Esplanade Room 157: Monday, February 23

3:30 PM – 5:00 PM
Nuclera

Cell-Free Protein Synthesis to Unlock Difficult Soluble and Membrane Targets
Recombinant protein production remains a major rate-limiting step in modern drug discovery. Biophysical and structural methods, from SPR and HDX-MS to cryo-EM and X-ray crystallography, routinely stall, because sufficient quantities of properly folded, functional protein are unavailable. These bottlenecks slow hit validation, mechanism-of-action studies, and structure-enabled optimisation across both soluble and membrane targets. Cell-free protein synthesis (CFPS) offers a different paradigm. By decoupling expression from cell growth, and viability, CFPS enables rapid, iterative design-make-test cycles, direct control over reaction conditions, and straightforward incorporation of non-standard components such as chaperones, ligands, cofactors, and membrane mimetics. In this talk, we introduce eProtein Discovery™™, an integrated CFPS-based system that combines sequence design and automated digital microfluidics-based multiplex protein screening to rapidly identify expression-ready, assay-ready protein conditions. We will first illustrate how the platform accelerates soluble protein production, highlighting case studies where parallel screening of constructs, tags, redox conditions, and other additives yields functional material suitable for biophysical and structural workflows in days rather than weeks. We then extend this approach to membrane proteins, focusing on the additional challenge of providing the right lipid environment. We will discuss co-translational insertion into nanodiscs, the impact of different membrane scaffold protein (MSP) sizes, and how lipid composition tunes stability and function. Case studies on transporters, membrane-bound enzymes, and GPCRs will show how eProtein Discovery systematically screens constructs, MSP variants, lipids, and additives to pinpoint conditions that produce active receptors and enzymes for downstream assays. Together, these examples demonstrate how CFPS can make a broad range of traditionally difficult proteins accessible for drug discovery, transforming protein production from a bottleneck into a programmable, front-end design space.

Speaker
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