RASopathies are a spectrum of rare childhood diseases showing characteristic facial features, growth and developmental delays, as well as cardiac defects. They include Noonan Syndrome, Cardio-facio-cutaneous syndrome, Neurofibromatosis 1, and Costello Syndrome. All share a common defect: hyperactivity of a specific signaling pathway called the MAP kinase cascade. This pathway lies downstream of the protein RAS, which gives this diverse set of diseases its name. Mutations that activate RAS/MAP kinase are very common in human cancers. Although the mutations in RASopathies are similar to those found in cancers, their inheritance and location within the body are different, giving rise to characteristic developmental defects within the affected child. Despite these differences, we believe that therapeutic strategies to treat RASopathies can be informed by the biology of RAS-mutant cancers.

The first step in RAS signaling to the MAP kinase cascade is the activation of the kinase RAF. An emerging model in the cancer field is that all RAS-mutant cancers require two RAF proteins to bind to each other (a process called dimerization) to trigger activation of the MAP kinase cascade. Whether RAF dimerization is a general property among RASopathies is not known. We hypothesize that RAF dimerization is a general property among RASopathies. This hypothesis will be tested in human cells by examining a large set of RASopathy mutations. We will also determine whether blocking RAF dimerization represents a potential therapeutic strategy for treating RASopathies. We have recently shown that RAS-dependent dimerization of RAF requires a specific protein called SRC, and that selective inhibitors of SRC block this dimerization. One of these, the drug dasatinib, is used orally for another purpose in humans and in well. We will test the hypothesis that dasatinib and related drugs can inhibit RAS/RAF signaling in cells expressing these RASopathy mutations through their actions on RAF dimerization. These studies will provide preliminary data to test our larger hypothesis: can inhibitors of RAF dimerization ameliorate disease progression in models of human RASopathies.