ORGANIC SEMINAR

Identification of a Novel Furin Inhibitor and Evaluating the Antibiotic and Cell-Penetrating Function of Cationic Amphiphilic Polyproline Helices (CAPHs)

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Abstract: Furin is a serine protease of the proprotein convertase (PC) family that processes many substrates and converts them to their biologically active forms. Its activity has been implicated in the pathology of SARS-CoV-2 whereby it cleaves an acquired furin recognition sequence on the spike (S) glycoprotein, prompting a conformational change and promoting infection. Previous findings in our research lab had identified the molecule tyrphostin-A9 as being an inhibitor of furin through a library screen. My studies have been aimed at derivatizing the molecular scaffold of tyrphostin-A9 to determine structure-activity relationships and elucidating its mechanism of action. Mechanistic analysis of the designed agents suggested an allosteric binding mode which is underrepresented for inhibitors of this protein.

Cationic amphiphilic polyproline helices (CAPHs) are molecules designed to display cationic and hydrophobic groups along a polyproline type-II helical scaffold. CAPHs were designed to penetrate mammalian cells and target intracellular pathogenic bacteria. My efforts in the structural optimization of CAPHs have focused on increasing these functional characteristics by way of hydrophobic modification. In one example, hydrophobic modification of CAPHs has led to improved antibiotic activity and targeting within mammalian cells. Additionally, with the rising interest of biologics as a therapeutic modality, the most optimal hydrophobic CAPH with regards to cell uptake was further leveraged with the aim of delivering large biomolecular cargo into cells. To this end, CAPH-GFP conjugates were prepared and evaluated for cell penetration and subcellular localization, thus highlighting the versatility of the CAPHs platform.

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