One of the hallmarks of eukaryotic cell signaling is the expansion of enzyme families to include hundreds of specialized members that carry out diverse biological processes. Protein kinases represent one such family, where a conserved protein fold and core biochemical function have been elaborated on through the introduction of distinct substrate specificities and divergent modes of regulation. Dissecting the molecular basis for specialization within this large enzyme family will guide our understanding of the architectures of cell signaling pathways and aid in the design of selective kinase-targeted drugs. These efforts may be augmented by the recent development of high-throughput biochemical approaches that couple the analysis of protein function to next-generation DNA sequencing. I will discuss my efforts to dissect the evolution and specialization of the protein tyrosine kinases involved in T cell receptor signaling using a high-throughput platform to interrogate kinase substrate specificity. These experiments point to divergent molecular recognition features of two essential kinases, Lck and ZAP-70, that ensure faithful signaling during the early stages of T cell activation. T cells play a central role in modern cancer immunotherapies, and these insights may be useful for the development and improvement of such therapies. Furthermore, the high-throughput biochemical techniques described in my talk will be valuable tools for the characterization of other signaling enzymes.

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Hosted by
Ruben Gonzalez