A Novel Approach to Cancer Treatment: Allosteric Inhibition of the Carbonic Anhydrase IX Isozyme for Anticancer Applications

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Due to lack of oxygen, the Hypoxia Inducible Factor pathway triggers the overexpression of the human Carbonic Anhydrase (CA) IX isozyme in many hypoxic tumors such as colon, brain, cervix, breast, lung, and kidney tumors. The CA IX controls intracellular pH (pHi) levels of hypoxic tumors by converting intracellular CO_2 into bicarbonate and transports it to the extracellular space. The inhibition of the CA IX would impair hypoxic tumor cells' ability to regulate pHi and poses a unique approach to cancer treatment. Targeting the CA IX also provides a more effective treatment approach for hypoxic tumors, which are resistant towards radiation and chemotherapies. Furthermore, current FDA-approved CA inhibitors, which are not actually used for anticancer applications, act on CA isozymes nonspecifically, causing high potential side effects. The goal of this project is to develop a novel CA IX selective inhibitor for anticancer applications. Through computational chemistry methods I discovered that Grayanotoxin (GTX) III allosterically inhibits the CA IX at Site 9, a novel allosteric binding site I identified. Thus, I am proposing that this interaction is a new molecular mechanism of action. GTX III is not selective to the CA IX; however, it does allosterically inhibit the CA IX, so I used GTX III as a template for designing novel CA IX selective inhibitors. Guided by the molecular interaction of GTX III and the CA isozymes, I designed a new class of 3800 novel allosteric-binding compounds. From these, I identified the top novel compounds that have CA IX selectivity and higher binding affinities towards the CA IX than some currently used FDA-approved CA inhibitors. My top novel CA IX specific inhibitors show promising potential as medication leads for anticancer applications.

Awards Won:
Fourth Award of $500