This summer, I worked in the Baker/Wilstermann lab on the Rare Disease Project, discovering the role of the protein BCS1L in mitochondrial rare diseases. BCS1L is a protein in the mitochondrial membrane that helps assemble the Rieske Fe/S subunit onto complex III, leading to fully assembled and functional Complex III, which is essential for the electron transport chain. When BCS1L acquires mutations, it causes four different rare diseases: Bjornstad Syndrome, Complex III Deficiency, GRACILE Syndrome, and Leigh Syndrome. These diseases have very DIFFERENT phenotypes; for example, Bjornstad manifests as weirdly-textured hair and sensorineural hearing-loss where GRACILE causes metabolism complications, growth retardation, and early death. Our lab was trying to connect the phenotypes and genotypes biochemically in order to predict what manifestations and at what severity a certain mutation would cause.

We decided to use yeast to study these mutations because their mitochondria are good models for humans. Yeast are also good at doing homologous recombination, which allowed us to replace their BCS1 gene with the human BCS1L gene (allowing normal expression of the gene to occur) using a technique called “delitto perfetto”. “Delitto perfetto” (Italian for “the perfect murder””) is a two-step process: replacement of the yeast BCS1 gene with the CORE plasmid - an intermediate piece of DNA that serves as a marker and a placement holder – and the replacement of the CORE plasmid with the human BCS1L gene. We confirmed the insertion of the CORE through replica plating – whether or not yeast grew on specific media – and PCR analysis. We tried to integrate the human BCS1L gene into our CORE yeast, but our DNA was contaminated, helping us integrate the gene into bacteria instead of yeast. We are currently redoing the integration of the human BCS1L and have successful integrated a mutated form of the human BCS1L gene.

Additionally, this summer, we did a lot of literature review. I read all the published case studies of BCS1L diseases and created a spreadsheet listing the genotype and the phenotypes associated with them. As I reviewed the studies, I realized there was a lot of overlap between the diseases definitions and diagnoses so I optimized the disease diagnoses by pulling their respective symptoms from three databases. Then, I rediagnosed each case according to the optimized disease definitions. This allows us to map each mutation onto the structure of BCS1L (created by Professor Baker) and will hopefully show us where the mutations impact the protein (i.e. assembly of the hexamer BCS1L, function of BCS1L, etc.).

The literature review allowed us to choose homozygous mutations to integrate into our yeast. I have made all the mutants; we will sequence them soon. Hopefully, we discover which regions correlate to structure and function and then can make predictions on what happens when we make mutations to the region. Finally, we will make new mutations to test our predictions. This research goes all the way to the patients; our research may empower patients to say, “I have _____ mutation. Based on what this region of the gene codes for, my life will look like ______.” This motivates me on days that are slow and tedious, as I have a reminder that my research is directly benefitting underrepresented people.

I have truly been changed by this summer’s research. I tend to be a perfectionist and hate making mistakes. However, research has humbled me, reminding me that God is the only perfect one, and He is the perfect creator of all things. God has also given me the opportunity to meet some wonderful professors, mentors, and fellow students, allowing me to thrive in the great research community that we have at Calvin.