Unlocking the secrets of zinc in cellular communication

The world of cellular signaling is full of key players. Undeniably, the interplay among proteins holds the key to unlocking the secrets of immune system functions. While protein-protein interactions often occur when molecules are in close proximity, some necessitate a special binding agent. Metal ions frequently take on this specific role, with zinc (Zn^{2+}) emerging as particularly proficient. Zn^{2+} exhibits remarkable ability to bind to various amino acid blocks, securely holding them and releasing them on demand. This project dives deep into the molecular basis of the first discovered Zn^{2+}-dependent protein heterodimer: the complex of CD4/CD8 (two sister coreceptors) and Lck (tyrosine kinase). CD4/CD8 bridges Lck through Zn^{2+} to get it close to the primary T cell receptor that activates the immune response. While CD4 and CD8 play somewhat equivalent roles in Lck binding, they differ entirely in their amino acid sequences, serving as distinct markers for two of the most critical immune cell types. $CD4^+$ T cells (bearing CD4 on their surface) are known as helper cells, stimulating other immune cells to fight infection, while $CD8^+$ T cells directly kill pathogens. Developmentally, they originate from common $CD4^+CD8^+$ cells, committing into specific subtypes with the involvement of the Lck. As Zn^{2+} determines the existence of CD4/CD8-Lck complexes, the project aims to address questions such as the optimal amount of zinc “glue” is for CD4-Lck and CD8-Lck, identification of specific key points in their sequences that enhance or diminish the prevalence of CD4/CD8-Lck, and the potential impact of CD4/CD8-Lck variants on cell response or directing $CD4^+CD8^+$ cells toward becoming more $CD4^+$ or $CD8^+$. The project will raise these questions through scrupulous biophysical characterization, employing model membranes that mimic the cellular environment, utilizing yeast-based libraries as platforms to seek CD4/CD8-Lck complexes with variated Zn^{2+} affinities (different stickiness), and finally, evaluating CD4/CD8-Lck pairs in model cell lines in terms of signaling response. These insights not only contribute to the fundamental understanding of cellular communication but also pave the way for potential therapeutic interventions in immune-related disorders.