KIF1A Mouse Models
Speaker: Dr. Cat Lutz, Ph.D., M.B.A., The Jackson Laboratory

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Visit kif1a.org/2019Conference to watch a recording of this presentation.
On the Way to a Rare-Disease Cure, Parents Tackle the High Price Tag of Research

“We need a mouse” campaign
Structure function of the protein

- Most of KIF1A mutations are identified in the motor domain resulting in a more severe phenotype.

- Current clinical variants identified in KIF1A can be classified into three category – autosomal recessive, de novo dominant, and familial dominant.

https://www.kif1a.org
Anterograde Axonal Transport

KIF1A is a kinesin-family motor involved in the axonal transport of synaptic vesicle precursors along microtubules.

Anterograde axonal transport supplies organelles and protein complexes throughout axonal processes to support neuronal morphology and function.
What are the mouse tools you need in your toolbox to match therapeutic strategies?

Need to understand the basic biology:

- What does a complete loss of function do in mouse?
- What do patient specific mutations look like in a mouse? Can you fix the wheel on a train?
- What if you can knock down the disease causing allele? how much do you have to knock it down? 10 or 90%?
- Can adding more Kif1a outcompete the dominant negative gene? Flood the track with good trains
- Is too much Kif1a a bad thing? Need to know--
Existing KIF1A mouse models

**KNOCK-OUT MOUSE**

- **Kif1a^tm1Noh**

  - Null mice were born alive but died within 24h because they did not suckle milk.
  - Show sever motor and sensory abnormalities
  - Reduced synaptic vesicles at synaptic terminals were observed.
  - Focal neuronal death were detected in brain.

- In short, mice to not tolerate loss of Kif1a

New efforts for KIF1A  
**preclinical models**

- **C57BL/6J-Kif1a<em2(I304I, P305L)Lutzy>**

  **Knock-in** strains. CRISPR/Cas9 mediated point mutations, I304I and P305L, are introduced to *Kif1a* gene

  - Body weight, neurological scores, strength, electrophysiology, etc

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**Survival**

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<th>Age (Days)</th>
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**Body Weight**

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**Hind limb suspension test:**

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This mutation is not well tolerated when all the trains on the track are stuck. But when half the trains are defective, we see subtle changes.
Existing KIF1A mouse models

**leg dragger (spontaneous from JAX)**

- JR#16894 strain has a spontaneous L181F missense mutation in Kif1a gene.
- Before 2 weeks old of age, HOM has similar body weight compared to their WT and HET littermates. At 3 weeks of age, HOM is smaller and lighter compared to their littermates with leg-dragging phenotype.
- Significant hind limb weakness is observed in HOM neonates as early as 9 days old of age.

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**Body Weight (g)**

- WT (n=3)
- HET (n=6)
- HOM (n=4)

**Latency to fall (sec)**

- WT (n=3)
- HET (n=6)
- HOM (n=4)
Neuromuscular junction (NMJ) staining in Kif1a leg-dragger model

Green: Presynaptic Vesicle
Red: postsynaptic neuromuscular junction
Additional efforts for KIF1A
preclinical models to answer therapeutic questions

- C57BL/6J-TG(CAG-Kif1a)
  - A mouse model to that expresses KIF1A in a constitutive manner
  - Allows us to genetically cross this mouse to other Kif1a models to answer the questions:
    1. Can overexpression rescue the Kif1a mouse?
    2. Is overexpression tolerated?

- C57BL/6J-TG(LSL-CAG-Kif1a)
  - This mouse model allows us “turn on” the Kif1a gene at any time in the life or disease course of the mouse
  - Allows us to genetically cross this mouse to other Kif1a models to answer the questions:
    3. Can we turn on the Kif1a gene later in life, and have a benefit?
Dear Yi-Ju and Cat,
From the bottom of our hearts, thank you. Thank you for your work, your presentation, for all you do. Thank you for being there with us, and thank you for loving Sus and so many kids like her. You guys mean the world to us. Here’s a picture from lunch!
Thanks so much!
Lutz Lab

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