



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

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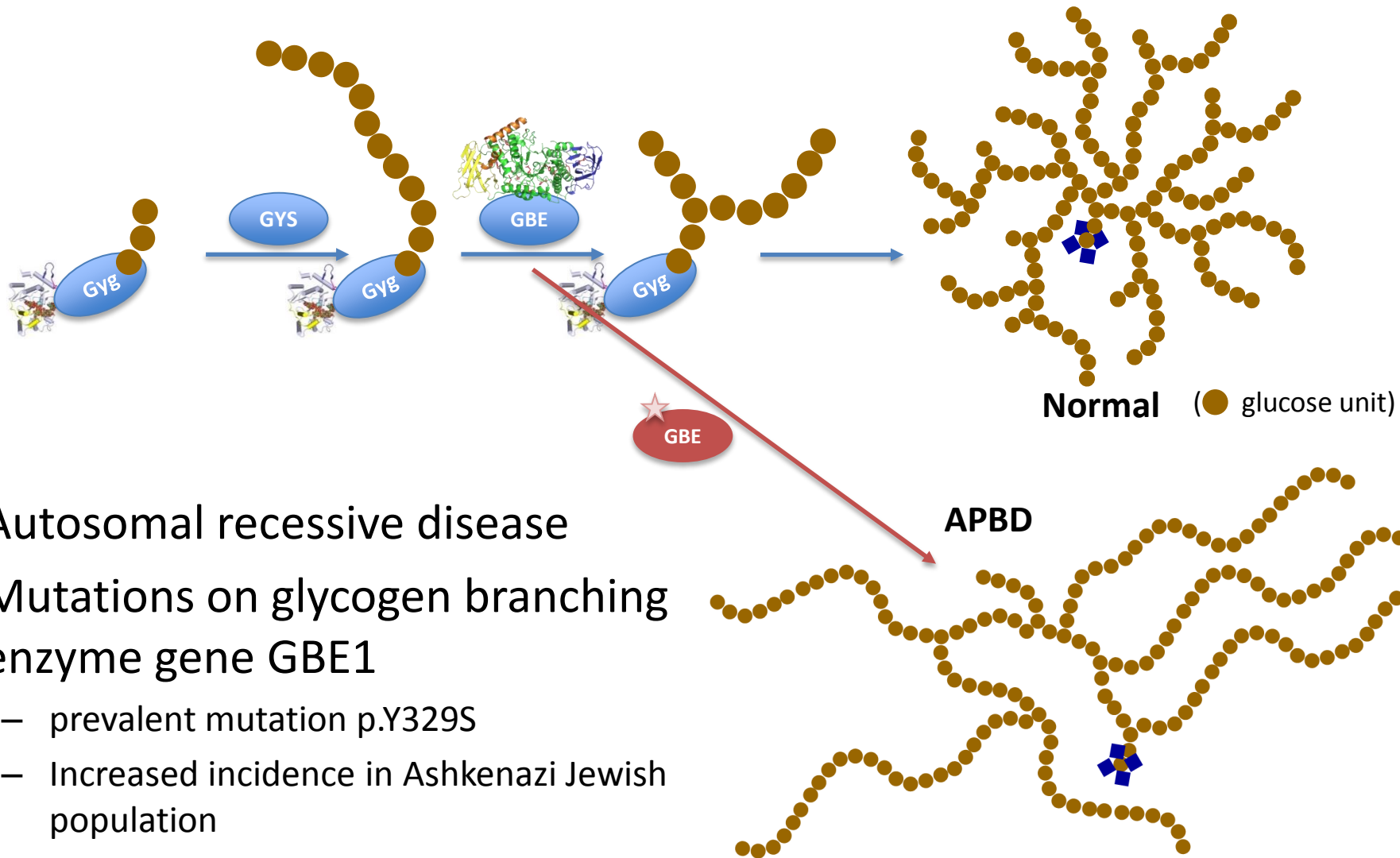


