Repurposing guaiacol for the treatment of adult polyglucosan body disease (APBD)

Orhan Akman
Dept of Neurology
Columbia University

Or Kakhlon
Dept of Neurology
Hadassah University Hospital

Wyatt Yue
Structural Genomics Consortium (SGC)
University of Oxford
APBD – an ultra-rare glycogen storage disease

- Autosomal recessive disease
- Mutations on glycogen branching enzyme gene GBE1
  - prevalent mutation p.Y329S
  - Increased incidence in Ashkenazi Jewish population
  - adult onset
- Polyglucosan in nerves and brain MRI
Multi-disciplinary team brought together by patient group

- Characterization of the disease
- Small molecule screening
- Translating proof-of-concept to therapy
HTS identified guaiacol as candidate

reduces polyglucosan formation in dose-response manner

inhibits activity of recombinant & lysate GYS

causes hyper-phosphorylation of GYS

active site docking of guaiacol on GYS model
Guaiacol behaves as GYS inhibitor in APBD mice

Prevents polyglucosan accumulation in liver

Reduced glucose tolerance

Increased life span to wild type levels
Conclusion

• Guaiacol was discovered by HTS assays:
  - reduce polyglucosan in mouse model and patient-derived cells
  - inhibit GYS activity moderately *in vitro* and *in vivo*
  - restrain polyglucosan accumulation in the liver and extend life span in an APBD mouse model

• These data and the lack of side effects in the animal warrant clinical trials with Guaiacol.
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