Mouse model for PMM2-CDG

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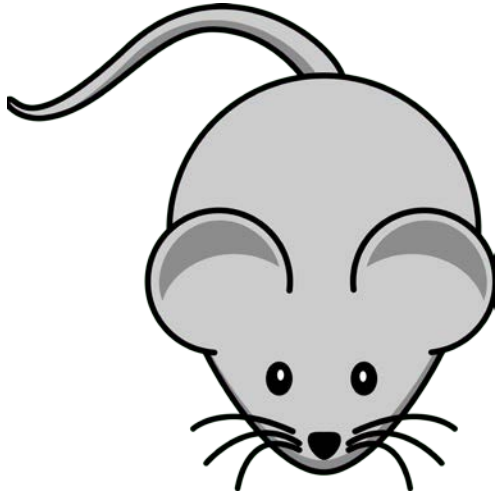
Children's Hospital of Philadelphia

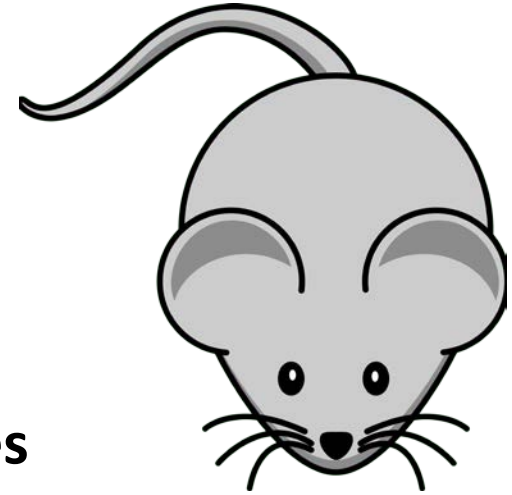
Mouse as a disease model



Uses

- Determine genetic causation
- Understand pathophysiology
- Use as a preclinical model

Mouse as a disease model



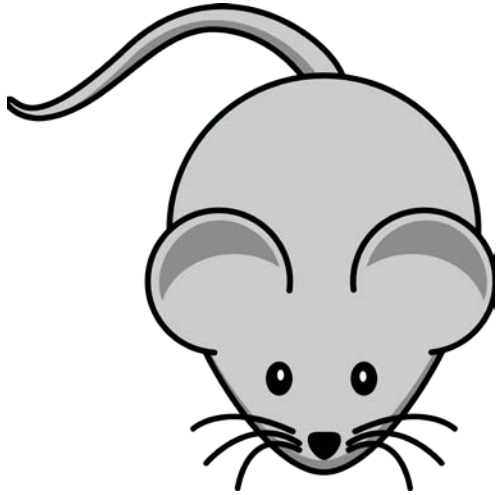
Uses

- Determine genetic causation
- Understand pathophysiology
- Use as a preclinical model

Advantages

- Genetic similarities with humans
- Tools for genetic manipulation
- Lifespan/Reproduction rate
- Size/Ease of handling/Cost

Mouse as a disease model



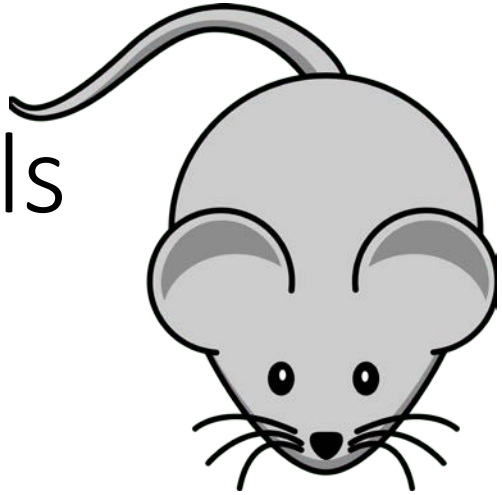
Uses

- Determine genetic causation
- Understand pathophysiology
- Use as a preclinical model

Challenges

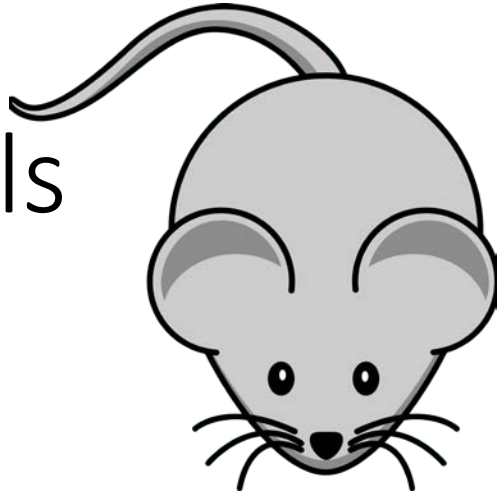
- Phenotypes
- Alternative physiology
- Predictive validity
- Inbred strain differences

