

## Bankhead-Coley Cancer Research Program

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Bridge (1-year project)*

**Project Title:** Anti-Tumor Activity of Sugar Analogs via Blocking Glycolysis Versus Glycosylation

**Project Summary:** The human body is made up mostly of cells that divide slowly, although cells that comprise hair, the gastrointestinal tract, and bone marrow (blood cells) grow quickly. Standard cancer chemotherapy attacks all fast-dividing cells in the body regardless of whether they are normal or tumor; that's why patients receiving chemotherapy lose their hair, have lower blood cell counts, and encounter intestinal problems. It is also why slow-growing tumor cells are the most difficult to cure. Since they survive standard chemotherapy, slow-growing cancer cells can give rise to more rapidly dividing cells that eventually become resistant to all drugs. In most, if not all, solid tumors there are pockets of slow-growing cells that reside in areas that receive little or no oxygen (hypoxic). Due to hypoxia, these tumor cells are forced to divide more slowly than the rest of the tumor cells that receive normal oxygen levels. Under hypoxia, cancer cells burn (or metabolize) sugar inefficiently and therefore need to take up much more of it to survive than normal cells in the body that are well-oxygenated. Thus, if they are fed false sugars such as 2-deoxyglucose (2-DG), their only energy source is cut off, and they literally starve to death. In contrast, normal cells, can withstand this treatment for two reasons. First, they take up less of this false sugar than tumor cells do. Second, because they are exposed to oxygen through normal blood flow, they can also utilize fats and proteins as alternative sources of energy. In contrast the slow-growing tumor cells, due to their lack of oxygen, cannot metabolize fats or proteins, and therefore, when their sugar metabolism is blocked with 2-DG, they die. As an outcome of testing our ideas in three in vitro models of hypoxia and in vivo in human tumor xenografts grown in nude mice, the FDA recently approved a Phase I clinical trial using 2-DG (to kill the slow-growing hypoxic cell population) in combination with a standard chemotherapeutic (taxotere—to kill the rapidly-proliferating well-oxygenated cells) in patients suffering from various types of solid tumors. The current research effort is focused on continuing these studies to expand the use of false sugars in raising the clinical efficacy of chemotherapy. The direction for the continuation of this work stems from the following three recent findings:

1. The glucose analog, 2-fluoro-deoxyglucose (2-FG), which is used to locate and identify tumors in patients by PET scan, has been found to be 3x more potent than 2-DG in killing hypoxic tumor cells in the in vitro models. Thus, Aim #1 is directed at determining whether 2-FG has better activity than 2-DG in killing hypoxic cells in vivo (first in laboratory animals and, if successful, then in a clinical trial).
2. The ubiquitous hypoxia-inducible factor (HIF) mediates resistance to 2-DG and 2-FG in hypoxic tumor cells. Results from Aim #1 will be combined with in vitro experiments in Aim #2, which are geared toward understanding how hypoxic tumor cells become resistant to these false sugars through up-regulation of HIF.
3. A select number of tumor cell types growing in the presence of oxygen are killed by 2-DG but not by 2-FG, which forms the focus of Aim #3. Each of these three

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specific aims are directly translatable to clinical treatment of cancer patients and are clearly in accord with the goals of the Bankhead-Coley Program.