
446 SNPs

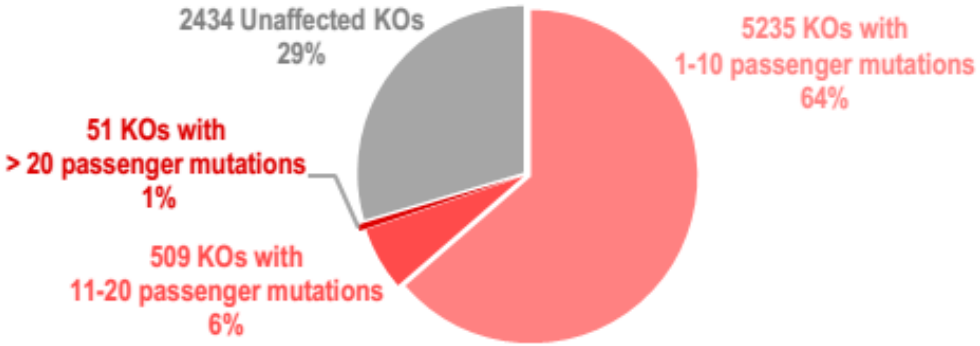
affecting 1084 genes

Possible caveats…

Be careful when using KO mice!

- **How many MGI KO mice might be carrying passenger mutations?**

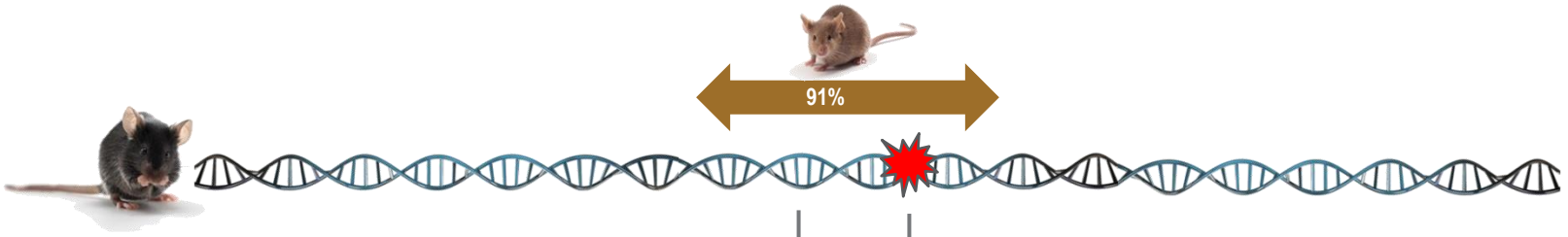




Possible caveats…

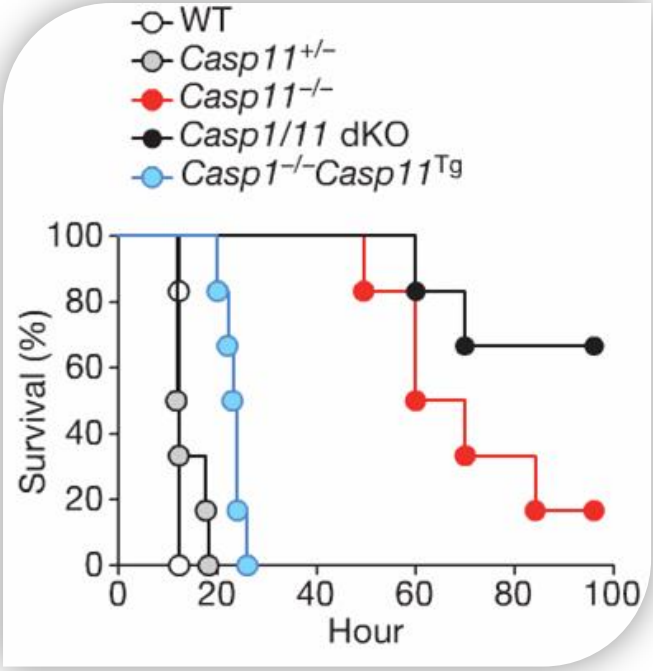
Be careful when using KO mice!