Types of genetic mouse models



- Transgenic

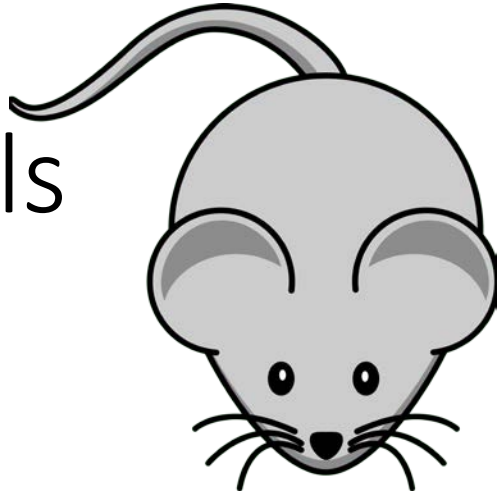
Types of genetic mouse models



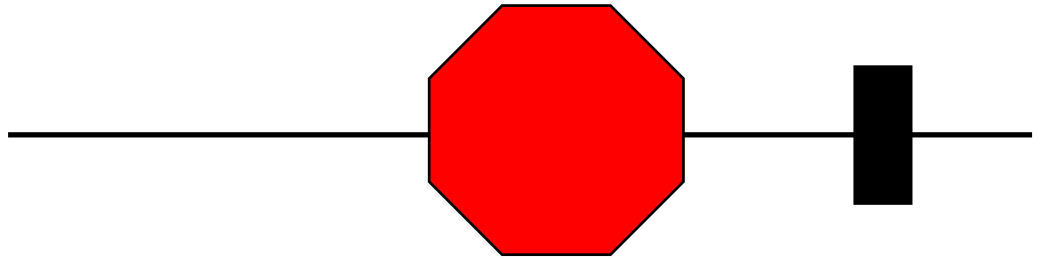
- Transgenic

- Knockin

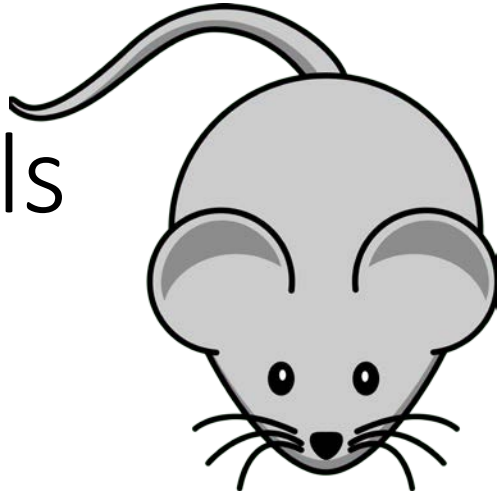
Types of genetic mouse models



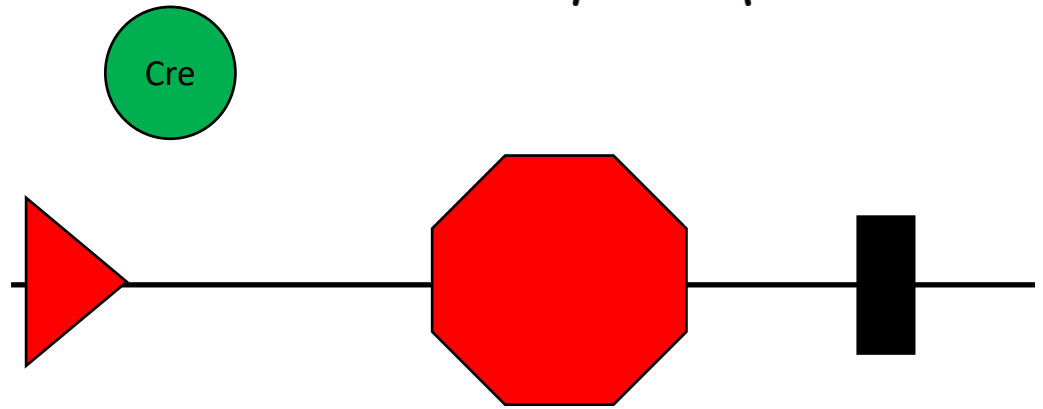
- Transgenic
- Knockin
- Knockout



Types of genetic mouse models



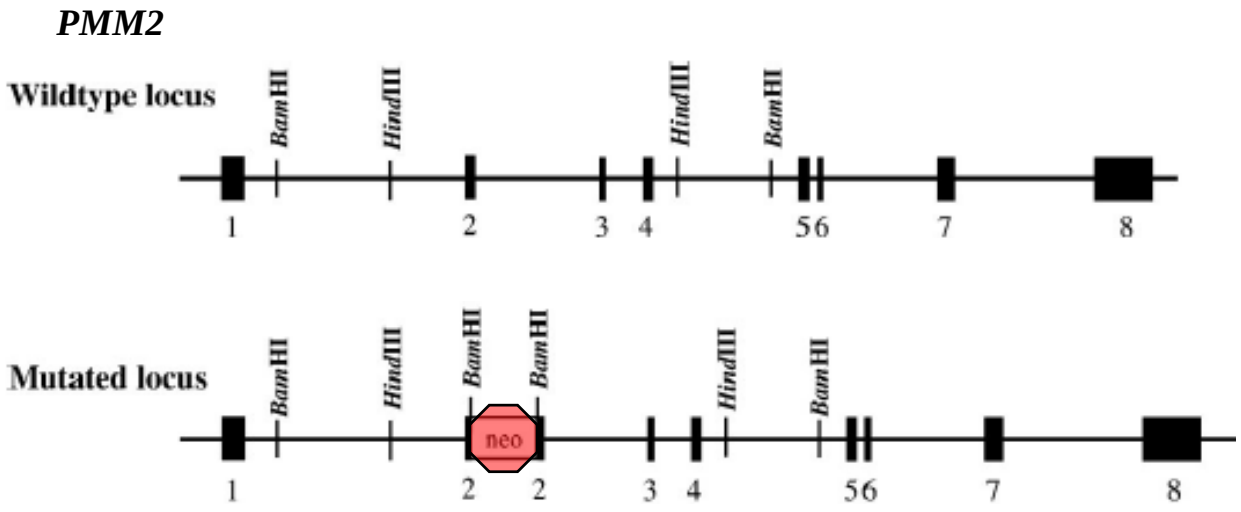
- Transgenic
- Knockin
- Knockout
- Conditional knockout



Current mouse models for PMM2-CDG

Knockout

- *PMM2* gene disruption
