High-altitude environments provide ideal testing grounds for investigations of mechanism and process in physiological adaptation. In this talk I’ll describe recent efforts to identify and characterize genetic mechanisms of physiological adaptation to high-altitude hypoxia in birds and small mammals. I’ll first describe efforts to identify mechanisms of hemoglobin adaptation to hypoxia in Andean birds (passerines and hummingbirds) and in North American rodents. These studies integrate evolutionary analyses of sequence variation with experimental studies of hemoglobin function to address questions about the genetics of adaptation. I will then describe an ongoing study of metabolic adaptation to high-altitude hypoxia in deer mice that involves a more genomic, systems-level approach.