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In This Issue

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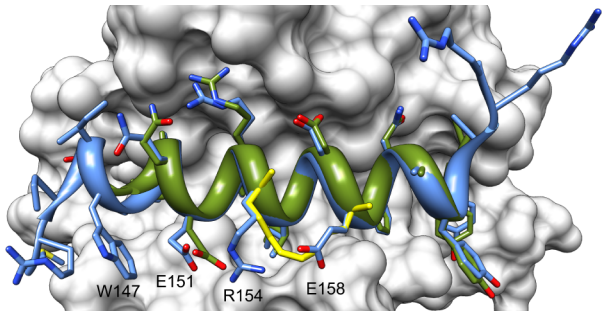
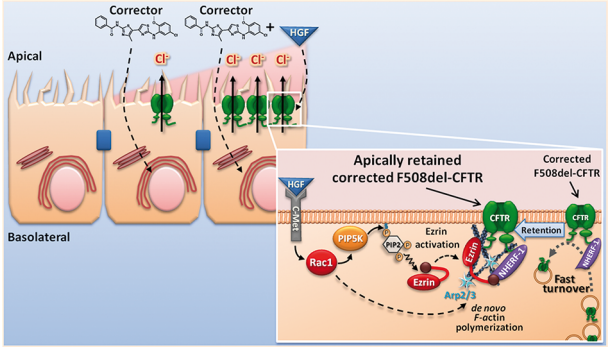
"STAPLING" NOT A STAPLE FOR IMPROVING PEPTIDE ACTIVITY



Peptides are attractive biomolecules for therapeutic development, and numerous methods for optimizing their activity, including increasing their target affinity, enhancing their stability, and improving their cell permeability, have been reported. For helical peptides, an attractive approach is to covalently link two residues on the same face of the helix, thus "stapling" or constraining the peptide into its helical conformation. However, Okamoto *et al.* (DOI: 10.1021/cb3005403) report that this strategy, when applied to certain Bcl-2 homology domain 3 (BH3) peptides, actually decreased target affinity and likely diminished cell permeability as well.

Using a variety of cellular assays, structural analysis methods, and molecular modeling, the authors determined that though the stapled peptide exhibited enhanced helicity, the structural modification actually disrupted a beneficial network of interactions within the bound peptide that ultimately negatively impacted it affinity to its target protein. The authors conclude that in designing therapeutic peptides alterations to the peptide structure should avoid perturbing favorable interactions within the peptide itself.

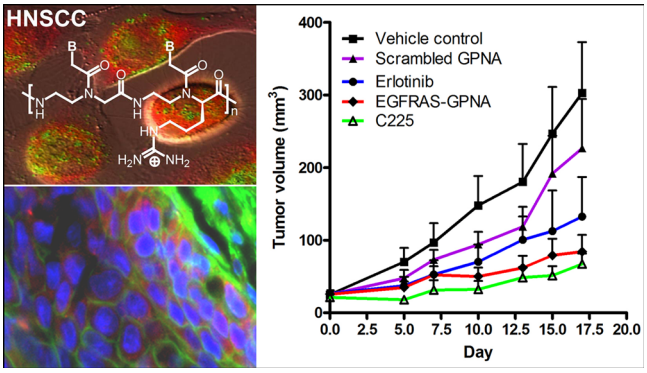
GETTING TO THE SURFACE OF CYSTIC FIBROSIS TREATMENT



Cystic fibrosis, a chronic, inherited disease characterized by sticky mucus buildup in the lungs and digestive system, is caused by mutations in a chloride channel called cystic fibrosis transmembrane conductance regulator (CFTR). Many of these mutations cause improper folding of CFTR, which prevents its translocation to the cell surface. Small molecules called correctors have been identified that partially restore mutated CFTR folding. However, the clinical efficacy of the correctors has been limited, likely in part due to the poor stability of the mutant CFTR at the plasma membrane. Moniz *et al.* (DOI: 10.1021/cb300484r) now report a strategy for prolonging retention of CFTR on the cell surface.

The actin cytoskeleton is responsible for anchoring CFTR to the cell membrane, and the GTPase Rac1 is an important actin regulator. The authors demonstrate that Rac1 activation with hepatocyte growth factor stabilizes mutant CFTR on the cell membrane. Insights into the mechanisms involved in CFTR localization gained in this study will guide improved strategies for cystic fibrosis treatment as well as that of other diseases rooted in protein trafficking dysregulation.

AN ANTISENSE STRATEGY THAT MAKES SENSE



Antisense therapy, in which mRNA is targeted to prevent the production of the protein it encodes, is a promising anticancer strategy given the many genes that are overexpressed in various cancers. An antisense approach has inherent advantages, such as the ability to more easily target drug-resistant mutations that arise during tumor progression, but most nucleotide-based compounds are inherently instable, exhibit nonspecific binding, and are not readily taken up by cells. Peptide nucleic acids (PNAs) are attractive nucleic acid mimics whose altered backbone structure endows them with resistance to both proteases and nucleases, though they are still not naturally cell-permeable. Toward development of PNAs as therapeutic agents, Thomas *et al.* (DOI: 10.1021/cb3003946) now report the development of cell-permeable, guanidine-based PNAs called GPNAs.

A GPNA 16 nucleotides long was designed to target the EGF receptor (EGFR), which is overexpressed in many human cancers. The GPNA exhibited antitumor activity in two mouse cancer models and inhibited an EGFR mutant resistant to the cancer drug cetuximab.

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