- **Inactivating 129-derived Caspase 11 passenger mutation**



casp1

casp11



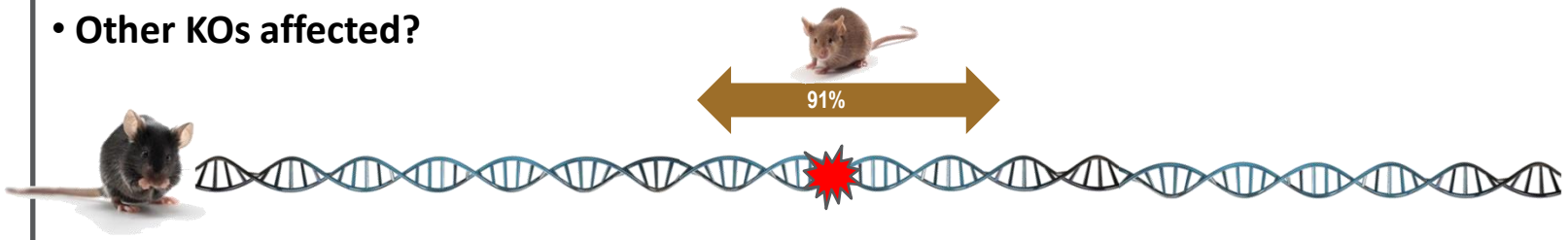
Casp11 deletion provides
resistance to LPS-induced lethal shock

Kayagaki et al., Nature, 2011

Possible caveats…

Be careful when using KO mice!

- **Other KOs affected?**



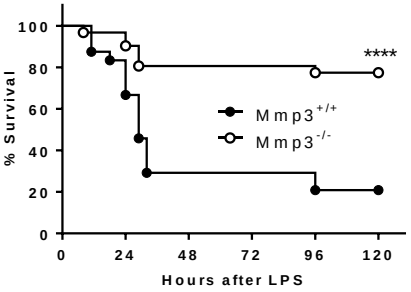
Gene symbol	ENSMUSG ID (ENSMUSG000000)	Total № of KOs	Gene symbol	ENSMUSG ID (ENSMUSG000000)	Total № of KOs	Gene symbol	ENSMUSG ID (ENSMUSG000000)	Total № of KOs
Alkbh8	25899	1	Trpc6	31997	1	Dnmt1	04099	3
Gucy1a2	41624	1	Pgr	31870	5	S1pr2	43895	3
Gria4	25892	7	Mtmr2	31918	2	Icam1	37405	4
Casp1*	25888	2	Kdm4d	53914	1	Icam4	01014	1
Casp11	33538	2	Piwil4	36912	2	Tyk2	32175	2
Casp12	25887	2	Fut4	49307	1	Pde4a	32177	2
Pdgfd	32006	1	Mre11a	31928	1	Ilf3	32178	1
Mmp13	50578	2	Gpr83	31932	2	Carm1	32185	1
Mmp12	49723	1	Izumo1r	31933	1	Smarca4	32187	1
Mmp3	43613	1	Panx1	31934	2	Ldlr	32193	1
Mmp1a	43089	1	Hephl1	31936	1	Gm6484	47822	1
Mmp10	47562	2	Mtnr1b	50901	2	Rab3d	19066	1
Mmp8	05800	2	Fat3	74505	1	Epor	06235	5
Mmp27	70323	1	Mbd3l2	47508	1	Elavl3	03410	1
Mmp20	18620	1	Mbd3l1	38691	1	Ecsit	66839	1
Mmp7	18623	1	Muc16	32134	2	Acp5	01348	1
Tmem123	50912	2	Pin1	32171	1	Bmper	31963	2
Birc2*	57367	2	Col5a3	04098	1	Npsr1	43659	1
Birc3	32000	2	Rdh8	53773	1	Dpy19l2	85576	1
Yap1	53110	2	Angptl6	38742	1	Tbx20	31965	1

