Classic Galactosemia 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 galactose from the diet, however, many symptoms of Galactosemia still surface later in life. In fact, nearly 87% of female Galactosemia sufferers displayed premature ovarian insufficiency, despite following 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. Evidence shows that internal galactose-1-phosphate levels can reach 1.0-2.0 g/day [4], however, the role of this endogenous galactose-1-phosphate in long term outcome is unknown. *Further, it is unknown how perturbations in carbon metabolism caused by GALT deficiency cause disease phenotypes to arise despite elimination of galactose from the diet.*

My **primary goal** is elucidating the broader role of *GALT* outside its well-known role in galactose catabolism.

My **hypothesis** is that previously overlooked metabolic roles of *GALT*, including glycosylation, play a central role in the pathology of Classic Galactosemia. I will use both the common mouse (*Mus musculus*) and *Saccharomyces cerevisiae* as model systems, due to their similar disease phenotypes to humans and ease of rapid analysis, respectively.

**Aim 1**: Characterize the functionality of Human *GALT* disease variants in the yeast, *Saccharomyces cerevisiae*.

**Approach**: I will use CRISPR/CAS9 to replace the *S. cerevisiae* *GALT* gene with Human disease variants. I will then characterize the functionality of each of these disease variants by assaying the growth of *S. cerevisiae* in galactose. **Hypothesis**: Human disease variants in which the active site is mutated will completed disrupt growth, while disease variants that are mutated elsewhere will result in a functional protein and will observe normal growth. **Rationale**: Identifying the human *GALT* disease variants which do not alter galactose catabolism, may help identify residues that are involved in the broader function of *GALT*.

**Aim 2**:Characterize genes that are deferentially regulated when *GALT* is deleted.

**Approach**: I will perform RNA-seq on the ovaries of adult wild type and *GALT* deficient mice that have been fed a galactose free diet from birth. **Hypothesis**: Deficiency in *GALT* will result in aberrant glycosylation and metabolic dysregulation, which will lead to changes in the regulation of numerous genes. **Rationale**: Genes that are deferentially regulated in the absence of *GALT* are possible targets for identifying novel pathways and processes in which *GALT* may be involved in and thus helps elucidate the pathology of Galactosemia.

**References**:

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