Discovering Novel Allosteric Antagonists for Purinergic Receptor P2X7, a Key Mediator in the Progression of Several Neurodegenerative Diseases

Smith, Reagan (School: Lewis &amp
Clark High School)
Chow, Emma (School: Lewis &amp
Clark High School)
Wang, Sabrina (School: Lewis &amp
Clark High School)

A growing body of evidence indicates that P2X7, a homotrimeric ATP-gated ion channel receptor, is a key mediator in neuroinflammatory signaling and cell death pathways in neurodegenerative disorders. In Parkinson’s and Alzheimer’s, studies have shown P2X7 to be upregulated, contributing to the progression of both diseases. Upon exposure to high concentrations of ATP, the receptor activates, promoting inflammasome assembly, cytokine release, and increased oxidative stress in central nervous system (CNS) cells. These downstream effects make P2X7 an important potential therapeutic target for mitigating inflammation and neuronal cell death. While multiple preclinical studies support the neuroprotective effects of P2X7 antagonism, clinical translation has been limited due to insufficient antagonist selectivity, suboptimal potency, and unfavorable pharmacokinetics. In this project, we aimed to identify novel small-molecule antagonists that preferentially bind to the P2X7 allosteric site and possess biochemical properties suitable for CNS delivery. We investigated important binding site residues and interactions specific to P2X7 by comparing simulated binding of the known P2X7 allosteric antagonist JNJ47965567 to other receptors in the P2X family. From there, we created a pharmacophore model for screening and docking simulations, identified three top candidate antagonists, and ran molecular dynamics simulations with each. Our data consisted of analysis from hydrogen bonds, root mean square deviations (RMSD), center of mass distances, and binding affinities. The three compounds identified were found to have comparable affinity for P2X7 to JNJ47965567, warranting further investigation into in vitro analyses for inhibition and efficacy.

Awards Won: