Gene awakenings to treat Angelman syndrome

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Autism is increasing at an alarming rate...
UBE3A in Angelman syndrome and autism

• Deletions or mutations of the UBE3A gene cause Angelman syndrome
  • Prevalence of 1 in 15,000
  • High autism comorbidity

• Increased UBE3A gene dosage is a common cause of autism (Dup15q syndrome)
  • Prevalence of 1 in 68 (~3% of those caused by increased copies of 15q11-q13)
Angelman syndrome

- Frequent laughter/smiling
- Movement or balance disorder
- Severe developmental delay
- Severe speech impairment
- > 90% have seizures
- > 80% have rhythmic EEG patterns
- ~ 75% have sleep disorders
Drop seizures
Drop seizures
Delayed onset and impaired walking
Delayed onset and impaired walking
Genetic imprinting of *UBE3A* provides a treatment strategy.
**Ube3a-YFP** knockin mice can be used to assess *Ube3a* allelic expression.
A high-content and high-throughput imaging-based assay can measure *Ube3a* allelic activation.
A high-content and high-throughput imaging-based assay can measure \textit{Ube3a} allelic activation.
A topoisomerase inhibitor unsilences *Ube3a* in neurons

Huang, Allen et al., *Nature* 2011
Topoisomerase inhibitors unsilence *Ube3a* in neurons *in vitro*.

**Graph:**
- UBE3A-YFP levels
- EC$_{50}$: 54±1.2 nM

**Images:**
- Vehicle
- Topotecan

**Diagram:**
- Maternal
- Paternal
- UBE3A-YFP
- Inactive analog

**Table:**
- **Drug**
  - Topotecan
  - Irinotecan

**Log[DRUG], M**
- 1.0
- 1.5
- 2.0
- 2.5
Paternal allele of *Ube3a* can be unsilenced in neurons cultured from Angelman syndrome model mice.
Can topotecan unsilence paternal *Ube3a* in neurons *in vivo*?
Topotecan is effective \textit{in vivo}

- Infused hemisphere
- Non-infused hemisphere

![Diagram showing Topotecan concentration in infused and non-infused hemispheres](image-url)
Intrathecal injections to test drug efficacy *in vivo*
Why inject intrathecally?

- Topotecan used intrathecally in patients to treat brain cancer (possibly ideal route for treating patients with Angelman syndrome)

Schedule: 2x per week, for 6 weeks, then 1 or 2x monthly for 1 yr.
Intrathecal topoisomerase inhibitor delivery is effective

Intrathecal injections as described in Zylka et al., Neuron, 2008
Will topoisomerase inhibitors unsilence *UBE3A* in human neurons?
Topotecan can restore paternal *UBE3A* expression in Angelman syndrome patient iPSC-derived neurons
Silenced *Ube3a* Mutated *Ube3a*
Silenced Ube3a

Mutated Ube3a
Cautious optimism for the treatment of Angelman syndrome

- *Ube3a* can be unsilenced *in vivo*
- The unsilencing of *Ube3a* is long-lasting (at least in some cells)
- Topo. inhibitors unsilence *UBE3A* in Angelman syndrome patient-derived cells
- These or similar compounds are candidates for the treatment of Angelman syndrome
- Multiple approaches for unsilencing the paternal *UBE3A* allele now exist
- Need to improve treatments and to develop biomarkers in Angelman syndrome
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