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# ***Miniaturizing Helical Motifs: Structural Design of Rigid Macrocyclic Peptides***

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Conference Room Orio Zanetto, Alfa Building

Helical motifs enable protein–protein recognition but are difficult to miniaturize. We define design principles that truncate complex helical bundles into short, rigid helical hairpins and macrocycles. Knob-into-hole helix packing combined with loop engineering using non-canonical amino acids yields conformationally stable  $\alpha$ -helical scaffolds. Macrocyclization through loop closure

further rigidifies these architectures, enabling high-affinity target engagement, exemplified by inhibitors of the p53–MDM2 interaction. Together, these results establish generalizable rules for transforming extended helices into compact, structurally precise macrocyclic peptides for targeting challenging protein–protein interfaces.