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De novo nanobody binder design using generative AI models

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In this study, we designed several novel nanobody sequences specifically interacting with green fluorescent protein (GFP) using protein generative artificial intelligence models. Inspired by recent advances in the domain of deep learning, we aim to design de novo nanobodies characterized by distinct complementarity-determining region 3 (CDR3) using state-of-the-art generative AI models. Based on the known GFP-antibody complex structure, the new backbone structures of complementarity-determining region 3 (CDR3) of nanobodies were generated by RFdiffusion and their probable sequences were obtained using ProteinMPNN. We employed three different approaches to predict the structure and binding affinity of the generated nanobodies. Among the generated sequences, 21 underwent experimental validation, of which 7 exhibited binding affinity, resulting in an observed binding success rate of approximately 33%. Subsequent to the identification of the binding nanobodies, we performed a comparative analysis to assess the effectiveness of computational metrics in the classification process. This study proposes an end-to-end pipeline that includes all stages from computational design to experimental validation, thereby showing the significant promise of computational nanobody design.