

Public Abstract: Macrophage-based immunotherapy for eradication of pre-existing breast cancer metastases

A patient initially diagnosed with breast cancer has several treatment options including surgical resection, chemotherapy, radiation, therapies targeted at blocking specific signaling within the tumor cells or T cell based treatments. Each of these therapies has some benefit but also comes with limitations, such as collateral damage to normal cells, the development of resistance or decreased efficacy due to a lack of T cells in solid tumors. However, once tumor cells have escaped (metastasized) to generate new micro-tumors, the therapeutic options become even more limited. We believe that it is possible to harness the functions of macrophages, to help the immune system to kill tumor cells, even those in established metastatic sites. We hope to develop a new treatment that induces a patient's own immune cells to eradicate metastatic tumor cells in a localized manner, representing a more effective and less toxic approach than current options.

Macrophages exhibit two general behaviors, either functioning to kill invading bacteria and "bad" cells or aiding wound healing by encouraging new blood supply and limiting immune/inflammatory responses. Unfortunately, tumor cells recruit macrophages and induce the wound healing functions providing extra blood supply and minimizing immune responses against the tumor. However, we have developed unique genetically modified mice that enable increased signaling by a pathway known as NF-kappaB to be induced specifically in macrophages and have reported that this can inhibit the process of metastasis in breast and melanoma tumor models. We have preliminary evidence that this is achieved both by direct killing of tumor cells by activated macrophages and by indirect effects that increase T cell infiltration into the tumors. This suggests the exciting possibility that we can turn the very cells that tumors have recruited to help them into agents that fight back against them. The benefits to this approach include: 1) the tumor cells are killed independent of oncogenic mutations minimizing the opportunity for development of resistance; 2) induction of the effects can be localized to dense populations of macrophages immediately adjacent to the tumor thus minimizing collateral damage; 3) even micro-tumors and existing metastases in occult sites could be impacted; 4) a patient's own immune defenses are mobilized such that effects of heterogeneity of mutations within tumor cells has less effect on outcome and the efficacy of other immune therapies (eg. checkpoint inhibitors) could be enhanced.

We believe that it is possible to target the macrophages that are being "educated" close to tumors and instruct them to exhibit immune responses, similar to those induced by a localized infection, that will both directly kill tumor cells in existing lung and bone metastases and also recruit additional T cell responses that could improve outcomes when combined with checkpoint inhibitors. We will use our transgenic mice to demonstrate that increasing NF-kappaB activity in tumor associated macrophages can be effective, to understand mechanisms and to determine timing and delivery of treatments to maximize benefits while limiting side effects. To move our findings into a clinical setting, we need to develop a translational method. Nanoparticles are being developed and tested in clinical trials as drug delivery systems for patients. We have tested the nanoparticles that we have developed to deliver siRNA and modulate macrophage behavior in cell culture and in basic delivery studies in mice. In these published studies we have shown that these nanoparticles can shift macrophages towards anti-tumor behaviors in cell culture, can deliver their "payload" to the desired specific cell types in mice, and that the particles themselves in mice show no toxicity. The next step is to gain evidence of significant therapeutic potential in our mouse models with existing lung and bone metastases. This is critical data that will be necessary prior to moving our formulations into early stage clinical trials.

Our goal is to develop a novel therapy that will limit or eradicate established breast cancer metastases in lung and bone and thus allow patients to survive and have more precious time to spend with their families.