**Specific Aims Draft #1**

Emberger Syndrome (ES) is a rare autosomal dominant disorder with incomplete penetrance. It is characterized by the co-occurrence of primary lymphedema with a predisposition to acute myeloid leukemia (AML). Common symptoms include widespread cutaneous warts, sensorineural deafness, and minor physical anomalies. While there are multiple treatments to help improve the lives of patients with ES, a cure has yet to be discovered. Various nonsense and frameshift mutations that affect the function of the GATA2 gene and result in haploinsufficiency are known to be the cause of Emberger Syndrome. GATA2 encodes for the *GATA2* protein, which belongs to a family of six transcription factors and is crucial to the development and function of hematopoietic stem and progenitor cells. *GATA2* is known to interact with numerous other proteins, including CEBPA. A cluster of mutations in CEBPA leads to a high risk of developing AML. *The molecular and cellular mechanisms responsible for the variable phenotypic expression of ES are not yet fully understood*.

***The long-term goal*** of our research is to understand the pathophysiological processes underlying Emberger Syndrome and GATA2 deficiency. In order to do that, we must first understand the complete role of GATA2 and its interactions with other proteins. **Here we will test the hypothesis that mutations that arise in GATA2 restrict interaction with CEBPA, resulting in an abnormal function of CEBPA and a higher risk for ES.** CEBPA encodes for the protein *CEBPA,* which is a transcription factor that acts as a tumor suppressor involved in the regulation of blood cell production in the bone marrow. It is believed that this regulation is disrupted, leading to the uncontrolled production of abnormal cells seen in AML. To test our hypothesis, we will pursue the following aims:

**Specific Aim 1:** To characterize expression of CEBPs (focusing on CEBPA) in patients with Emberger Syndrome and compare it to expression levels of non-affected patients.

**Approach:** We are able to use microarray to determine expression levels and can then compare these expression levels between different samples.

**Specific Aim 2:** To look for correlation between different GATA2 mutations and CEBP expression levels.

**Approach:** We are able to use the CRISPR/Cas9 system to introduce various mutations in the GATA2 gene. Controlling which mutations to insert will allow us to determine if specific GATA2 gene mutations have any effect on CEBPA gene function.

Determining if (and how) specific GATA2 mutations affect CEBPA gene function could provide an answer as to why patients suffering from Emberger Syndrome are more likely to develop acute myeloid leukemia. This would allow for more confident genetic screenings to confirm the presence of ES, which would maximize opportunities for enhancing the lives of patients.