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Membrane Proteins: New Approaches to Probes, Technologies, and Drug Design, Part II

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This second part of the *SLAS Discovery* special issue "Membrane Proteins: New Approaches to Probes, Technologies, and Drug Design" focuses more on the technologies required to develop chemical/biological applications for these important drug targets and also enable the identification of novel chemical matter for lead optimization.

One of the key requirements for biochemical and biophysical assays is to preserve the correct functionality and conformation of the membrane protein in the extraction and isolation from the biological lipid bilayer environment. Often, this requires reconstitution back to the natural lipid environment or into the environment that is closely mimicking native lipid bilayer, such as synthetic lipids and surfactants/detergents. Traditionally, membrane protein extraction has been done using detergent molecules. Detergent molecules disturb the biological native lipid bilayer and replace the lipids in the protein–lipid interactions.

In the lead-off review article, Overduin and Esmaili[1] give an overview of a new and emerging protein–lipid reconstitution methodology utilizing styrene maleic acid (SMA) polymers. The SMA polymers are capable of extracting and self-forming protein–lipid nanoparticles (SMALPs) that include endogenous native lipids and proteins ligands without resorting to synthetic detergents or artificial lipids (see inset figure in the cover that illustrates such a SMALP complex). Direct extraction of the membrane protein–lipid assembly makes the SMALP system attractive compared with nanodisc or other membrane scaffolding protein-based techniques that usually require detergent initially to break the bilayer into lipid–protein vesicles.

The same scheme with isolated membrane proteins emphasizing the importance of new methods for protein tool generation and lipid extractions is continued in two back-to-back articles on the multidrug resistance protein 4 (MRP4). In the first article, Hardy et al.[2] describe functional recombinant overexpression of MRP4, an important method for any membrane protein target. In the latter article, the same authors demonstrate the usage of novel solubilization agents, such as SMA and novel detergents (Calixar), for this important model protein system.[3]

Recent developments in small-molecule discovery for human equilibrative nucleoside transporter (ENT) inhibitors are reviewed by Rehan et al.[4] The authors also discuss recent progress to heterologously produce and isolate functional recombinant ENTs in different detergent systems.

The special issue concludes with three articles showing new screening tools and assays to find a new chemical matter for medically relevant membrane protein targets. In the first screening-specific article, Scott et al.[5] developed a yeast-based assay to screen for compounds that rescue the ability of the retinitis pigmentosa rhodopsin disease mutant model to activate an associated downstream G-protein-coupled receptor: G-protein-signaling cascade.

In the article from Shen et al.,[6] a novel screening platform for the identification of the ligands for the orphan receptors is described. The homogeneous, in-cell binding assay can be used to study membrane protein interaction in medium-throughput screening and has the potential for small-molecule target deconvolution.

In the final screening article, Wood and Wright[7] establish a new high-content imaging assay to capture extracellular ligand–receptor interactions in a high-throughput screening format using intact cells.

Hopefully, these articles[1–7] can be used as model cases and starting points that can be applied to many other similar membrane protein targets and for the hit-to-lead discovery process.

References

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