Public Abstract

**Rationale and Objective of the Proposal:** In tissues, such as the epidermis, it is well established that precancerous cells remain hidden and are kept dormant for years by cues from normal neighbors. However, at a critical stage in tumor progression, normal cells in the surrounding microenvironment not only permit the transformed cell to form a tumor but actively cooperate in the process. It is also well known that proper communication among different neighboring cell populations is critical for normal breast development. Wnt and Hedgehog signaling are two pathways that are frequently linked and transmit developmental signals to maintain normal breast homeostasis. The aberrant activation of one developmental pathway therefore leads to coordinated distortion in the other pathway resulting in inappropriate communication between neighboring cells that facilitates tumor development. Wnt1 protein, when produced in excess, induces breast tumors in mice composed of large numbers of basal cells with stem cell features. We have shown that the neighboring stromal cells reactivate a second (Hedgehog) developmental pathway. Importantly, Hedgehog reactivation correlates tightly with tumor formation, suggesting that it may provide critical support for tumor onset and therefore have potential as useful marker and therapeutic target. Our experiments will test whether active stromal Hedgehog signaling provides a tumor-sustaining cancer stem cell niche that is important for Wnt-1 tumor formation, by using genetically engineered mice that carry reporters that permit us to visualize these signals and to disrupt specific communications between cells.

**PI's Career Goals:** My long-term goal is to become an independent investigator who can make meaningful contributions to translational research on breast cancer. This proposal will greatly expand my training in breast cancer research by equipping me with strong foundation in genetic immunological and molecular approaches to the study of preclinical mouse models. The project will deepen my understanding of three areas: breast cancer stem cells (CSCs); the tumor microenvironment; and the role of developmental pathways in human breast cancer. I will be working closely with my mentor (Pamela Cowin, Ph.D.), who is a leader in links between breast development and breast cancer and has a prior strong background in studying cell-cell interactions. A committee of scientists, belonging to the NYU Cancer Center, who have expertise in breast cancer stem cells, tumor microenvironment and translational research, will also guide me in this project. This research proposal has the potential to reveal novel biomarkers of the activated tumor microenvironment that I could continue to study from a translational perspective as diagnostic tools and therapeutic targets.

**Interim Outcomes and Contributions to the Field:** Basal-type breast cancers are initially responsive to therapy but rebound in a highly aggressive manner. Treatment, to date, is ultimately ineffective and patients with this subtype of breast cancer have very poor outcome. Currently, we understand little about the etiology of this tumor subtype and therefore fundamental research into causative factors is essential at this stage. A significant proportion of invasive human breast cancers develop in the context of unopposed Wnt signaling due to loss of a Wnt antagonist (sFRP). Hedgehog pathway upregulation has also been reported in human breast cancer cells and their surrounding stroma. Wnt1 mice recapitulate these aspects of human breast cancer and provide a valid experimental model. They develop tumors due to excess Wnt, show abnormal Hedgehog pathway activation in basal as well as stromal cells, and are enriched in basal cells with stem cell features that share many molecular hallmarks of basal breast cancer. This proposal addresses fundamental mechanisms of tumor onset and progression and has the potential to reveal novel biomarkers of the activated tumor microenvironment. Information about these critical steps in tumorigenesis and progression is required for the logical development of strategies to identify, track and therapeutically eradicate the tumor-initiating cancer stem cell source and to eliminate the supportive niche provided by neighboring stromal cells that sustain tumor development.