- Homozygous lethal around E2.5
- Functional glycosylation machinery is essential in early development

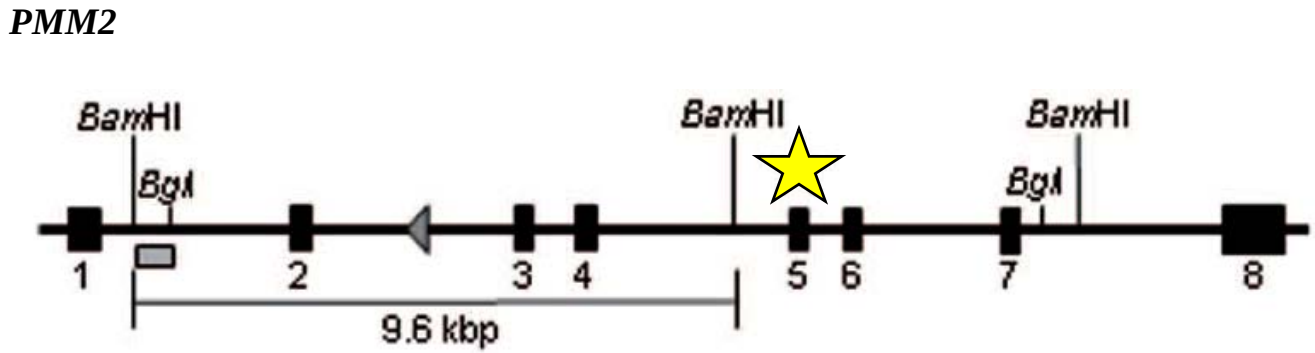


Thiel et al. 2006. Mol Cell Biol. 26:5615-20

Current mouse models for PMM2-CDG

Knockin #1 and #2

- #1 - R141H (R137H in mice)
  - Most common human mutation
- #2 - F122L (F118L in mice)
  - Synthetic predicted mild mutation
- *Pmm2*$^{R137H/R137H}$
  - Embryonic lethal before E5.5
- *Pmm2*$^{F118L/F118L}$
  - Viable, fertile, without major phenotypes
  - PMM2 enzyme activity ~ 40% WT

