Jung-Mo Ahn, Med Chem (Los Angeles) 2017, 7:11 (Suppl)
DOI: 10.4172/2161-0444-C1-036

Crafting α-helix mimetics for targeting protein-protein interactions

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Protein-protein interactions are one of the fundamental processes that regulate numerous key cellular pathways. Since α-helical structures are frequently found on the interfaces of protein complexes, short helical peptides derived from such proteins have been considered as a valuable tool for research and clinical applications. However, peptides in general may suffer from drawbacks that can severely compromise their effective *in vivo* use, such as rapid enzymatic degradation, poor bioavailability, and lack of membrane permeability. Thus, small molecules that mimic functions of helical peptides would be of great interest in targeting and disrupting protein-protein interactions that take place inside cells. To the end, we have designed oligo-benzamides as versatile scaffolds to emulate protein helical surfaces. The rigid oligo-benzamide scaffolds can present multiple functional groups corresponding to the side chains found on one helical face. In addition to the outstanding α-helix mimicry, oligo-benzamides can be efficiently synthesized by following high-yielding and iterative steps in solution- and solid-phase. Nuclear receptors like androgen receptor and estrogen receptor recruit a variety of coactivator proteins to exert their functions, and many of the molecular recognition are triggered by consensus LXXLL motifs. We have designed oligo-benzamides based on the sequence and structure of the helical LXXLL motifs, and they demonstrated utilities in disrupting NR-coactivator protein complex formation, inhibiting NR-mediated gene transcription, and blocking NR-mediated cell proliferation in prostate and breast cancer cell lines. These exciting results indicate that oligo-benzamides are effective tools to mimic functions of α-helices and may have a high potential in biomedical research.

Biography

Jung-Mo Ahn has received his PhD in Chemistry from the University of Arizona and completed his Postdoctoral studies in the Scripps Research Institute. He is Associate Professor in Chemistry at the University of Texas at Dallas and a Council Member of the American Peptide Society. His research mainly focuses on structure-based design of peptidomimetics targeting protein-protein interactions.

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