

## Glutamate receptors as a potential therapeutic target for the treatment of INCL

Rozzy Finn  
 Laboratory of Dr. David Pearce  
 Sanford Children's Health Research Center  
 Sioux Falls, SD

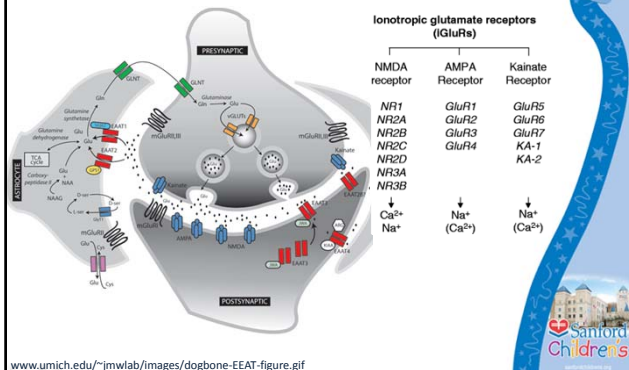


## Talk Outline

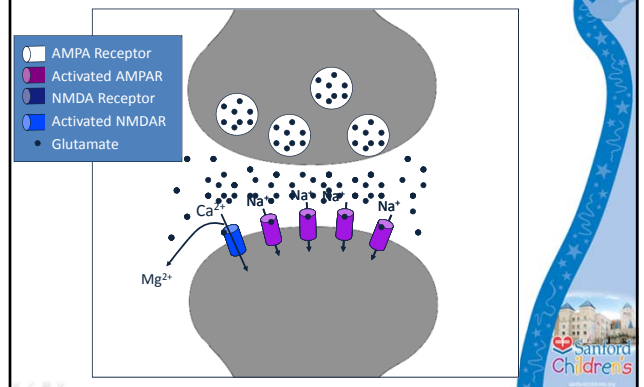
- Glutamate receptors
  - Function
  - Use in previous therapeutics
- Rationale for looking at glutamate receptors in INCL
- Experimental results of our investigation of glutamate receptor function in the *Cln1*<sup>-/-</sup> mouse
  - Cell culture via agonist treatments
  - Surface crosslinking in brain samples
- Implications for INCL therapeutics
- Future directions
  - Memantine, Dextromethorphan, Ketamine
  - AMPA/kine CX546



## Glutamate Receptors and the Glutamatergic synapse



## Glutamatergic Synapse Simplified



## Glutamate Receptor based therapeutics

- Dysfunction of the glutamatergic system has been implicated in numerous psychiatric disorders, such as Schizophrenia, Alzheimer's disease, depression, anxiety and attention-deficit hyperactivity disorder (ADHD)
- Memantine in AD



## Glutamate-mediated cell death

Linked to neurodegeneration in a number of diseases

In moderation, exposure to glutamate transduces excitatory messages.

In excess, exposure can induce death via over activation of receptors

Treating cells with an excess of glutamate receptor agonists also induces death in neurons

By measuring the extent of cell death that results from a treatment, we can gain information about glutamate receptor function