Wyatt Yue

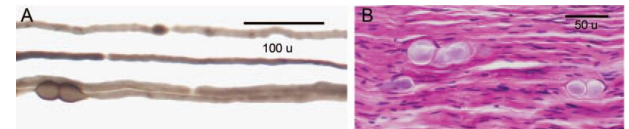
*Structural Genomics
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University of Oxford*



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

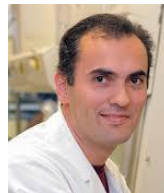


APBDRF
ADULT POLYGLUCOSAN BODY DISEASE RESEARCH FOUNDATION

 **Hadassah Medical Center**
Or Kakhlon



**COLUMBIA UNIVERSITY
MEDICAL CENTER**
Orhan Akman



SGC



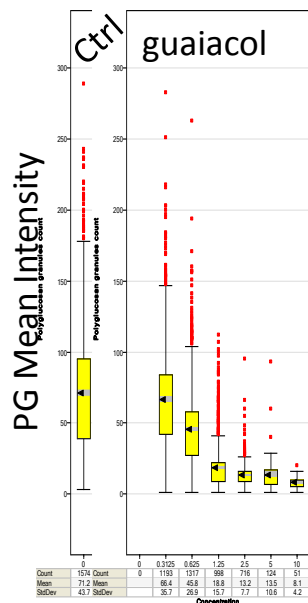
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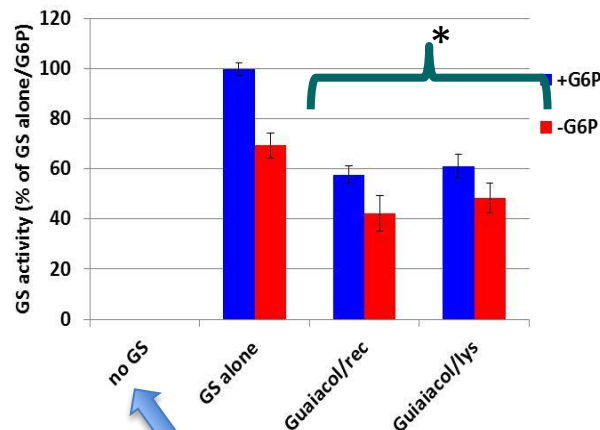
- Characterization of the disease
- Small molecule screening
- Translating proof-of-concept to therapy

HTS identified guaiacol as candidate

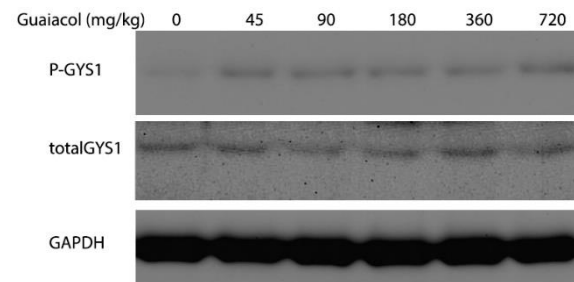
reduces polyglucosan formation in dose-response manner



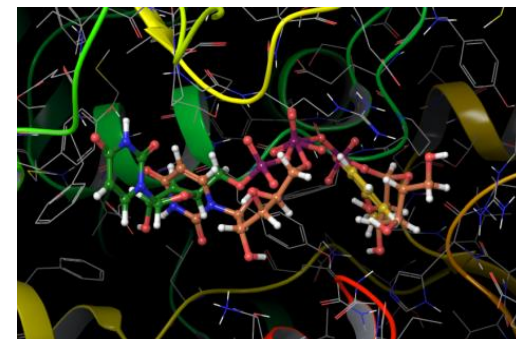
inhibits activity of recombinant & lysate GYS



