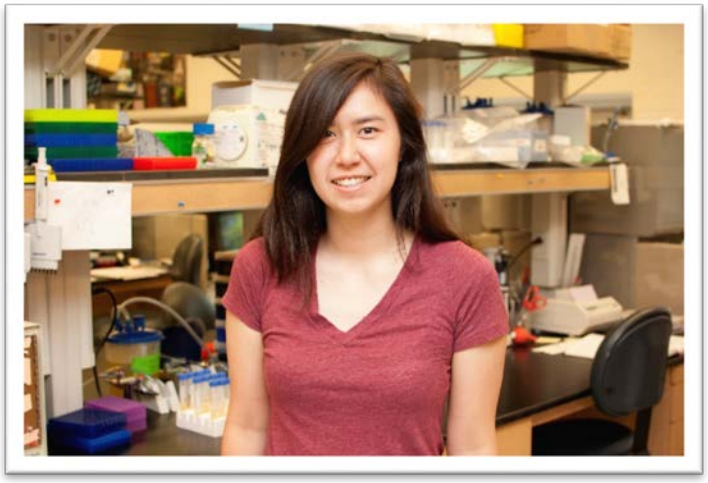
CENTER FOR RNA BIOMEDICINE



RNA Innovation Seminar

Monday, November 26th at 3:00pm
ABC Seminar rooms, Biomedical Research Science Building (BSRB), 109 Zina Pitcher

Molly Kuo
MD/PhD candidate
Antonellis Lab

"Determining the role of cysteinyl-tRNA synthetase (CARS) variants in human disease"

Abstract: Aminoacyl-tRNA synthetases (ARSs) are essential enzymes responsible for charging tRNA molecules with cognate amino acids. Consistent with the essential function and ubiquitous expression of ARSs, mutations in 32 of the 37 ARS-encoding loci have been implicated in severe, early-onset recessive phenotypes. Previous genetic and functional data suggest a loss-of-function mechanism; however, our understanding of the allelic and locus heterogeneity of ARS-related disease is incomplete. Cysteinyl-tRNA synthetase (CARS) encodes the enzyme that charges tRNACYS with cysteine in the cytoplasm. To date, CARS variants have not been implicated in any human disease phenotype. In collaboration with the NIH Undiagnosed Diseases Program, we identified four patients with complex syndromes that include microcephaly, developmental delay, and brittle hair and nails; each patient carries bi-allelic CARS variants. Here, I will present clinical and genetic evidence that are supportive of CARS mutation pathogenicity. Our protein expression studies and yeast complementation assays indicate that each CARS variant causes a loss-of-function effect. I will also present RNA-seq analyses examining differential gene expression between patient and control cells. This work will improve our understanding of the role of CARS in disease, and will provide insight into potential therapies for patients.