Abstract

What are the mechanisms -- evolutionary and biophysical -- by which proteins evolve new functions? How does the sequence of a protein determine the particularities of its fold, properties, and functions? All natural proteins are the result of evolution, so the premise of my lab's work is that a synthesis of evolutionary analysis of a protein's history with experimental analysis of its biochemistry and biophysics can illuminate questions at the heart of both fields. We use ancestral protein resurrection (APR) -- a strategy that allows us to physically re-create proteins as they existed in the deep past and experimentally recapitulate evolutionary changes in their sequence, structure, and function. I will report on our studies using APR to understand the diversification of function in the steroid receptors, a group of hormone-regulated transcription factors of extraordinary biological and medical importance in humans and other animals. These studies have allowed us to gain insight into how the biophysical architecture of ancient proteins shaped their evolution and how the architecture of modern proteins reflects their histories.