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CHEMISTRY SEMINAR 291

Evolutionary Biochemistry

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ABSTRACT

How does protein biochemistry shape protein evolution? How do new biochemical features evolve? To answer these questions, the Harms lab studies protein evolution using phylogenetic analyses, computational and experimental studies of protein "sequence space", and rigorous studies of protein biochemistry. I will discuss two ongoing projects. In the first, we ask the deceptively simple question: why can't we predict the combined effect of mutations by summing their individual effects? Through a set of computational and experimental studies, we demonstrate that universal thermodynamic considerations explain why mutations do not combine additively. Inspired by these results, we are developing quantitative, mechanistic models to account for non-additivity between mutations—potentially leading to predictive models of protein evolution. In the second project, we are investigating the evolution of the innate immune protein S100A9. This protein can exist as either a pro-inflammatory homodimer or as an antimicrobial heterodimer with the protein S100A8. We found that the heterodimer arose from an ancient homomeric interface that was maintained after gene duplication. The key historical mutations that conferred inflammatory and antimicrobial activity have different effects when introduced into the homodimer versus the heterodimer. This allowed a small protein to acquire new functions without compromising existing functions. We suspect this may be a general mode my which multifunctional protein evolve.