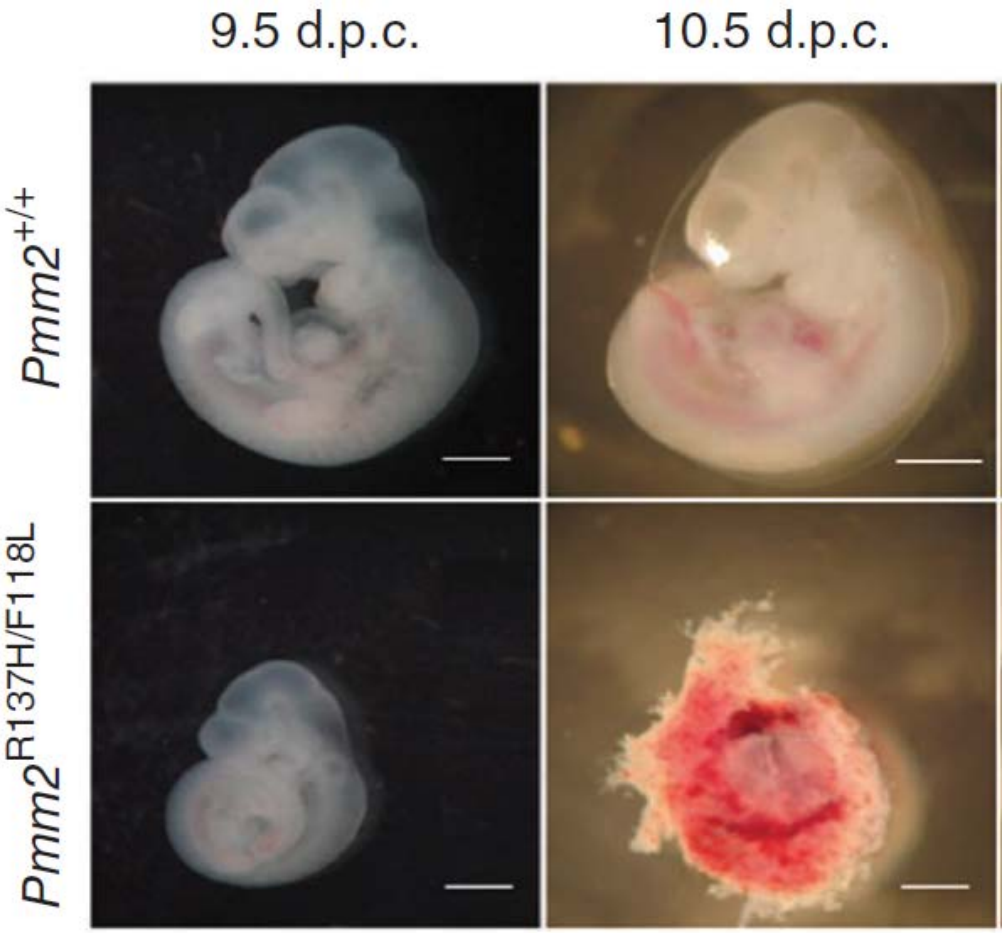


Schneider et al. 2011. Nat Med. 18:71-3

Current mouse models for PMM2-CDG

Knockin #1/#2

- *Pmm2*$^{R137H/F118}$
  - Embryonic lethal ~E9.5-E10.5
  - Small
  - Tissue degradation
  - PMM2 enzyme activity = 11% WT
  - Rescue with mannose to mothers

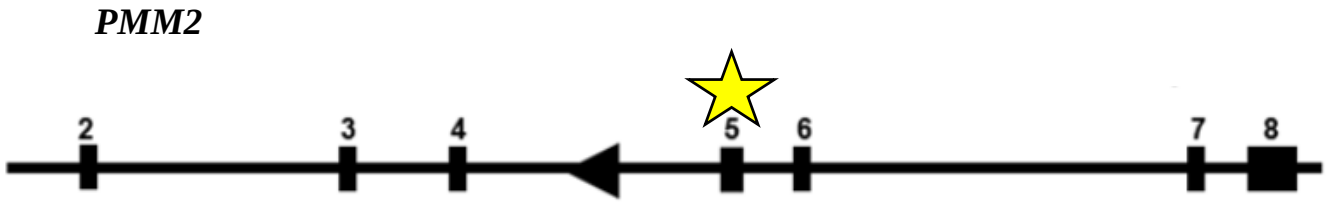


Schneider et al. 2011. Nat Med. 18:71-3

Current mouse models for PMM2-CDG

Knockin #3

- #3 - F119L (F115L in mice)
  - 2nd most common human mutation
- *Pmm2*$^{F115L/F115L}$
  - Embryonic lethal in more than ½
  - Rescue with mannose to mothers

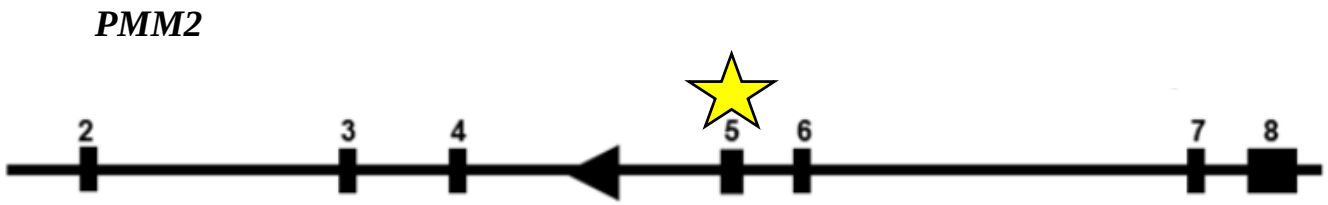


Chan et al. 2016. Hum Mol Genet. 25:2182-2193

Current mouse models for PMM2-CDG

Knockin #1/#3

- *Pmm2*$^{R137H/F115L}$
  - Most common human genotype
    - (R141H/F119L)
  - ½ embryonic lethal
  - No effect of mannose



