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Spotlights on Recent *JACS* Publications

A NEW WAY TO DISMANTLE PATHOGENIC PROTEASES

Stephan A. Sieber and colleagues have identified a set of small molecules that use a unique mechanism to inactivate an enzyme responsible for virulence in pathogenic bacteria (DOI: 10.1021/ja4082793).

A common strategy in developing drugs to treat bacterial and viral infections is to inhibit proteases, enzymes that many pathogens rely on to survive and flourish. So far, many protease inhibitors have been designed to block the active site of these enzymes through formation of a covalent bond to an amino acid that is important for catalysis. But this strategy is not always effective because in some cases this reaction is reversible.

Now Sieber and colleagues have identified several small molecules that dismantle a protease critical for virulence of the bacteria *Staphylococcus aureus* in a new way. The small molecules bind to the bacterial protease and trigger the formation of an inactive protein assembly. The researchers found them by screening a suite of known active-site-directed protease inhibitors. While unique in its own right, the work could inspire the development of inhibitors of other multimeric proteases that would be useful drugs to treat bacterial and viral infections.

Deirdre Lockwood, Ph.D.

NEW FLUOROPHORES EXTEND SPINACH'S COLOR PALETTE

Researchers wishing to track proteins in vivo can fuse green fluorescent protein (GFP) or its variants to their sequence of interest and follow the molecules microscopically. Likewise, for RNA there's "Spinach", a fluorophore-binding RNA aptamer—a relatively short segment of RNA. Just fuse Spinach to your RNA, add DFHBI to the culture medium, and watch where the dye goes. Unfortunately, DFHBI's spectral properties do not align well with typical biological filter sets, making for subpar imaging. Now, Samie Jaffrey and colleagues report a series of "plug-and-play" fluorophores that extend and improve Spinach's properties (DOI: 10.1021/ja410819x).

The team modified DFHBI's imidazolinone ring. Replacing a methyl group with a trifluoroethyl (DFHBI-1T) or aminoethyl group (DFHBI-1AE) red-shifts both emission and excitation maxima, making Spinach more compatible with GFP filter sets. Another variant, DFHBI-2T, shifts the excitation and emission maxima even further to overlap YFP.

DFHBI-1T produces brighter images than DFHBI thanks to higher signal and lower background. DFHBI-2T opens up the GFP channel for multiplexing. And, unlike fluorescent proteins, these dyes can be swapped simply by changing the culture media.

"The different fluorophores described here provide a 'plug-and-play' system for RNA imaging in living cells," the authors write. In the meantime, more red-shifted dyes are in development.

Jeffrey M. Perkel

SMART PROBE TAKES AIM AT OXIDATIVE STRESS

Roger Y. Tsien and colleagues have designed a fluorescently labeled peptide probe that detects areas of elevated hydrogen peroxide in cell culture and mouse models (DOI: 10.1021/ja411547j). It could be applied to image areas of oxidative stress and target the delivery of therapeutics to these regions.

Inside the body, a buildup of hydrogen peroxide leads to oxidative stress that can cause cell damage. Excess hydrogen peroxide and oxidative stress appear in a wide range of illnesses, including diabetes, cardiovascular disease, neurodegenerative disorders, and cancer. So researchers have made probes to trace areas where hydrogen peroxide is accumulating in the body. They also hope to curtail the effects of oxidative stress by delivering drugs to these locations. Now Tsien and co-workers have designed a probe that could do both of these things.

The probe is made of two peptide domains. It selectively reacts with hydrogen peroxide to cleave apart, releasing a domain that can penetrate cells, potentially carrying a therapeutic cargo. The probe is dually fluorescently labeled so its reaction with hydrogen peroxide makes it change color. The work could help researchers pinpoint areas of oxidative stress and target therapies to treat a variety of conditions, such as asthma.

Deirdre Lockwood, Ph.D.

HOLLOW SPHERES LEND CONTROL TO CARBON NANOTUBE GROWTH

To fully exploit the promise of nanomaterials, scientists need to be able to grow them with exact specifications. Unfortunately, the extremely small size of these materials makes such control very difficult. Despite almost two decades of work, researchers still struggle to control carbon nanotube (CNT) alignment, density, diameter, length, and number of walls.

CNTs grow well from metal spheres, but metal spheres tend to stick together at temperatures ideal for nanotube growth. Irregularities in sphere size and placement in turn create irregularities in the CNTs. To generate uniform arrays of nanotubes, some researchers have tried dotting the spheres with molecules that can act as spacers, but these ligands reduce the metal's ability to aid nanotube growth.

Toru Maekawa and colleagues overcome this dilemma with ligand-coated hollow spheres (DOI: 10.1021/ja410794p). As in previous designs, the ligands provide control and prevent agglomeration. But in the nanotube growth environment, the spheres shrink and the ligands partially detach, leaving a still-uniform but much more active bed of metallic spheres to catalyze nanotube growth. This process creates high-quality, dense forests of triple-walled carbon nanotubes. Current CNT applications mostly use masses of CNT fragments, but potential applications for such high-density arrays include microelectrode arrays, sensors, and fuel cell components.

Jenny Morber, Ph.D.

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