

Bankhead-Coley Cancer Research Program

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Project Title: A Novel Class of Anticancer Agents Targeting Cyclin-Dependent Kinases

Project Summary: Breast cancer accounts for a large number of cancer-related fatalities. Unfortunately, the available anti-cancer drugs are woefully inadequate in effectively treating this devastating disease. However, there is reason for optimism because our knowledge of how breast cancer cells proliferate uncontrollably is increasing rapidly. In particular, protein enzymes called Cyclin-dependent kinases are known to become hyper-activated in breast cancers. Importantly, preventing the production of these proteins in mice using genetic approaches prevents breast cancer induced by the Her2/neu oncogene. Equally importantly, genetically inactivating these proteins has little or no harmful effects on the growth and development of these mice. The Her2/neu oncogene becomes activated in about 30 percent of human breast cancers. This indicates that if a drug were available that inhibited the Cyclin-dependent kinases that drive cancer cell proliferation, such agents would block the growth of cancer cells with relatively minor toxicity. Numerous pharmaceutical companies have developed Cyclin-dependent kinase inhibitors for just this purpose. Some of these drugs are currently undergoing clinical testing against human cancers. The problem with these agents is that they are likely to inhibit many other types of kinases resulting in unanticipated toxic side-effects. In addition, these drugs block only some of the actions of Cyclin-dependent kinases, but leave other actions of these proteins unaffected. We have recently identified a new class of Cyclin-dependent kinase inhibitors. These inhibitors block all of the actions of Cyclin-dependent kinases because they function by decreasing the levels of these proteins in breast cancer cells. In addition, they are highly specific for Cyclin-dependent kinases and are therefore expected to exhibit fewer and less severe side effects. In laboratory experiments, these drugs potently inhibit the proliferation of both human and mouse breast cancer cells. This grant explores how these drugs function to inhibit the growth of breast cancer cells. Animal studies will be performed to examine the toxicity of the drugs and to determine the proper dosage for treating animals. Finally, studies will be performed in which mice with breast cancer driven by the Her2/neu oncogene are treated with or without drugs to determine whether drug treatment inhibits tumor growth or causes tumor regression. If the drugs significantly inhibit breast cancer growth and improve survival in mice, these results will provide the necessary rationale for performing clinical trials with the hope that this novel class of anti-cancer drugs will be an effective weapon against breast cancer in humans.