Abstract

The goal of this project is to accelerate the preclinical development of a new drug for the most common and universally fatal brain tumors - malignant gliomas.

Malignant gliomas are highly hypoxic tumors, and the cells from the poorly oxygenated areas of the tumor have increased resistance to treatment. Our in press data (Oncotarget) suggest that mitochondrial adaptation of glioma cells to hypoxia is controlled by the mitochondrial protease and DNA-binding factor Lon. In vitro, Lon over-expression is associated with glioma resistance to the two most common treatment modalities: radiation and chemotherapy with temozolomide. In vivo, Lon over-expression causes accelerated tumor growth and shortens survival. Lon down-regulation using siRNAs decreases glioma cell proliferation, migration and survival in hypoxic conditions, but siRNA use is impractical in clinical setting. Through collaboration with another UCI faculty (Dr. Chris Vanderwal), we now have a specific, small molecule Lon inhibitor (coumarinic compound 4-CC4). CC4 is very effective in our glioma cell cultures, and has a synergistic activity with the standard of care therapies such as temozolomide. Furthermore, the coumarinic molecules are small, and have the ability to cross the blood-brain barrier. There are a number of coumarinic compounds already in clinical use.

The specific goal of this revised ICTS proposal is to test CC4 safety in normal cells and healthy animals, as well as CC4 efficacy in a well-established mouse model of glioma. In our reformulated proposal, we have addressed all the reviewer’s suggestions, including the careful planning of new toxicity experiments. The completion of these steps will allow us to determine if CC4 is a potentially effective anti-glioma treatment.

Two specific aims are proposed:

Specific Aim 1: To determine whether CC4 treatment at relevant, anti-glioma doses causes toxicity in a panel of normal human cell lines. The effects of Lon protease down-regulation using either siRNA or shRNA in normal human cell lines has been extensively reported – and is usually mild. However, the effects of using the CC4 inhibitor are yet to be studied. The aim of this goal is to determine the effects (reduced proliferation, induction of apoptosis) of a wide range of CC4 concentrations on different cell lines derived from human tissues (lung fibroblasts, neural stem cells, epithelial cells, HUVEC).

Specific Aim 2: To determine whether CC4 is safe and effective (i.e., can inhibit Lon activity) in vivo. The goal of this aim is to determine the maximum tolerated dose (MTD) of CC4 in nude mice and to test whether the CC4 administration at the maximum tolerated dose (MTD) leads to Lon protease activity inhibition in both subcutaneous and intracranial glioma models, proving that CC4 can penetrate the tumor and cross the blood-brain barrier.

If successful, this research will open the field of mitochondria-targeted therapy as a modality to overcome the treatment resistance of malignant gliomas. The final aim of this project is to generate the data needed for a new R01 application to develop this compound for clinical use through the FDA’s Office of Orphan Products Development grant program.