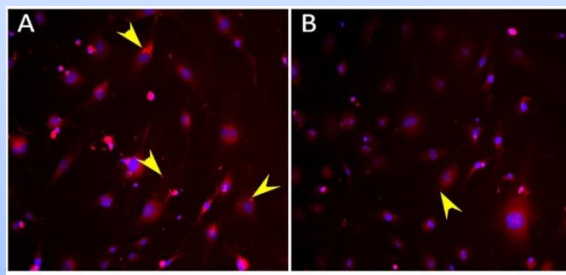
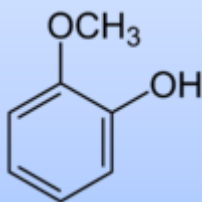
causes hyper-phosphorylation of GYS



active site docking of guaiacol on GYS model

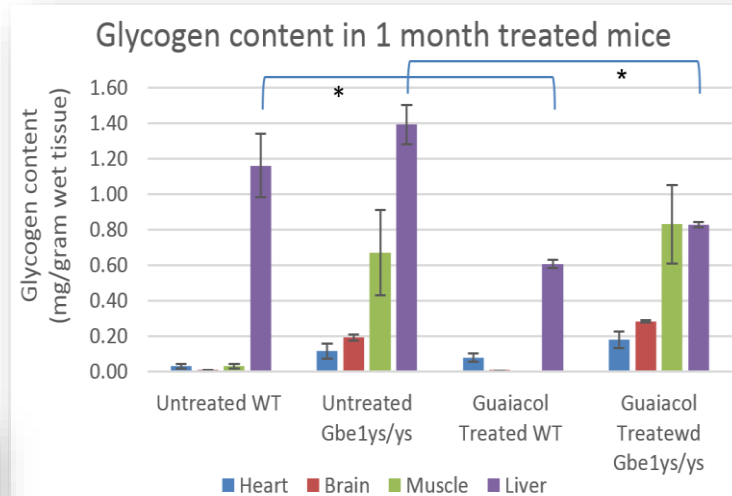


HTS on APBD mouse model of the LOC library (1700 cpds)

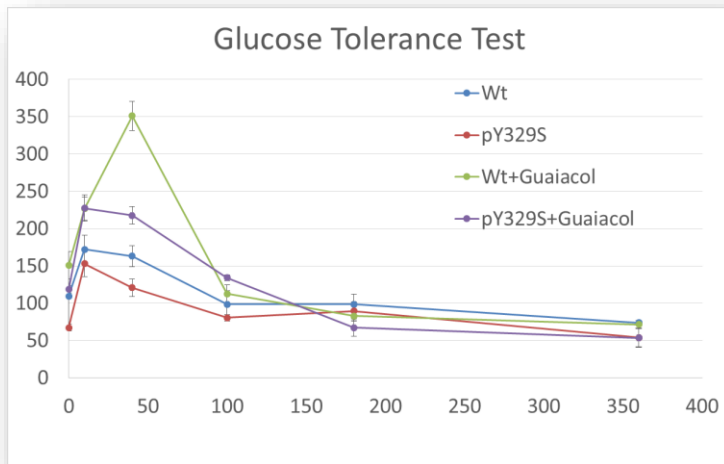


Guaiacol behaves as GYS inhibitor in APBD mice

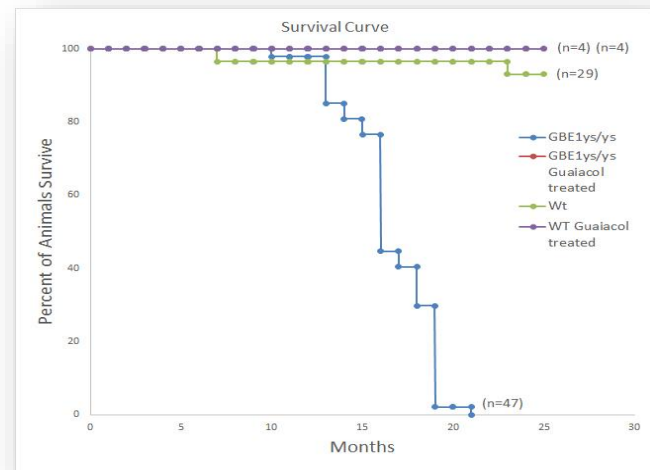
Prevents polyglucosan accumulation in liver



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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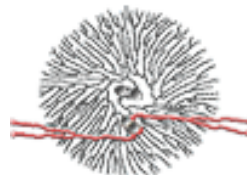
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