

Bankhead-Coley Cancer Research Program

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Bridge (1-year project)

Project Title: Combining Anti-Angiogenesis Strategies and Radiotherapy

Project Summary: Radiation therapy is one of the primary forms of treatment for cancer. In fact ~70percent of all patients who are cured of their cancer receive radiation treatments. Still, many patients are not cured and ultimately succumb to their disease. There are many reasons for the treatment failures, including the aggressive growth of the cancer and the ability of cancer cells to spread (metastasize) to other organs in the body. Both are critically influenced by the state of the tumor vasculature (the blood vessel network that supports the growth of the cancer). For these reasons, there has been a great deal of interest in cancer research in developing new anticancer drugs that target the tumor blood vessel network. For the past 10 years this research team has been involved in evaluating novel vascular targeting therapies using mouse and human tumor cells grown in tissue culture or immune suppressed mice. The investigations have shown that such treatments can have a profound effect on the response of tumors. When used in combination with radiotherapy, they can amplify the anti-tumor effects of radiation. Many of the agents and concepts that the team has studied have begun to enter clinical trials in cancer. However, the initial clinical studies have made it increasingly clear that much remains to be done to most effectively apply this new approach to cancer treatment in patients. Preclinical investigations will provide a better understanding of how vascular targeting therapies act on tumors and interact with radiation therapy. This is the goal of the current grant work. The preclinical studies are designed to develop treatment approaches that will maximize the anticancer effects of vascular targeting therapies. One question that will be addressed is whether tumors that have very extensive blood vessel networks will be more susceptible to vascular targeting therapies. The answer to this important question is currently unknown. But if this is the case, as the team hypothesizes, it would mean that by measuring how extensive the blood vessels are in a tumor, a physician could identify those cancer patients who would benefit the most from receiving a vascular targeting therapy. A second question is focused on determining how a tumor is able to grow its own blood vessels. The current belief is that tumor cells release factors that cause existing blood vessels in the normal tissues to branch and grow towards the tumor. The tumor then incorporates these blood vessels as its own. Recently it has been suggested that the tumor may also recruit cells circulating in the blood stream to help form its own vasculature. To test whether this theory is valid, the team will isolate and label these circulating cells with a fluorescent stain so that it can be determined whether they are attracted to the tumor and contribute to blood vessels being formed. Should this be the case, it would allow the team to develop new treatment strategies to interfere with that process and thereby hamper the ability of the cancer to create its own vasculature. Thirdly, these studies will examine whether the cells that make up the blood vessels in a tumor can be targeted using a virus that is not capable of growing but can infect the cells of the tumor blood vessels. The team will use it to deliver a molecule that will kill those cells and thereby deprive the tumor of its vasculature. The final aspect of these studies involves the use of several vascular targeting therapies in combination in order to maximize the anti-tumor activity.

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Preliminary findings from the team's research indicate that this is not only feasible but leads to greater effects in tumors than any single vascular targeting therapy. Ultimately the goal is to test the best combination of vascular targeting agents with radiation. Thus, the overall focus of this grant is to develop and investigate novel vascular targeting strategies directed at improving cancer therapy when used alone or in combination with radiation therapy.