Designing Tailored Proteins for Advanced Chemical Biology Applications: Super-Selective Drug Delivery, Chemical Recognition, and More

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De novo protein design has been historically used to validate the principles governing the process of biomolecular folding and assembly. However, *de novo* design of proteins and peptides from physical principles may have an even greater impact when applied to recognizing and organizing nanomaterials and chemicals. We pursue that bio-hybrid structures can be engineered to assemble in a structurally-specific manner, and this presents a promising way of addressing current limitations in nanoscale assembly. Computational methods, including molecular dynamics simulations, quantum chemical calculations, and machine learning techniques, have been used to predict the structure and function of these molecules and guide their design. In the first part, I will describe the computational design of miniprotein for a photo-switchable calcium indicator by hybridizing an EF-hand motif with spiropyran by considering the unique coordination bond geometry of calcium, attention was given to stabilizing a structure that can maintain its geometry. The motif-swapped dimer form of the indicator was achieved through structural modeling and sequence optimization. Experimental characterization revealed CB7.F candidate with Phe sequence have the ability selectively bind Ca ion compared to Zn and Mg ions, NMR structure of the designed proven its swapped dimeric complex.

A second challenging area of interest in *de novo* protein design has been the selective delivery of therapeutic drug into the targeted organ with high bioavailability which is a grand challenge in drug development. Previous approaches preferentially used enriched receptors on the tissue as a target for receptor-mediated transcytosis. However, due to the ubiquitous expression of target receptors in other tissues, it is mechanistically challenging to engineer a selective binder on the specific tissue while sparing on-target off-tissue binding on other tissues. Here, I will present the principle of super-selectivity for the first time to a protein scaffold by carefully tuning the valency to the surface density of receptors to achieve high avidity and selectivity. These findings offer a new direction for further investigation into the use of protein drug. Our approach provides a potential solution to elucidate diease physiology and to develop selective drug delivery with high bioavailability.

References

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