Abstract: Iron-sulfur (Fe-S) proteins are found in all kingdoms of life and carry out some of the most kinetically demanding reactions in the biosphere. In this talk, I will discuss my group’s efforts to understand how the remarkable biological functions of Fe-S clusters derive from their unique electronic structures. Foundational to this line of inquiry is the development of methods for manipulating a cluster’s composition, structure, and properties: incorporating spectroscopically useful isotopes in specific metal sites, altering a cluster’s elemental composition and coordination environment, and preparing substrate-bound states. Examples will be given from biological and synthetic systems.