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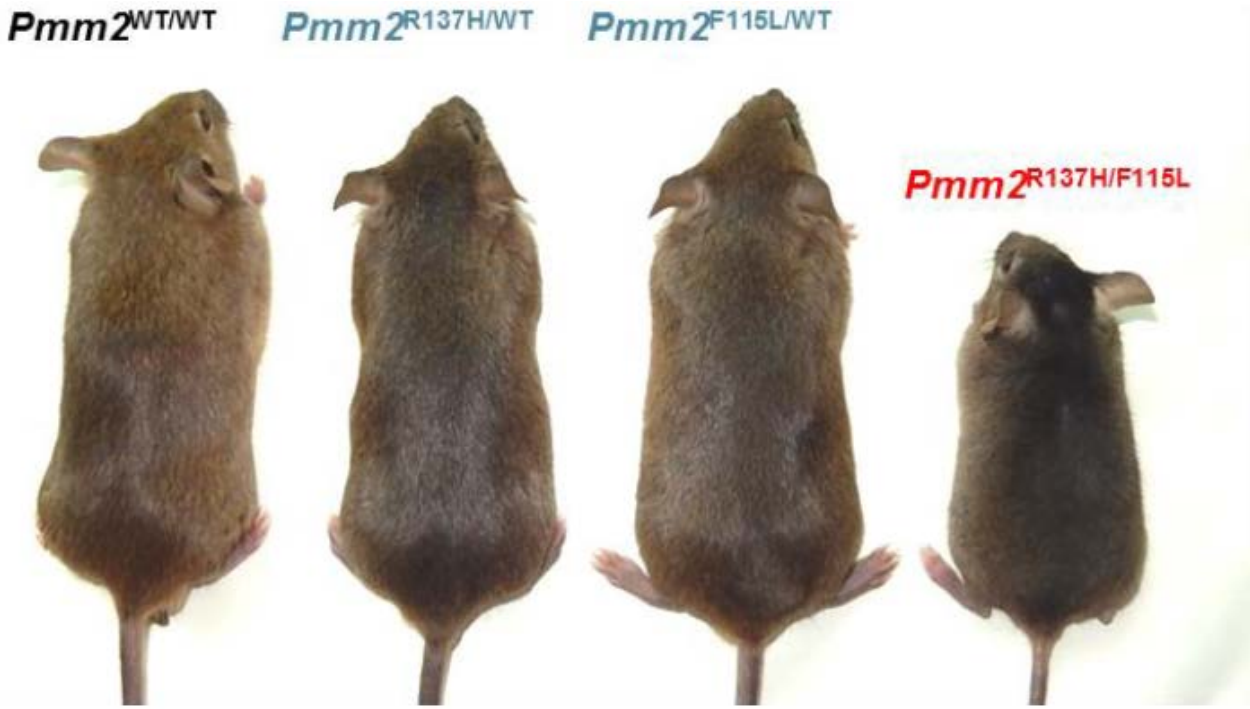
Current mouse models for PMM2-CDG

Knockin #1/#3

- *Pmm2*$^{R137H/F115L}$
  - ½ die by postnatal day 65
  - Small
  - Hypotonia in hind limbs (6%)
  - Curvature of the back (29%)
  - Heart, liver, kidney abnormalities
  - Decreased glycosylated plasma proteins
  - Normal plasma transferrin glycosylation
  - PMM2 enzyme activity = 15-16% WT
  - No histologic brain abnormalities



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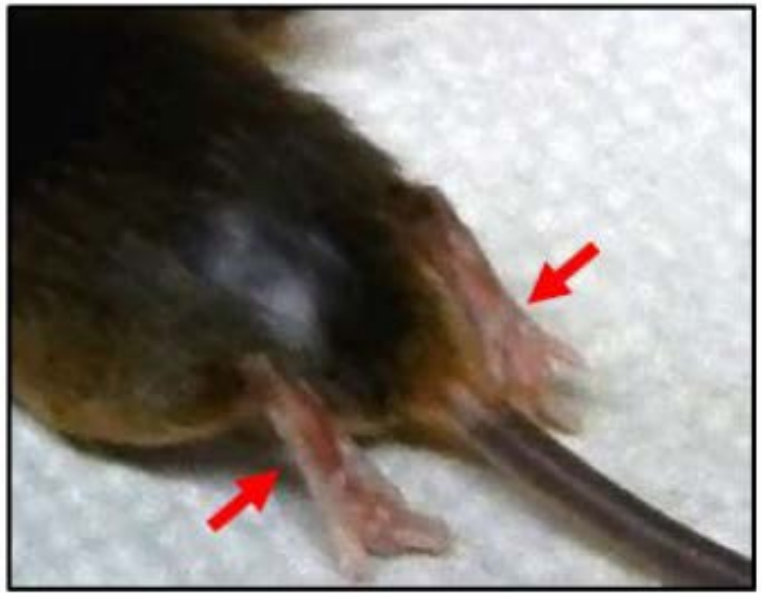

