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Spotlights on Recent *JACS* Publications

DRUG TARGET BINDS WITH A LITTLE MORE BACKBONE

Kristian Strømgaard, Per Jemth, and colleagues quantify the contribution of important hydrogen bonds in the binding of a common mammalian protein domain and potential drug target (DOI: 10.1021/ja402875h).

Many important components of mammalian cells, such as scaffolding proteins in synapses and recognition motifs in enzymes, share a protein binding domain called the PDZ domain. Researchers hope to make drugs to inhibit the domain's interaction with proteins to treat conditions including ischemia and pain. Although researchers have shown how amino acid side chains of protein ligands interact with the domain, it has been unclear how much backbone hydrogen bonds contribute to these binding interactions.

To determine their role, the researchers make amino acid modifications to weaken backbone hydrogen bonding in the interaction of four different PDZ domains with peptides representing natural protein ligands. The hydrogen bonding network significantly contributes to the binding affinity of these interactions, they find. This work could clear the way for future progress in developing drugs targeting the PDZ domain to treat pain and other conditions. **Deirdre Lockwood, Ph.D.**

NANOCRYSTALS SPROUT ARMS WITH TUNABLE LENGTHS

Owing to their unique optical and electronic properties, highly branched nanostructures have long captured researchers' attention. But while many types of multi-pod nanostructures have been reported in the literature, few methods exist for the controlled preparation of structures based on soft matter systems, such as surfactant- or block copolymer-based micelles.

Now, a team led by Mitchell A. Winnik and Ian Manners reports a new polymerization technique that enables researchers to control the growth of multi-armed crystalline micelles (DOI: 10.1021/ja404100w). The complex nanostructures emerge when block copolymers, or polymers composed of multiple monomeric species, self-assemble onto the surface of polymer-based nanocrystals. The nanocrystals serve as initiators for the formation of "arms" made of cylindrical micelles. The team shows they can create monodisperse structures with tunable arm lengths and compositions.

By cross-linking the multi-armed micelles and dissolving the nanocrystal core, the team demonstrates a new way to create interesting linear nanostructures known as non-centrosymmetric AB cylindrical diblock co-micelles. Such complex micelle architectures may one day find use in the creation of superlattice structures and other optical and electronic devices. **Christine Herman, Ph.D.**

LOCATION, LOCATION, LOCATION

In cellular biology, it is not only which proteins are present but where they are that determines their function. A transcription factor is useless in the cytoplasm, for instance, while signaling events often occur near the cell membrane. By altering protein location, researchers can tweak biology. Now Shinya Tsukiji, Itaru Hamachi, and colleagues describe a strategy for doing so (DOI: 10.1021/ja4046907).

Self-localizing ligands (SLLs) are small, modular, organic compounds in which one module specifies a cellular address and the other a protein target. The team develops SLLs to target the inner leaf of the plasma membrane, the cytoskeleton, and the nucleus using a lipopeptide, anti-cancer agent, and DNA-binding dye, respectively, and couples those to small molecule ligands (e.g., trimethoprim) of the intended interaction partners (e.g., DHFR).

Translocation occurs within minutes, and excess free ligand reverses the reaction. In one case, the team kick-starts a signaling pathway that requires kinase translocation to the plasma membrane using an SLL instead of the normal stimulus. Using orthogonal SLLs, they target two sets of proteins to two different addresses simultaneously in the same cell.

"The SLL-induced protein relocation technique will become a powerful new chemical approach for probing the role of protein localization and spatiotemporally regulated signaling in cell biology," they write. **Jeffrey M. Perkel**

MICROTUBULE MODIFICATION METHOD COULD DRIVE DRUG DISCOVERY

Tarun M. Kapoor and colleagues introduce a strategy to probe and target the protein interactions of microtubules, tube-shaped polymers that serve as tracks for intracellular transport in eukaryotes (DOI: 10.1021/ja405199h). Microtubules are important anti-cancer drug targets because cells stop dividing when microtubule function is disrupted. The team's strategy can be used to study microtubule biochemistry and function, and may also help identify microtubule-protein interactions specific to cancer. Drugs targeting these interactions could be used to selectively inhibit the growth of cancer cells.

Efforts to develop such drugs have been limited by our understanding of how microtubules interact with other proteins. Studying the interactions of microtubules with drugs and proteins is particularly challenging due to the dynamic nature of these polymers and the lack of approaches for their efficient and selective labeling, as would be needed to append a chemical probe to specific amino acid sites.

Now Kapoor and colleagues have found a way around these challenges. They express tubulin, the protein that comprises microtubules, in the budding yeast *Saccharomyces cerevisiae*, and introduce non-natural amino acids at specific sites in the protein using a method called amber suppression. They then add a fluorescent probe to the modified sites using click chemistry. Researchers could also use the method to identify new proteins that interact with microtubules and to recapitulate post-translational modifications. **Deirdre Lockwood, Ph.D.**

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