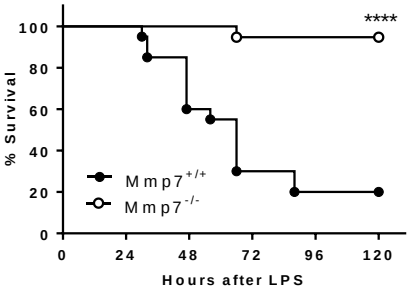
Possible caveats…

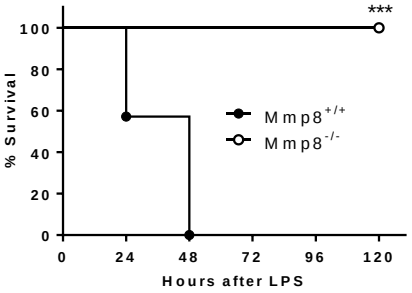
Be careful when using KO mice!

- **Other KOs affected?**

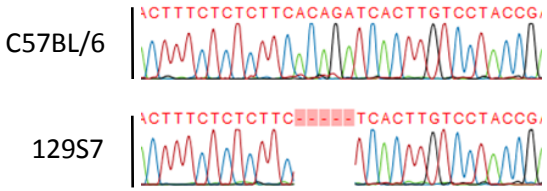
Mutated Casp11

