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Spotlights on Recent *JACS* Publications

PEPTIDE–DNA "NANOCOCOONS" INSPIRED BY VIRUSES

Scientists have long looked to nature for inspiration in their efforts to build complex systems out of simple building blocks. Now, Rong Ni and Ying Chau report a new peptide-DNA complex that mimics the architecture of a capsid—the protein shell of a virus—and holds promise for applications in gene delivery (DOI: 10.1021/ja507833x).

The team has rationally designed a 16-amino acid peptide with functional segments for binding DNA and forming β-sheets much like naturally occurring capsids. The peptide co-assembles with DNA into virus-like nanoparticles, termed "nanococoons". The structures are ellipsoid-shaped and, at 65 nm × 47 nm, roughly the size of a virus. The researchers propose that the DNA serves as a template to help the peptide strands organize themselves, while the lateral association of the peptide β-sheets helps stabilize the complex and, in turn, organizes the DNA contained inside.

The result is an extremely stable structure that is resistant to enzymatic degradation. The new method enriches the toolbox available to researchers developing functional peptide-DNA-based nanomaterials and represents a new avenue for constructing virus-inspired therapeutics.

Christine Herman, Ph.D.

BUILDING A BETTER URANYL-BINDING PROTEIN

Heavy metals represent significant biological and environmental pollutants, and researchers actively seek reagents that can capture them. Recently, an artificial protein—super uranyl binding protein, or SUP—with strong selectivity and sensitivity for uranyl (UO_2^{2+}) ions was described, but how it achieves these properties is unknown. Now Laura Gagliardi and colleagues use molecular dynamics and free-energy simulations to answer that question (DOI: 10.1021/ja5087563).

The team models the binding of wild-type SUP and various mutants to uranyl ions. They find that the metal is coordinated to four amino acids in the SUP binding pocket via five planar hydrogen bonds, and that a second hydrogen-bonding sphere stabilizes the structure. Mutation of key amino acid residues in the binding pocket reduces the computed strength of these interactions, thereby explaining these mutants' poor binding properties. Similarly, modeling the binding properties of other cations explains the protein's molecular selectivity.

The authors apply their model to design a new mutant with stronger uranyl binding and selectivity than SUP, and the resulting protein experimentally validates those predictions, binding uranyl 45% more tightly. "To our knowledge, this is the first application of MD and free-energy simulations to understand and improve uranyl–protein interactions," they write.

Jeffrey M. Perkel

LIGHT POWERS CHEMICALLY ACTIVATED MOLECULAR SWITCH WITHOUT WASTE

Chemically powered molecular switches can deliver drugs or move nanoscale objects when activated by a chemical reactant, like an acid or a base. However, activation via an acidic fuel followed by resetting using base produces unwanted salts. Accumulating waste products and side products can limit the lifetime of these switches, thus restricting their utility in cascading networks that could perform complex tasks.

Ivan Aprahamian and his colleagues want to extend the lifetime of a chemically powered switch by eliminating waste product formation (DOI: 10.1021/ja511135k). To do this, they have utilized a molecule called merocyanine that releases acid when activated by light. They pair this reversible acid generator with a hydrazone molecular switch that moves when protonated.

The two-component system can be switched 100 times without generating any waste. This recyclability of the process will be beneficial in future industrial applications. A water-soluble version of the switch can be cycled for 20 times before the merocyanine is destroyed through hydrolysis. Further development of the water-soluble system could create a switch for controlling biological processes like protein activity or targeted drug delivery, the researchers predict.

Melissae Fellet, Ph.D.

NANOPARTICLE TRANSPORTS DRUG PACKAGES AND PROVIDES DELIVERY RECEIPT

Delivering cancer medications directly to tumors may someday improve therapeutic efficacy while reducing side effects related to off-target interactions. Nanoparticles offer a potential vehicle for targeted drug delivery; however, challenges remain, such as intracellular transport, premature release, and tracking delivery. To overcome these obstacles, Shiyong Liu and colleagues have developed a self-reporting nanoparticle that can penetrate cell membranes and then, and only then, release the medication (DOI: 10.1021/ja5105848).

The researchers construct the drug carrier from a single-molecule lipid particle with a hyperbranched core and a hydrophilic guanidine-functionalized corona layer. These so-called prodrug amphiphiles elongate blood circulation and facilitates cellular penetration. They incorporate an inactive drug—the anticancer medication camptothecin—inside the nanoparticle, along with a gadolinium complex. This magnetic resonance contrast agent "turns on" when freed inside the cell, allowing the researchers to detect the moment and location of release.

Because tumor cells have a reductive interior, the researchers have designed their drug delivery system to specifically release the drug and contrast agent in a reductive intracellular milieu. In a proof-of-principle experiment, the researchers find that their nanoparticle provides a stronger magnetic resonance signal and 70-fold higher cytotoxicity within a tumor cell than in a non-reductive milieu.

Erika Gebel Berg, Ph.D.

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