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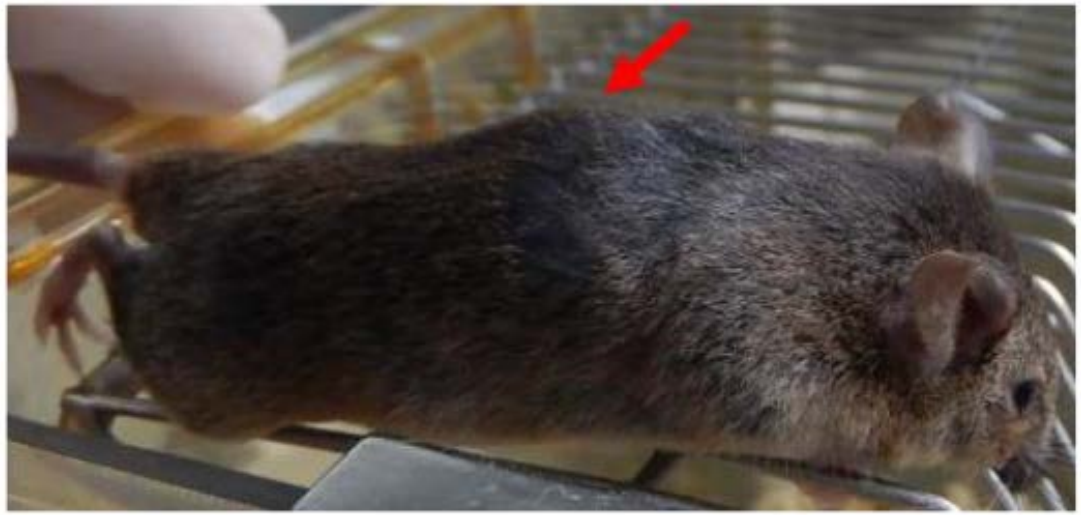


Chan et al. 2016. Hum Mol Genet. 25:2182-2193

Current mouse models for PMM2-CDG

Conclusions

- Range of phenotypes from early embryonic lethality to normal
- *Pmm2*$^{R137H/F115L}$
  - Most common patient genotype
  - Reproduces several human PMM2-CDG phenotypes
  - Available through Jackson Labs
  - Significant embryonic lethality
  - Significant postnatal lethality
  - No histologic brain phenotype

The Jackson Laboratory

B6.129S6-*Pmm2*$^{tm1.1Jins}$/J

Stock No: 031895 | Pmm2^{F115L}

Available

B6.129S6-*Pmm2*$^{tm2.1Jins}$/J

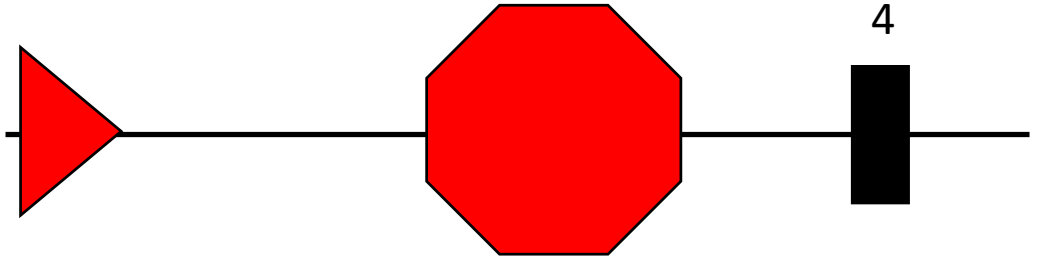
Stock No: 031897 | Pmm2^{R137H}

Available

New mouse model for PMM2-CDG

New mouse model for PMM2-CDG

- Conditional knockout allele
- Floxed *PMM2* exon 3
- Remove exon 3 with Cre



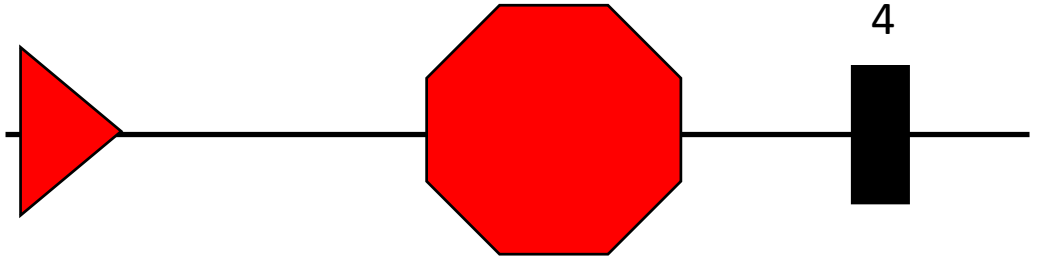
Pmm2$^{tm1c(EUCOMM)Wtsi}$

New mouse model for PMM2-CDG

- Conditional knockout allele
- Floxed *PMM2* exon 3
- Remove exon 3 with Cre
- IMPC validated embryonic lethal

