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Double-shell protein scaffold technology enables high-resolution structure determination of proteins smaller than 40 kDa using single particle cryo-EM

Researchers at Stanford University and SLAC have developed a double-shell protein scaffold system that enables structure determination of flexible proteins smaller than 40kDa at near atomic resolution using single particle cryogenic electron microscopy (cryo-EM). X-ray crystallography, NMR and more recently cryo-EM have made breakthroughs in solving high-resolution structures of macromolecules, however visualization of proteins smaller than 40 kDa at high resolution has proven difficult with the structural biology techniques available today. To break the resolution limit, researchers have invented a double shell protein scaffold which sandwiches the protein of interest with an interior and exterior protein shell via fusion. This cage-like structure consists of an inner shell comprised of 24 copies of apoferritin, forming a rigid shell that can be readily identified in cryo-EM images. The outer shell, made of maltose-binding protein (MBP), is more flexible, allowing access for small molecule or peptide compounds to enter the interstitial space and bind the target of interest. This technique has proven successful in solving the structure of the 11kDa KIX domain of the CREB-binding protein (CBP) at 3-4 Å. End to end implementation of the double-shell technology can be commercialized, from designing the DNA plasmid, to expression and purification of the caged protein, to cryo-EM structure determination. Additionally, high-resolution structure determination of small flexible therapeutic protein targets can enable structure-based drug design not previously possible.

Applications

- High-resolution structure determination of flexible proteins smaller than 40 kDa
- Structure based drug design of therapeutics for flexible small protein targets
- Commercialization of double-shell technology via DNA plasmid design, expression and purification of caged protein and cryo-EM determination

Advantages

- Structure determination of proteins smaller than 40kDa
- System can be used with or without ligands

Patents

- Published Application: WO2022076389
- Published Application: 20230357363

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