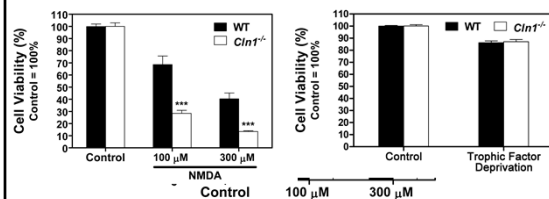


## Why Glutamate Receptors in INCL?

- Studies suggest there is a disruption in glutamatergic function in INCL
  - *Cln1<sup>-/-</sup>* neurons recover more efficiently from glutamate-induced calcium spikes (Ahtainen *et al.*, 2007)
  - Evidence of an imbalance in glutamatergic excitation and GABAergic inhibition in INCL patient autopsy samples (Sitter *et al.*, 2004)
  - PPT1 may protect neurons from KA-induced excitotoxicity in rats (Suopanki *et al.*, 2002)
  - motor coordination deficit (Griffey *et al.*, 2006; Macauley *et al.*, 2009).
    - Glutamatergic transmission within cerebellar granule cells drives motor coordination (Hashimoto *et al.*, 1999; Jensen *et al.*, 1999)
- Attenuation of AMPA receptor function in the *Cln3<sup>-/-</sup>* mouse improves motor coordination and lessens the disease phenotype (Kovacs and Pearce, 2008; Kovacs *et al.*, 2010)
- Based on this line of reasoning, we were drawn to investigate glutamate receptor function in the *Cln1<sup>-/-</sup>* mouse

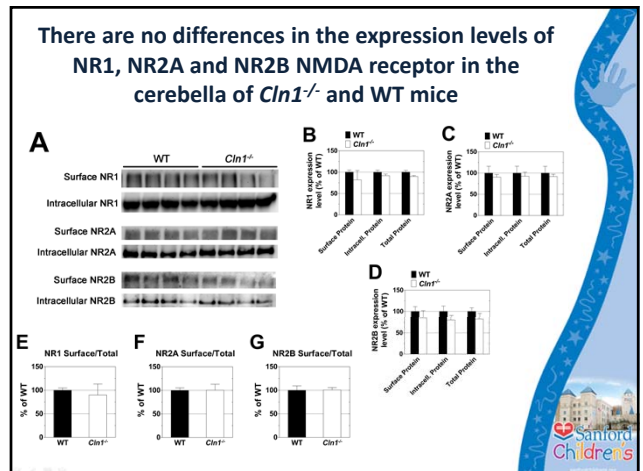
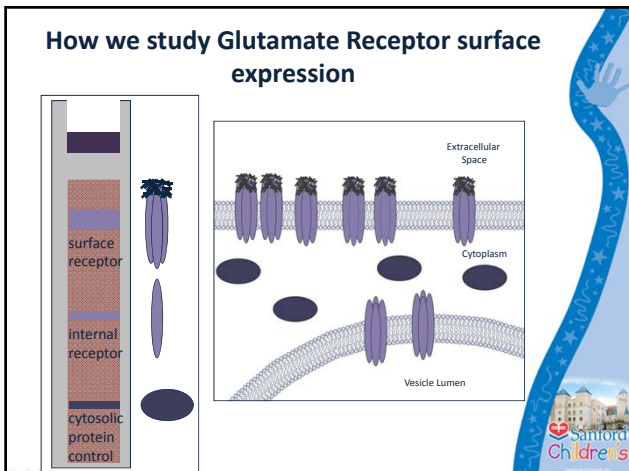
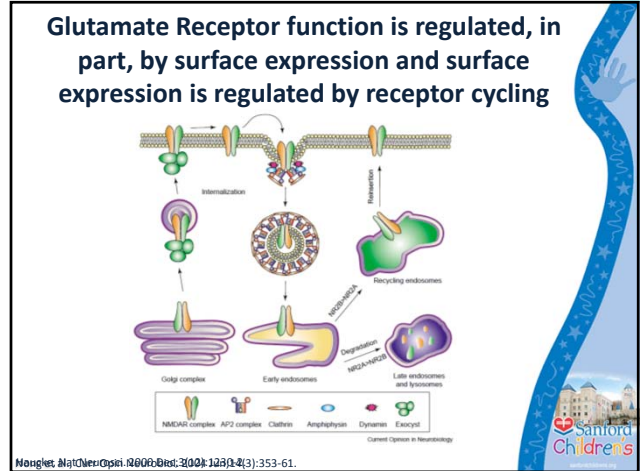
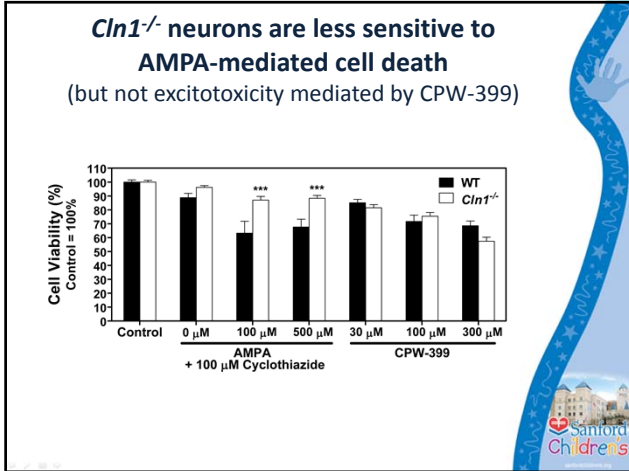