IMPC

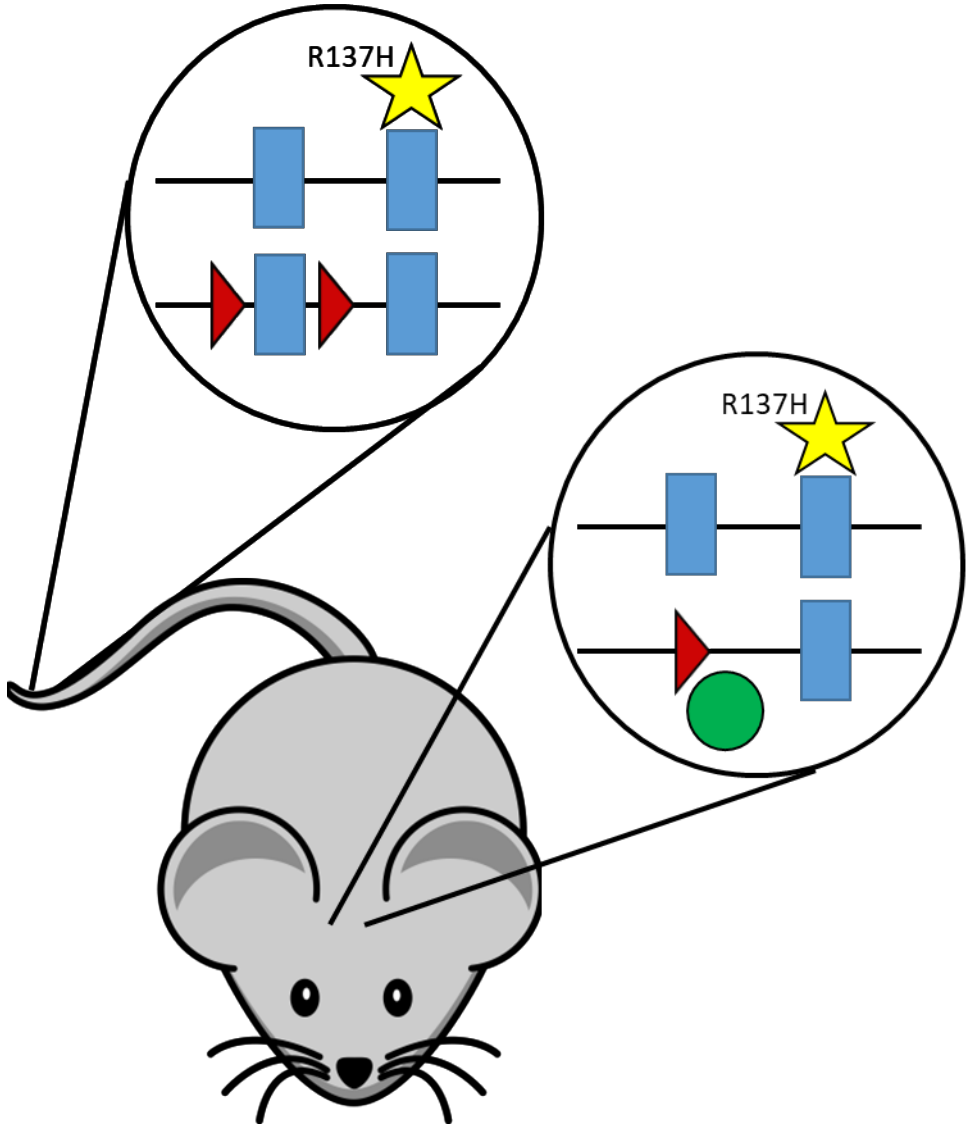
International Mouse Phenotyping Consortium



