Allosteric Inhibition of the Carbonic Anhydrase IX for Anticancer Applications

Naidu, Nandini (School: Valley Catholic High School)

In hypoxic conditions tumor cells have evolved to alleviate their intracellular acidity with the overexpression of the human Carbonic Anhydrase IX isozyme (CA IX) (Haiden). As a result, the CA IX is overexpressed in many hypoxic tumors such as gliomas, mesotheliomas, bladder carcinomas, breast, lungs, brain, and kidney tumors, among others (Supuran). Targeting the CA IX poses a unique opportunity for cancer treatment. Grayanotoxin (GTX III), a naturally occurring small molecule, has inhibitory effects on multiple isozymes in the CA family. GTX III was used as a scaffold for designing analogs that could be CA IX specific inhibitors. Computational docking analyses were carried out by docking the 6 analogs (A, B, C, D, E, and F) to multiple CA isozymes (CA I, II, IV, IX). Following this, in vitro experimentation, CO2 stopped flow and fluorescence assays were carried out. After comparing the computational data to the biological data a potential computational binding threshold was identified wherein of -80 kcal/mol must be passed computationally in order to indicate inhibition of the CA IX biologically. This threshold identification will expedite the process of creating analogs with stronger binding efficacy and identifying top contenders for synthesis and biological testing. The stopped flow CO2 assays showed that analog D was CA IX specific. The specificity of analog D is also strengthened by the fact that the fluorescence assays conducted show that analog D did not inhibit the voltage-gated sodium ion channels. (GTX III has been known to bind to voltage gated-sodium ion channels.) Based on the results of the computational and biological data analog D shows promise as a potential medication lead for anticancer applications.

Awards Won:

Second Award of $2,000