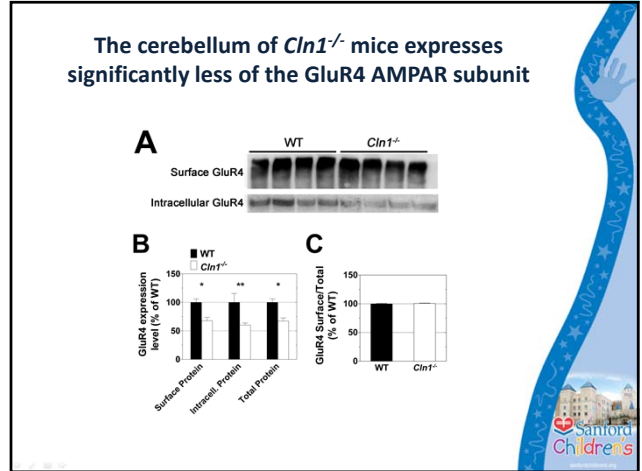
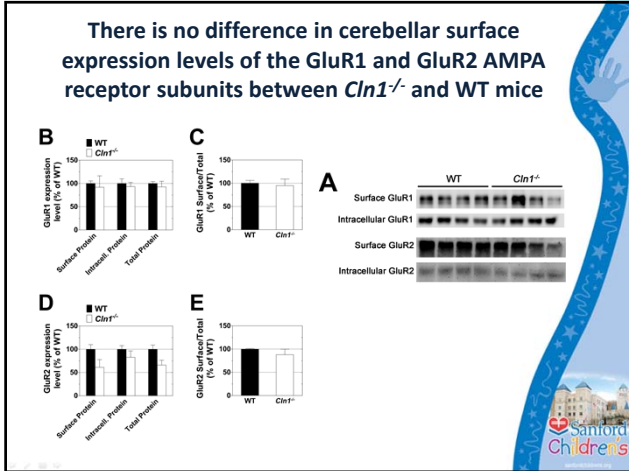
## *Cln1<sup>-/-</sup>* neurons are more sensitive to NMDA-mediated cell death.



This effect is specific to glutamate receptor overactivation







## Conclusions

- We have shown *Cln1*<sup>-/-</sup> cerebellar granule neurons are:
  - more sensitive to NMDA receptor-mediated cell death
    - Could be altered expression of NR2C and NR3 NMDA receptor subunits.
    - There are also a number of other ways that NMDA receptor function is regulated.
      - Posttranslational modification of receptor subunits, interacting proteins, spatial distribution of ion channels, etc
  - less sensitive to AMPA receptor-mediated toxicity
    - Could be mediated by the decrease in expression level of the GluR4 AMPA receptor subunit.
- Lack of PPT1 enzyme activity has a significant effect on glutamatergic function.

**This presents new therapeutic targets for INCL.**

## Future directions

- Treat mice with glutamate receptor targeting compounds already approved for use in humans
  - NMDAR antagonists
    - Memantine
    - Dextromethorphan
    - Ketamine
  - Positive allosteric modulator of AMPAR
    - Ampakine CX546
- After treatments examine rescue of motor coordination phenotype and extent of cell death

## Acknowledgements

Pearce Lab

**Dave Pearce**

**Attila Kovács**

Timothy Curran

Andrew Cardillo

This research was  
supported by Hayden's  
Hope Foundation

