Learning from nature: designing glutamine-based single α-helices to inhibit protein-protein interactions

Prof. Xavier Salvatella[a]
ICREA Research Professor
xavier.salvatella@irbbarcelona.org

The interactions between helical motifs and globular proteins offer opportunities for therapeutic intervention. Their modulation with small molecules is however challenging mainly because they bury large surfaces. Linear peptides that display the residues that are key for binding can be targeted to globular proteins when they form stable helices, which in most cases requires their chemical modification. Here we present rules to design peptides that fold into single α-helices by instead concatenating glutamine side chain to main chain hydrogen bonds recently discovered in polyglutamine helices[1,2]. The resulting peptides are uncharged, contain only natural amino acids, and their sequences can be optimized to interact with specific targets. Our results provide design rules to obtain single α-helices for a wide range of applications in protein engineering and drug design [3].

References:

1. Eftekharzadeh, B. et al; *Biophys J*. **2016**, 110, 2361-2366.
2. Escobedo, A. et al.; *Nat. Commun.* **2019**, 10, 2034.
3. Escobedo, A. et al.; *Nat. Commun.* **2022**, 13, 7073.