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De novo design of albumin-binding peptides with non-canonical amino acids

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Traditional approaches for discovering protein-binding peptides have relied on mutagenesis-based modifications of natural products or high-throughput screening of vast random libraries containing trillions of variants. Nevertheless, these methodologies are inherently limited by their labor-intensive nature and substantial time requirements. Recent deep learning advances (e.g. RFdiffusion, AF3) in protein design and structure prediction have enabled generation of high-affinity binders, overcoming conventional limitations. Meanwhile, therapeutic peptides incorporating non-canonical amino acids (ncAAs) demonstrate enhanced stability and therapeutic efficacy compared to natural counterparts. However, current computational peptide design methods are limited to canonical substrates as building blocks, creating a significant gap between computational design capabilities and the chemical diversity achievable through synthetic biology approaches. Cell-free protein synthesis (CFPS) systems address this limitation by enabling efficient ncAA incorporation outside natural translation constraints. These systems provide a seamless platform that bridges computational design with chemical diversity expansion. Therefore, we aim to leverage deep learning technologies for initial peptide design and subsequently utilize CFPS to incorporate ncAAs, discovering binders with enhanced binding affinity and stability.