Classic Galactosemia (CG) is characterized by the inability to metabolize the monosaccharide galactose, prompting a buildup of galactose in the bloodstream [1]. Galactosemia is caused by a variety of loss of function mutations in the *GALT* gene, which encodes a galactose-1-phosphate uridylyltransferase, the second enzyme in the Leloir pathway [1]. Phenotypes of galactosemia are manifested in a wide variety of symptoms, including kidney failure, liver damage, cataracts, abnormal bleeding, jaundice, failure to thrive, and intellectual disabilities [2]. Galactosemia can be managed by excluding exogenous sources of galactose (diet), however, in females, 87% displayed premature ovarian insufficiency, even when put on a galactose restricted diet from birth [2]. Furthermore, known biochemical markers of galactosemia, namely elevated levels of erythrocyte galactose-1-phosphate and urinary galactitol, do not correlate with the long term outcome of premature ovarian insufficiency [3]. Evidence shows that endogenous galactose-1-phosphate levels can reach 1.0-2.0 g/day [4], however, the role of endogenous galactose-1-phosphate in long term outcome is unkown. *Further, it is unknown how perturbations in galactose metabolism caused by GALT deficiency cause disease phenotypes to arise, even when galactose is eliminated from the diet.*

My **primary goal** is elucidating the broader role of *GALT* outside its well known role in galactose catabolism. I will use both the common mouse (*Mus musculus*) and *Saccharomyces cerevisiae* as model systems, due to similar disease phenotypes to humans and high throughput phenotyping, respectively.

Aim 1: Identity conserved amino acids in *GALT* that are crucial to enzymatic activity and function. **Approach**: I will align the amino acid sequences of human disease variants to the wild type sequence to identify amino acids that are critical to function. I will then characterize the phenotypes of these variants via growth of *S. cerevisiae* in galactose expressing these human *GALT* gene sequences. **Hypothesis**: Most common human disease variants will result reduced growth rates in *S. cerevisiae*, while some disease variants will not cause a change in growth on galactose. **Rationale**: Identifying human *GALT* disease variants which do not alter galactose catabolism, may help identify residues which are involved in the broader function of *GALT*.

**References**:

1. Isselbacher KJ, Anderson EP, Kurahashi K, Kalckar HM (1956). "Congenital Galactosemia, a single enzymatic block in galactose metabolism". Science. 13 (123): 635–6. doi:10.1126/science.123.3198.635

2. Guerrero NV, Singh RH, Manatunga A, Berry GT, Steiner RD, Elsas LJ. Risk factors for premature ovarian failure in females with galactosemia. J Pediatr. 2000;137:833–41.

3. Berry GT., 2014. Classic Galactosemia and Clinical Variant Galactosemia. Retrived from: <https://www.ncbi.nlm.nih.gov/books/NBK1518/>

4. Berry GT, Moate PJ, Reynolds RA, Yager CT, Ning C, Boston RC, Segal S. The rate of de novo galactose synthesis in patients with galactose-1-phosphate uridyltransferase deficiency. Mol Genet Metab. 2004;81:22–30.