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De novo design of hyperstable and functional β-Sheet protein architectures



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Recent advances in de novo computational protein design provide unprecedented engineering freedom to create new-to-nature proteins with tailored structures and functions. Our group has focused on β-sheet–based proteins, which offer attractive scaffolds for designing ligand-binding pockets and frameworks that support flexible functional loops, but often face a fundamental tradeoff between stability and function. To address this challenge, we have developed design principles that combine physics- and deep learning–based methods to program stability and function in de novo β-sheet protein folds. These approaches have been experimentally validated through complementary biochemical, biophysical, and X-ray crystallographic studies.

We demonstrate these principles in two distinct fold families. First, we developed stabilization strategies for de novo NTF2-like domains that introduce buttressing elements on the convex face of curved β-sheets while preserving pocket geometry and accessibility, enhancing function. Applying this strategy to a de novo luciferase showed that structural buttressing can not only enhance thermal stability, but also modulate catalytic behavior. Second, we designed novel immunoglobulin-like (Ig) scaffolds—single- and two-domain architectures not found in nature—with hyperstability, high structural accuracy, and the robustness to accommodate pre-existing or de novo-designed binding loops. Together, these approaches demonstrate that structural stabilization and functional-site optimization need not be mutually exclusive, opening new opportunities for the computational design of functional β-sheet–based proteins.

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