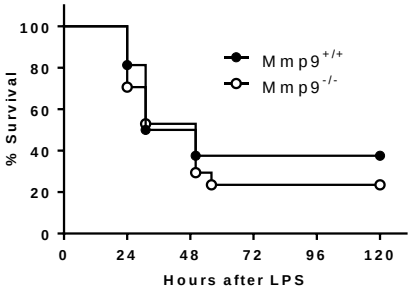


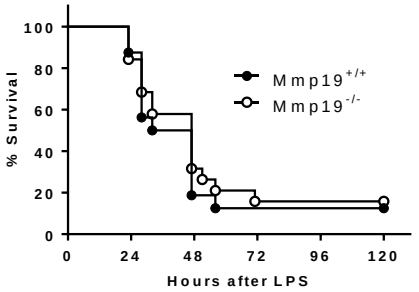




Wild type Casp11



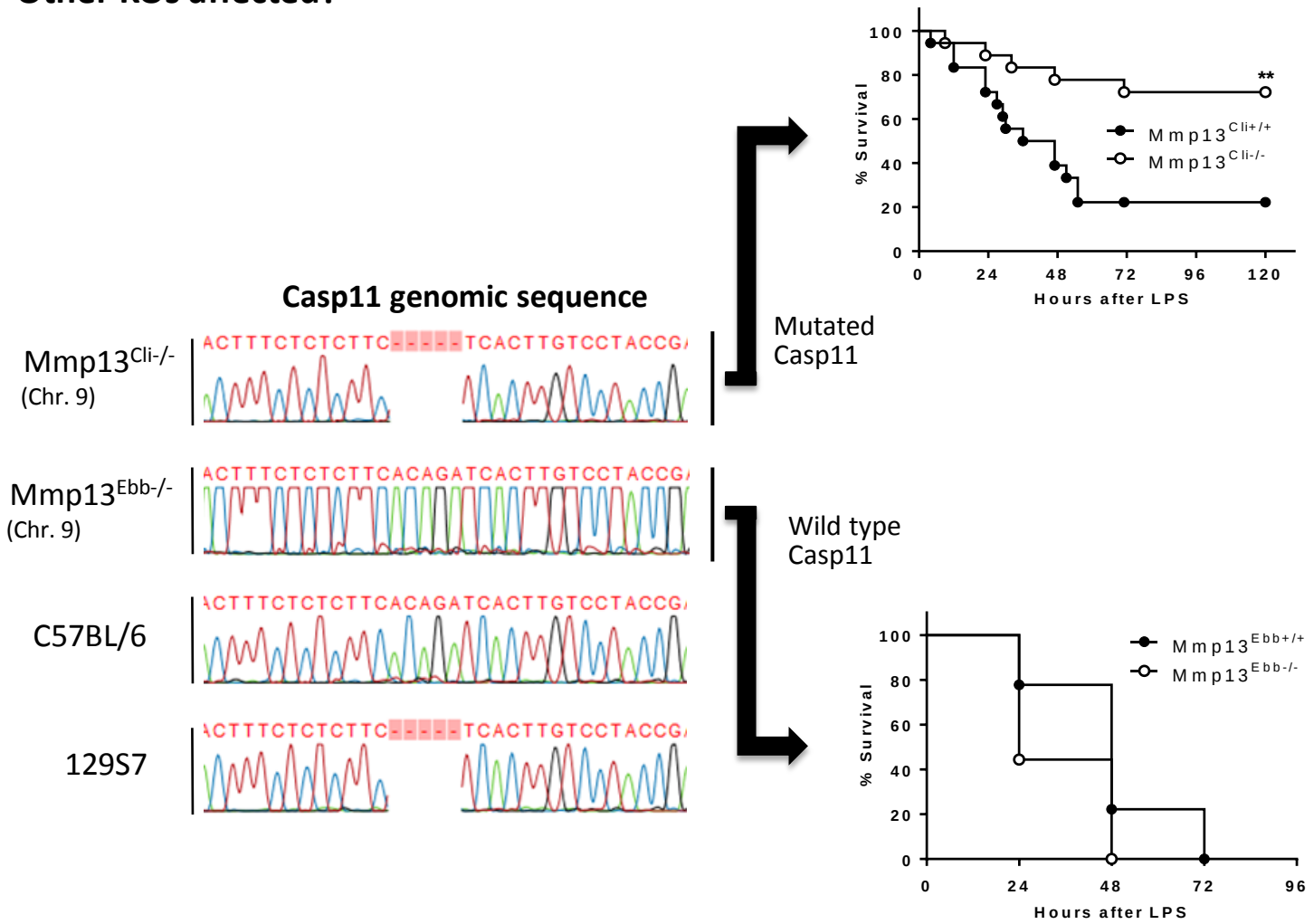




Possible caveats…

Be careful when using KO mice!

