Intracellular Biologics as Next-Generation Therapeutics

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Current drugs (i.e., small molecules and biologics) are effective against only ~20% disease relevant human proteins. Modulation of the remaining ~80% "undruggable" targets requires alternative modalities. Numerous attempts are being made to deliver biologics into mammalian cells, usually by leveraging the endocytic processes. Unfortunately, most of the endocytosed materials remain entrapped inside the endosomal/lysosomal pathway and poor endosomal escape represents a key bottleneck during the development of intracellular biologics. We recently discovered a family of cyclic cell-penetrating peptides (CPPs), which deliver all major drug modalities (e.g., small molecules, peptides, proteins, and nucleic acids) into the cytosol of mammalian cells in vitro and in vivo with unprecedented efficiencies. We have elucidated their mechanism of cellular entry by endocytosis and endosomal escape. We have also applied the cyclic CPPs to develop cell-permeable peptides and proteins as potential treatments of previously intractable diseases caused by excessive protein-protein interactions (e.g., calcineurin-NFAT, Keap1-Nrf2, and Ras-Raf interactions) or genetic mutations (e.g., cystic fibrosis and MNGIE).

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[2] Sahni, A., Qian, Z., and Pei, D. *ACS Chem. Biol.* **2020***, 15*, 2485-2492.