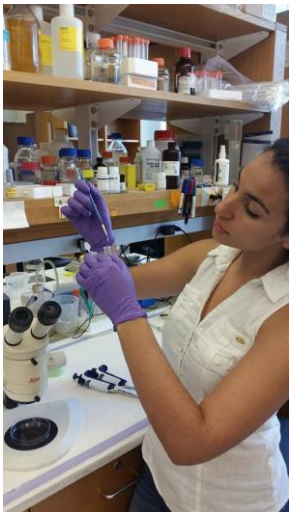

The Effects of NANCI lncRNA on Nkx2.1 Expression
Isis Cendan (COL 2017)
Advisor: Stewart Anderson

Brain-lung-thyroid syndrome (BLT) is a rare disorder that affects the three aforementioned organs causing congenital hypothyroidism, respiratory distress syndrome and benign hereditary chorea. It was understood that BLT resulted from a mutation in one of the two Nkx2.1 genes. However, a clinical study observed that a BLT patient had both Nkx2. 1 genes intact. After further study, they noticed, a deletion of a region adjacent to Nkx2.1; something else seemed to be affecting Nkx2.1, indirectly resulting in BLT. The project I participated in studied the effects of NANCI, a long noncoding RNA adjacent to Nkx2.1, which is thought to affect Nkx2.1 gene function. A long noncoding RNA is a strand of RNA that is not translated to protein.

We hypothesize that NANCI regulates Nkx2.1 through a DNA looping mechanism. 50 kilobases upstream of the Nkx2.1 gene is are Gli binding sites that have been known to regulate the expression of Nkx2.1. Nonetheless, the Gli binding site seems to be too far from Nkx2.1 to accomplish this regulation on its own. Therefore, NANCI might be facilitating and stabilizing a DNA loop, which would bring the Gli binding site near the Nkx2.1 gene, allowing Gli to regulate Nkx2.1.

In addition, Nanci and Nkx2.1 are both expressed in the medial ganglionic eminence (MGE), the caudate putamen and the hypothalamus of the brain. An impressive trait of the MGE is that 50-60% of cortical interneurons are born in this structure and eventually migrate to the striatum and the cortex as a result of Nkx2.1 expression. Therefore, we believe that NANCI regulates the expression of Nkx2. 1 levels, affecting cortical interneuron specification and/or migration, how it travels to the striatum and the cortex.

Our findings show that the deletion of both NANCI genes results in a decrease of Nkx2.1 expression, relative to the wild type mouse, and is directly correlated to a decrease in the age of the embryonic mouse. Since DNA looping occurs in cells early in the embryonic stages, this may support the idea that NANCI is a DNA looping stabilizer. In addition, mice that are heterozygous for both the Nkx2.1 gene and the NANCI gene show a 32% decrease of the interneuron,

parvalbumin, in the striatum and a parvalbumin increase of 17% in the cortex. These results support the hypothesis that NANCI is necessary to indirectly regulate the migration of cortical interneurons. When Nkx2.1 is activated, interneurons will migrate into the striatum and, when Nkx2.1 is inactivated, the interneurons migrate to the cortex. It seems that NANCI is inactivating Nkx2.1 sooner than what is seen in the wild type, causing the interneurons to start their migration into the cortex early on.

Working in the Dr. Anderson's lab under David Tischfield has allotted me valuable lessons, which taught me how to engage in research experiments more independently. As a result, I have emerged a more confident and knowledgeable student, ready to partake in future scientific endeavors.