Fooling a protein into folding

Much like a ball of yarn is expertly knitted into a beautiful sweater, a long chain of amino acids folds into a particular shape and becomes a functioning protein. Except, a protein is able to do that all by itself, without any knitter, through a process known as 'protein folding'. Understanding folding and gaining the ability to control it can get us one step closer to understanding how life works, and to modulate it as per our wish. A group of TIFR scientists from Mumbai, Bangalore and Hyderabad have now found a general way to control the folding of a given target protein. They did this by designing a molecular decoy (a "xeno-nucleus"), which is a small synthetic protein that resembles a part of the original protein itself, and makes folding faster. The results have been published in the paper: Anirban Das, Anju Yadav, Mona Gupta, Purushotham R, Vishram L. Terse, Vicky Vishvakarma, Sameer Singh, Tathagata Nandi, Arkadeep Banerjee, Kalyaneswar Mandal, Shachi Gosavi, Ranabir Das, Sri Rama Koti Ainavarapu*, and Sudipta Maiti* J. Am. Chem. Soc. *2021*, 143, 44, 18766–18776, https://doi.org/10.1021/jacs.1c09611

The scientists have discovered a *general* strategy for designing a peptide that can specifically catalyze the folding of a given target protein. Their method is inspired by early work in the field of protein folding which attempted to identify a "folding nucleus", that is, a part of the protein which folds first, and enables the rest of the protein to fold. They use the folding nucleus of the target protein as a template, and stabilize its conformation using covalent modifications. When this small 'xenonucleus' peptide is supplied as an external catalyst, it can in principle make the rest of the unfolded protein accept this as the nucleus, and fold around it. This changes the kinetics of folding, and in principle gives options to specifically tag unfolded proteins. The concept is demonstrated using ubiquitin as a target protein. The work takes a significant step towards the long-held goal of engineering protein folding barriers with artificial external agents. This has potential applications in areas ranging from cell biophysics to pharmaceutical chemistry.