Public Abstract

Breast cancer begins as a disease localized to the breast tissue and in and of itself can lead to tremendous pain and disfigurement. However, for many if not most breast cancer patients, the spread of cancer cells from the original breast tumor to distant organs, a process termed metastasis, is the leading cause of death. Roughly 1 in 1000 women in the United States develop some form of breast cancer, yielding greater than 200,000 new patients every year. Current estimates indicate that, of those patients, up to 30% diagnosed with early-stage (non-metastatic) breast cancer will go on to develop metastatic disease and 6-10% of patients already show signs of metastasis at diagnosis. Treatment options are still incredibly limited, particularly for those patients whose disease involves critical sites such as the lung or bone. These two metastatic sites are also the most frequently observed in breast cancer, and patients with lung metastasis in particular are at grave risk due to the essential role played by the lung in providing oxygen to the entire body. Importantly, despite causing approximately 90% of cancer-based mortality, clinical trials specifically targeting metastasis account for less than 8.5% of all cancer-focused therapy trials with breast-cancer metastasis focused trials representing roughly 1/10th of those. To improve this disparity, it is critical to perform fundamental studies to elevate understanding of how breast cancer metastases form and evolve leading to novel therapeutic approaches to treat this devastating disease.

A key theme that has emerged from studies over the past decade is a critical role for the immune system in the spread of breast tumor cells to the lung. The immune cells involved are highly diverse in nature and play rather conflicting roles in this disease. Some immune cells directly serve to aid the tumor, increasing its ability to survive and grow within the lung while others are at work to detect and defend against the cancer. A leading current theory is that the balance of these opposing functions is critical to determining patient response to therapy and survival. Intriguingly, my lab and others have found that one particular type of immune cell, called a monocyte, participates in both of this contrasting functions of the immune response. At the heart of the dual-role played by these cells may be the fact that monocytes have the ability to change their form and function depending on the context and environment they find themselves. In some states these cells actively provide growth support to the tumor in others actively seeking out and killing the tumor cells, though our understanding of what drives these different states is poor at best. In addition, it is quite clear that monocytes are the source of a host of factors that influence the cells around them (tumor cells, immune cells, etc.…) though the exact nature of this influence is largely unexplored. Our understanding of these lynchpin cells has been hindered by a lack of truly specific tools with which to study them. Most available reagents impact not only monocytes but other related populations, making it very difficult to truly understand how monocytes themselves contribute to breast cancer metastasis.

In the studies in this proposal we seek to harness a new tool developed by my lab which allows us to specifically deplete (or remove) monocytes in animal models of breast cancer metastasis. This tool, a monocyte-specific antibody, will allow us to detail the specific functions of monocytes in the lung metastatic site. Moreover, as this antibody can be delivered at various times during the progression of metastatic breast cancer we will be able to determine how the role of monocytes varies at the earliest onset of metastasis through to the highly-patient relevant late stages of metastatic disease. Through these studies we intend to delineate the specific-contribution of monocytes to breast cancer metastasis, with special emphasis on how these cells influence outcome and survival. Additionally, we will combine this unique monocyte-specific reagent with a cutting-edge approach termed single cell RNA sequencing which will allow us to investigate not only how monocytes themselves evolve during the progression of metastasis but how their presence and function impacts the networks of cells that co-exist around them in the metastatic tumor. Our studies will shed new light the importance of monocytes for both support of and defense against metastasis. In recent years, several monocyte-focused clinical trials have been undertaken, based on the clear contribution of these cells to cancer and cancer metastasis. Unfortunately, the results of these studies have been almost universally disappointing. Evidence largely points to this not being due to a misunderstanding of the importance of monocytes to cancer and metastasis but because we don't currently understand how best to harness them for the benefit of our patients. The fundamental studies outlined in this proposal will lay the groundwork for a new class of therapies aimed at guiding the response of monocytes to specifically promote the anti-metastatic features and functions of these interesting cells while conversely blocking those functions that support tumor growth and spread.