An *in vivo* small molecule screen to identify therapeutics for NGLY1 deficiency

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Introduction

-NGLY1 deficiency is caused by loss-of-function mutations in the gene *NGLY1*
-Chracterized by developmental delay, elevated liver transaminases, intellectual disability, seizures, and alacrima
-NGLY1 deficiency is a rare disease, and approximately 60 patients have been identified since 2012
-There is no treatment developed specifically for NGLY1 deficiency, and current treatment options are limited

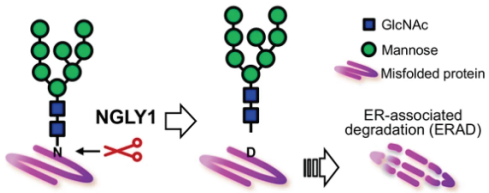

Figure 1. The enzyme NGLY1 is a deglycosylase that removes N-glycans from substrate proteins (Zhang and Hagen, 2017).

Methods

-We used a *dNGLY1*-KO fly model (Rodriguez et al., 2018) to screen for compounds that may serve as therapeutics for NGLY1 deficiency
-*dNGLY1*-KO flies are viable through late pupal stages, however adult flies never eclose
-Therefore, we selected adult lethality as the phenotype for our drug screen

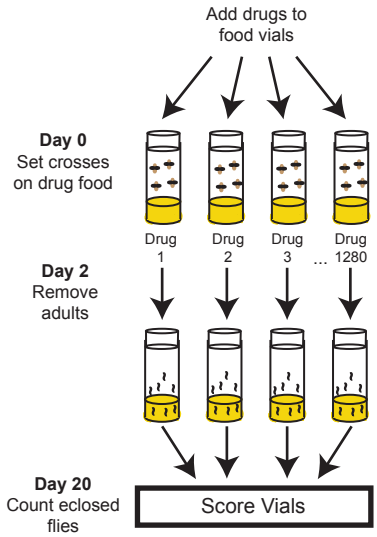

Figure 2. Screening strategy to identify compounds that rescue lethality in *dNGLY1*-KO flies.

Results

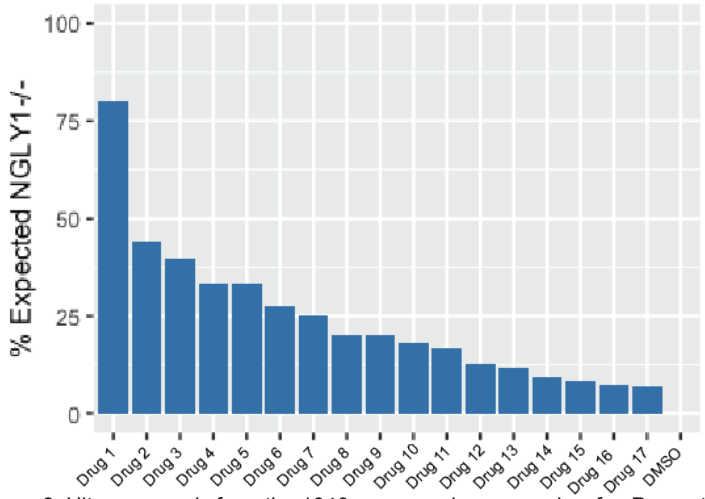

Figure 3. Hit compounds from the 1040 compounds screened so far. Percent expected *dNGLY1*-KO was calculated from each cross based on the number of heterozygous *dNGLY1*-/+ flies that emerged from each cross using the marked balancer chromosome *CyO*.

-Primary screening from 1040 of the 1280 compound library has been completed
-We identified 17 hit compounds (1.6% hit rate) that rescued lethality in *dNGLY1*-KO flies
-In addition, four compounds were lethal to heterozygous *dNGLY1* deficient flies, suggesting these compounds may be contraindicated for NGLY1 deficient individuals or carriers

Discussion

-We identified 17 compounds that may serve as potential therapeutics for NGLY1 deficiency
  -However, further experiments are necessary to confirm hits and to identify the optimal dose
-Hit compounds fell into 5 categories, and we observed multiple hits in the serotonin and dopamine signaling pathways
-By taking a drug repurposing approach, we have identified compounds that are already approved by the FDA in order to quickly translate our findings into the clinic

References and Funding

Rodriguez, T. P., Mast, J. D., Hartl, T., Lee, T., Sand, P., & Perlstein, E. O. (2018). Defects in the neuroendocrine axis contribute to global development delay in a Drosophila model of NGLY1 Deficiency. G3: Genes, Genomes, Genetics, 8(7), 2193-2204.

Zhang, L., & Ten Hagen, K. G. (2017). Signaling: Enzymatic insights into an inherited

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