Evaluation of the Efficacy of novel HK and GADPH Inhibitors in Cancer Cells

Chaz J. Heikkila
Swenson College of Science and Engineering
University of Duluth Minnesota
Heikk089@d.umn.edu

Introduction

The rapid, uncontrolled growth of tumor cells is characterized by elevated aerobic glycolysis and the repression of oxidative phosphorylation (OXPHOS), known as the Warburg effect[1]. Although glycolysis is inefficient in producing ATP when compared to OXPHOS, cancer cells preferentially activate glycolysis in order to preserve carbon skeletons for biosynthesis, prevent reactive oxygen species (ROS)-induced cell death and sustain growth in hypoxic or acidic environments[1]. The metabolic differences between normal and cancerous cells offer therapeutic strategies that involve preferentially killing cancer cells by inhibition of glycolytic enzymes. Major pharmacological targets of the glycolytic pathway include hexokinase (HK), phosphofructokinase (PFK) and glyceraldehyde 3-phosphate dehydrogenase (GADPH). Already, HK inhibitory molecules such as 3-bromopyruvate, a pyruvate analog, and lonidamine, an indazole carboxylic acid derivative, are undergoing clinical trials for the treatment of various types of cancer[1]. As promising enzyme targets for tumorigenesis attenuation, my project objective was to synthesize and evaluate the efficacy of novel HK and GADPH inhibitors.

Using organic reaction techniques such as reduction, bromination and base-catalyzed coupling, a library of over 30 HK and GADPH inhibitors was established for in vitro kinetic assays. After several rounds of structure optimization, our compounds show potent inhibition of GADPH and HK and are non-cytotoxic. We are currently increasing the water solubility of our molecules to improve cellular uptake for in vivo analysis. Ultimately, the efforts of the past seven months in the lab have resulted in potential tumor inhibitors that will soon undergo animal testing by trained graduate students. And the research experience has been highly rewarding in itself.

This research has sparked my passion for scientific discovery and clarified potential professional goals. From organic synthesis to NMR spectroscopy and in vitro biological analysis, I have partaken in various aspects of pharmaceutical design that will be invaluable to future endeavors as a clinical pharmacist and post-doctoral fellow. For the first time in my life, I feel a genuine sense of ownership and pride in my work that motivates me to achieve long-term goals in pharmacological research and education.

Furthermore, this research has developed a personal confidence in my ability to add value to research teams and achieve autonomy in my work. Beginning as an undergraduate research volunteer, I have progressed to a grant-funded lab technician who now trains and directs new volunteers. Overall, I am grateful to be participating at the forefront of cancer therapy discovery and excited for the direction my career path is taking as a result of this research.

References

1. Lopez-Lazaro, Miguel. (2008) The Warburg effect: why and how do cancer cells activate glycolysis in the presence of oxygen? *Anti-Cancer Agents in Medicinal Chemistry* 8: 305-312.