Cell-penetrating Mini-proteins

Gregory L. Verdine

Departments of Stem Cell and Regenerative Biology,
Chemistry and Chemical Biology, and
Molecular and Cellular Biology,
Harvard University
12 Oxford Street, Cambridge, MA 02138 USA

One of the most vexing problems in life science is that of "undruggability," the difficulty of targeting certain biological macromolecules in vivo using existing drug or ligand discovery technologies. It has been estimated that as many as 80-90% of all potential targets, including many that have been extensively validated in humans and in animal models, are undruggable. The Verdine laboratory is developing powerful new chemistry-based platform technologies to address these undruggable targets. Specifically, the lab is developing cell-penetrating mini-proteins, molecules that, like protein therapeutics, possess the ability to target large flat surfaces, but that, like small molecules, are fully synthetic and hence can be modified at will. Progress on the development of one class of cell-penetrating mini-proteins – hydrocarbon-stapled alpha-helical peptides – will be reviewed in this talk.

Schafmeister, C. E.; Po, J.; Verdine, G. L. “An All-Hydrocarbon Cross-Linking System for Enhancing the Helicity and Metabolic Stability of Peptides,” *J. Am Chem. Soc.* 2000, **122**, 5891-5892.

Walensky, L. D.; Kung, A. L.; Escher, I.; Malia, T. J.; Barbuto, S.; Wright, R.; Wagner, G.; Verdine, G. L.; Korsmeyer, S. J. “Activation of Apoptosis in Vivo by a Hydrocarbon-Stapled BH3 Helix,” *Science* 2004, **305**, 1466-1470.

Bernal, F.; Tyler, A. F.; Korsmeyer, S. J.; Walensky, L. D.; Verdine, G. L. “Reactivation of the p53 Tumor Suppressor Pathway by a Stapled p53 Peptide,” *J. Am. Chem. Soc.* 2007, **129**, 2456-2457.

Moellering, R. E.; Cornejo, M.; Davis, T.; Del Bianco, C.; Aster, J. C.; Blacklow, S. C.; Kung, A. L.; Gilliland, D. G.; Verdine, G. L.; Bradner, J. E. “Direct Inhibition of the Notch Transcription Factor Complex,” *Nature* 2009, **462**, 182-188.