- **Other KOs affected?**



Possible caveats…

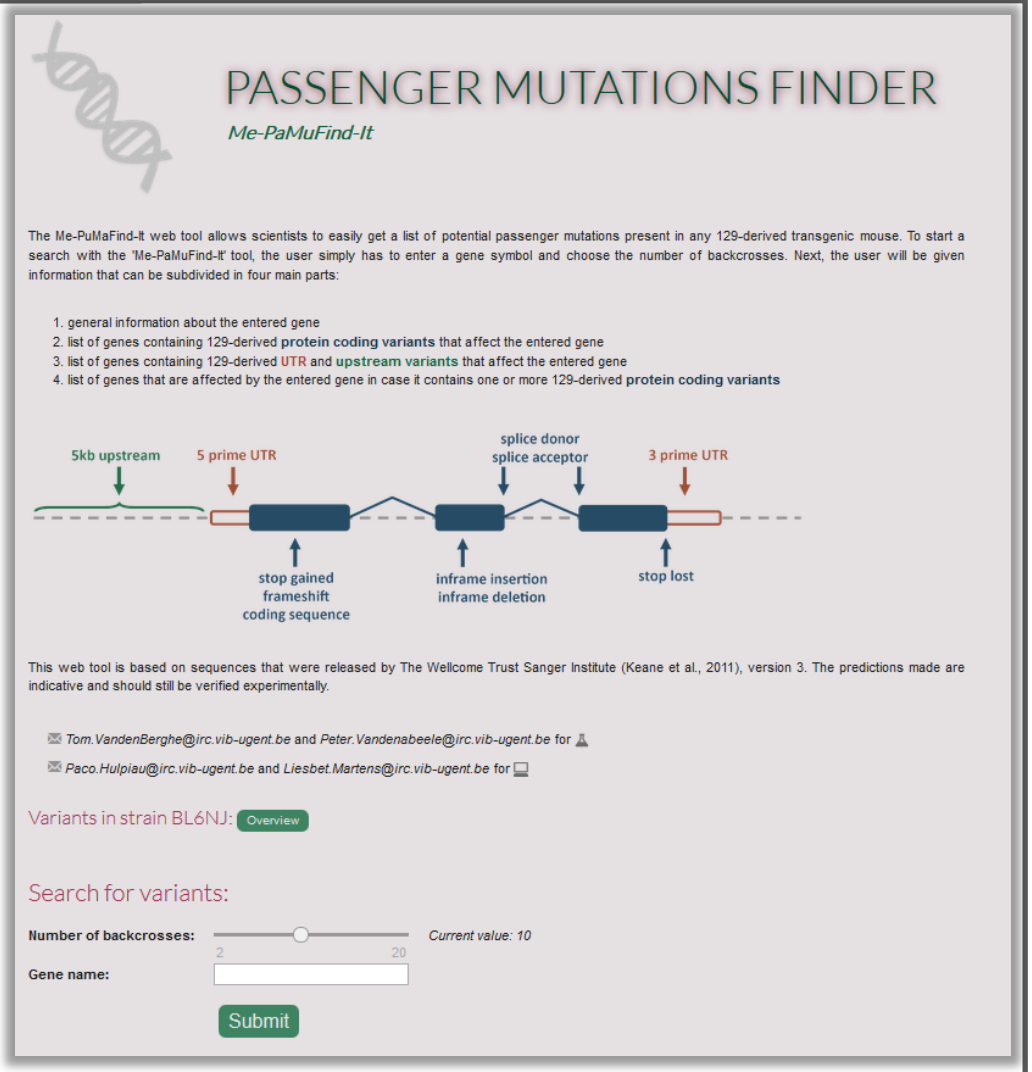
Be careful when using KO mice!

- **Webtool** = Me-PuMaFind-It

Estimate impact on your particular Knockout mouse!