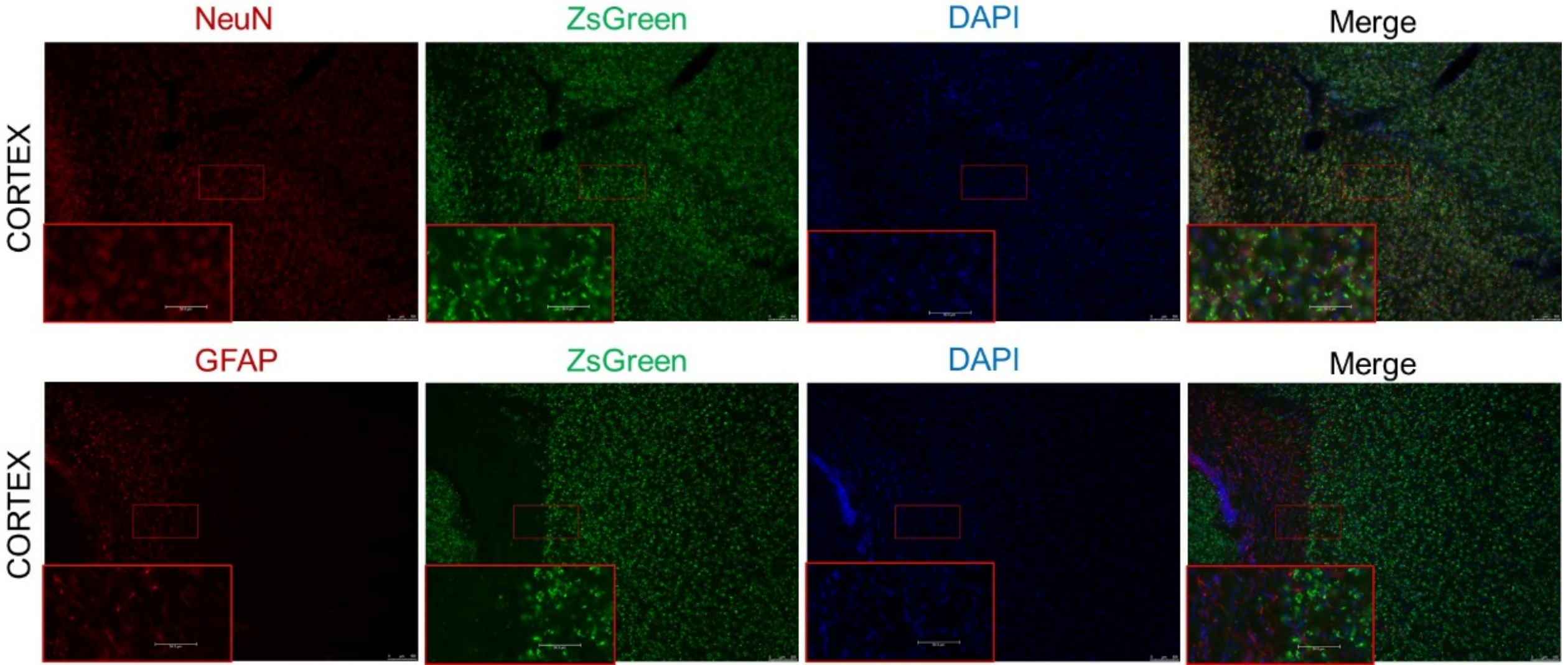
Pmm2$^{tm1c(EUCOMM)Wtsi}$

New mouse model for PMM2-CDG

- Generate conditional knockout/knockin mice
- Generate cell type-specific Pmm2 deficiency with Cre
- Avoid embryonic lethality
- Model severe Pmm2 deficiency in isolated cells/organs for pathophysiologic studies
- Neurologic phenotypes

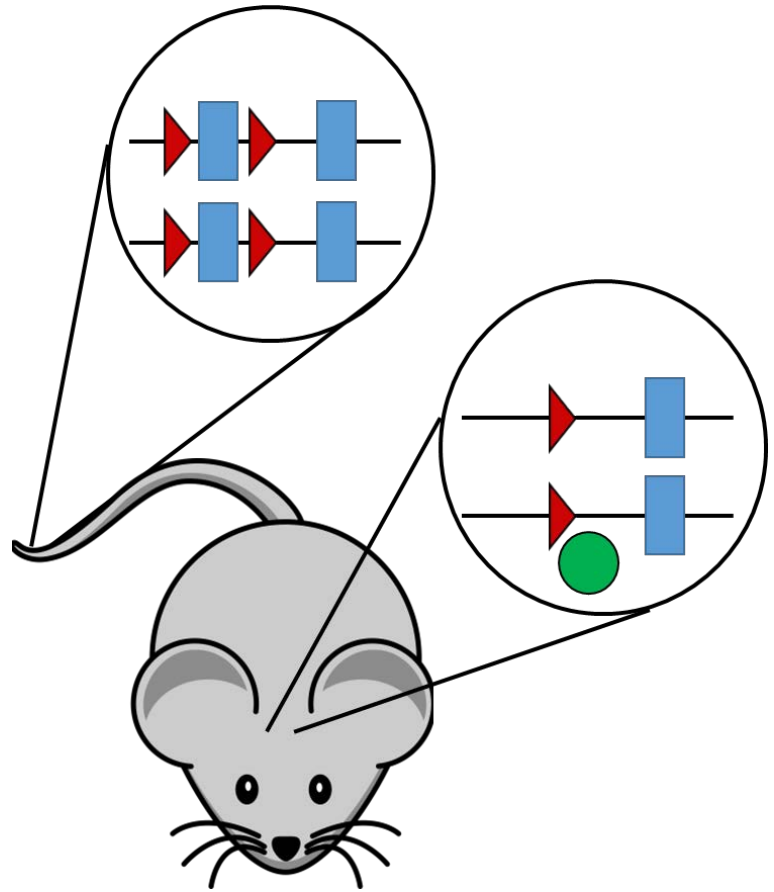


Cre-dependent ZsGreen characterization of *Snap25-IRES-Cre*



New mouse model for PMM2-CDG

- Currently breeding *Pmm2*$^{R137H/+}$, *Pmm2*$^{fl/fl}$ and *Snap25*$^{Cre/+}$ together
- *Pmm2*$^{fl/fl}$; *Snap25*$^{Cre/+}$ mouse



Acknowledgements

Contributors

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- Zhou Laboratory
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