Galactosemia Foundation
Linked for Life.

Toward Improved Long-term Outcome in Classic Galactosemia

Dr. Judith L. Fridovich-Keil

Despite neonatal or even pre-natal diagnosis and rigorous life-long dietary restriction of galactose many children and adults with classic galactosemia grow to experience a constellation of significant long-term complications; current intervention is inadequate to prevent these problems. Here we propose a new approach to intervention that follows from data we published recently using a fruit fly model for classic galactosemia, and also from preliminary studies described here using patient fibroblasts and blood samples. The strength of this new approach derives both from the data on which it is based, and also from the idea that it shortcuts the drug discovery process by proposing to "re-purpose" existing drugs or nutritional supplements that are already used safely in humans.

The first Aim described here proposes to identify genes and biological pathways that are expressed differently in patients with mild vs. severe long-term outcomes by comparing gene expression patterns in samples of blood from these two groups. In a pilot study of RNAs isolated from four blood samples representing pairs of patients with mild vs. severe long-term outcomes, the biological pathway expressed most differently between the patient pairs was oxidative stress response – exactly the same pathway expressed most differently between control and affected animals in our fruit fly model of classic galactosemia. Following replication and extension of this result with larger sample sets we propose to screen existing databases to identify known drugs and nutritional supplements predicted to counter the gene expression or functional changes associated with severe long-term outcome in patients.

The second Aim described here involves testing the impact of drugs or nutritional supplements predicted from Aim 1 to counter the gene expression or functional changes correlated with severe outcome in patient samples. Considering our preliminary data, the first compounds we will test will be known antioxidants and supplements that counter mitochondrial dysfunction, e.g. vitamin C, creatine, taurine, nicotinamide, and ubiquinone. We will test these and other promising drugs or supplements for impact on biomarkers in patient derived induced pluripotent stem cells in culture, and for impact on a long-term movement outcome in the fruit fly whole animal model of classic galactosemia. These experiments will lay the groundwork for future studies ultimately bringing the most promising drugs or supplements to clinical trial in patients.