Decide to regenerate in defined genetic background

Eg using genome engineering technologies such as CRISPR/Cas



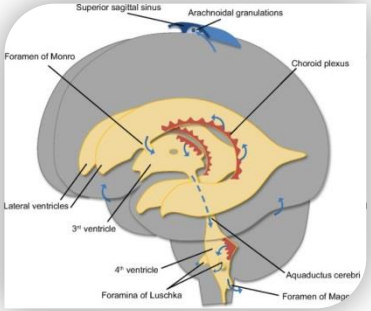
Vanden Berghe et al, Immunity, 2015

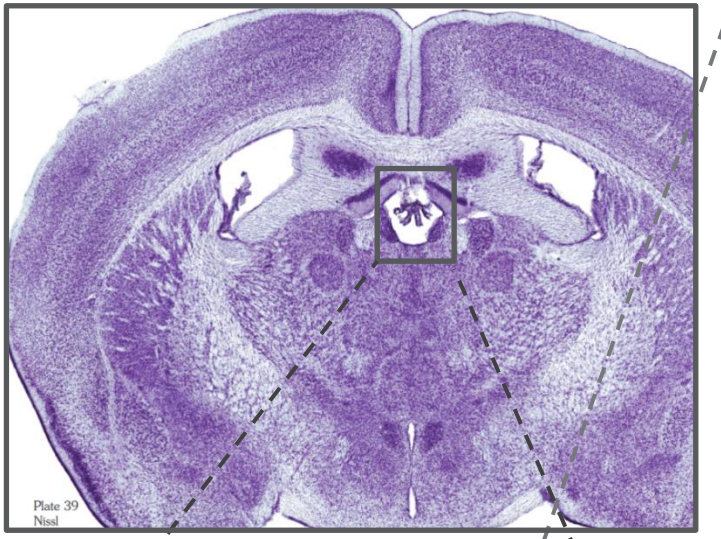
http://me-pamufind-it.org/

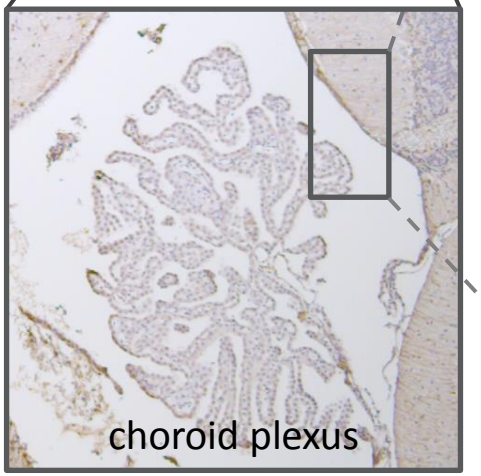
Usefulness!

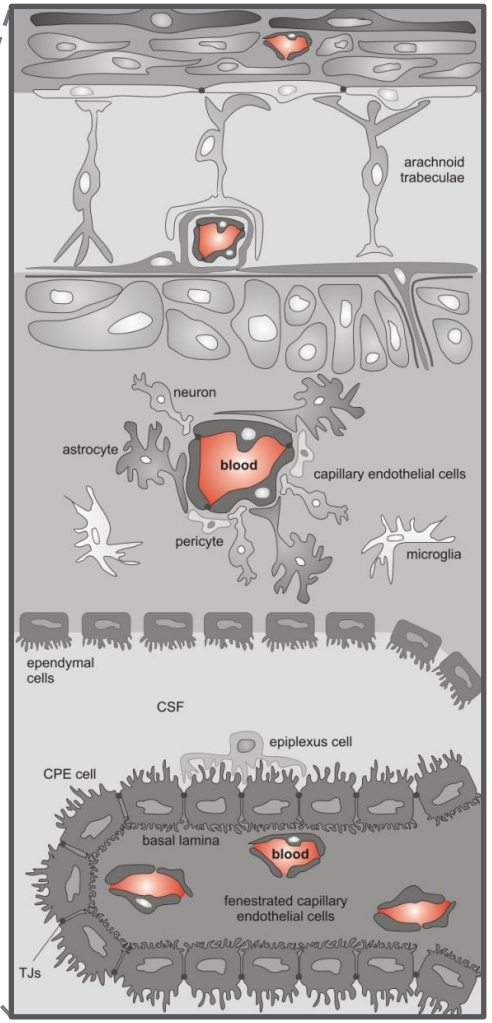
Detailed analysis possible of ‘difficult to reach’ organs

- **Choroid plexus**









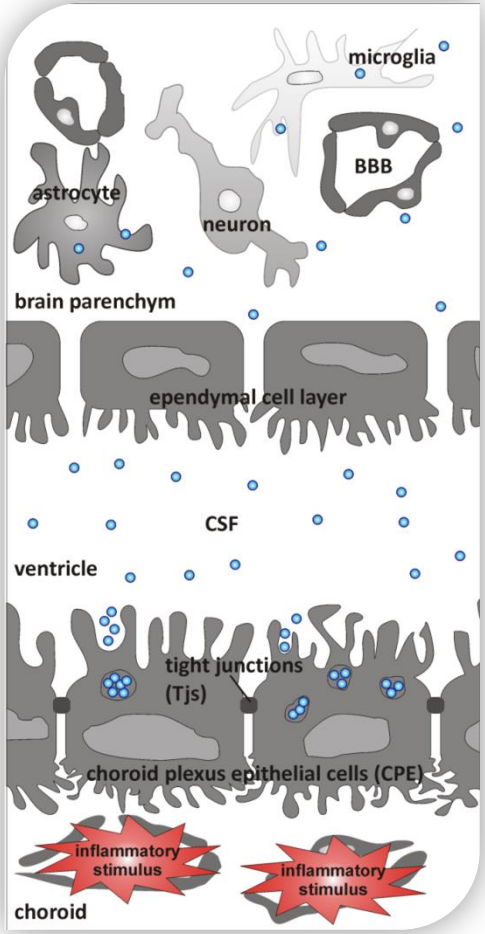
Demeestere et al., DDT, 2015

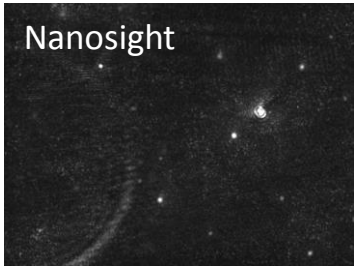
Demeestere et al., BBI, 2015

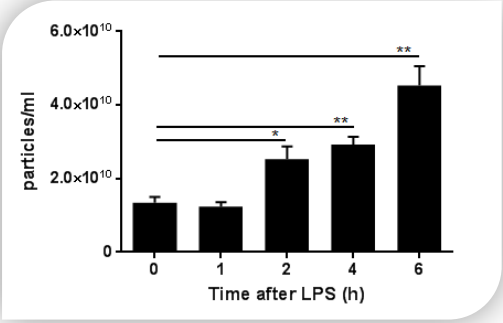
Usefulness!

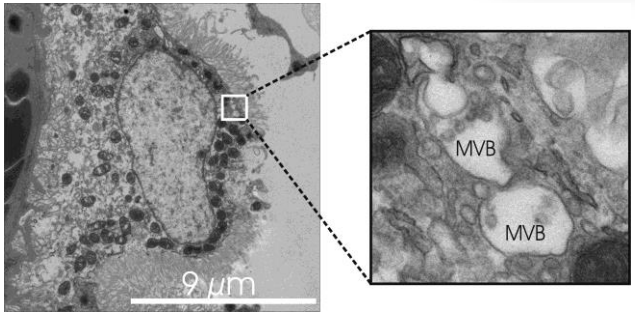
Detailed analysis possible of ‘difficult to reach’ organs

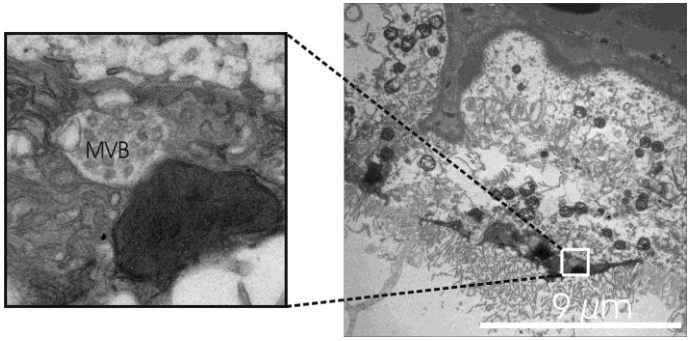
- **Blood cerebrospinal fluid barrier**











Balusu et al., under review

Inflammation Research Center
Mouse Genetics in Inflammation
Lab Prof. Claude Libert

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Ghent University

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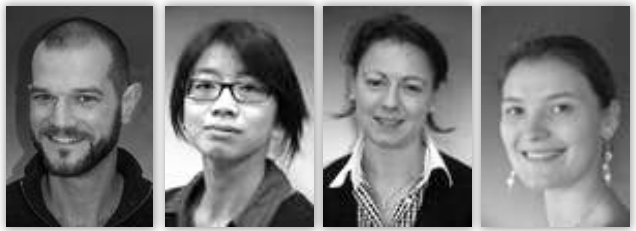
Inge Bruggeman
Tatyana Divert



Bioinformatics Core Facility

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Liesbet Martens