Susan G. Komen
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Therapeutic strategies to restore the immunosurveillance against breast cancer

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Public Abstract:
The immune system is an important defense against tumor progression. However, some tumors are able to escape the control of the immune system by suppressing its function. In our preliminary studies, we have identified a series of molecules that are secreted by cancer cells and cause immunosuppression through increasing a specialized cell type called MDSCs. Some of the molecules are previously known to also drive the proliferation of tumor cells themselves. MDSCs inhibit T cells and blunt the anti-tumor immunity. Depletion of MDSCs delays tumor progression and reduces distant metastasis in animal models. In breast cancer patients, MDSCs increase as tumors progress. Based on these findings, we aim to therapeutically target the identified molecules, block the generation of MDSCs, and determine the consequent effects on both the immune system and tumor progression. Specifically, we will pursue the following specific aims. First, we will investigate the relative contribution of MDSC-mediated immunosuppression to tumor progression. We aim to understand that, compared to the mechanisms inside of tumor cells, to what extent MDSCs drive tumor progression through suppressing the immune system. These data will provide insights into potential efficacies of treatment preventing the generation of MDSCs. Second, we will carefully test possible strategies of blocking MDSCs, and establish feasible regimens that may be translated into clinical applications. Because some of the molecules that mediate the production of MDSCs also play roles in regulating the generation of normal while blood cells, we need to carefully adjust the dosage and experiment different combinations of drugs to maximize the reduction of MDSCs and minimize the impact on normal cells. Finally, we will test the link between the identified molecules and MDSCs using patient-derived xenograft models. These models are established by directly transplanting pieces of fresh human breast tumors into mice. Tumors are able to grow in mice and have been shown to retain most clinical features including therapeutic responses to different treatments. These models faithful represent the original tumors in patients. Extending our discoveries and therapeutic strategies to these models will represent one step closer to the clinic. Taken together, our project has the potential to determine not only therapeutic strategies but also biological markers that may be used to treat and identify patients with weakened anti-tumor immunity, and who might benefit from restoration of normal immune function. The normalization of immune system may represent a patient-friendly way to treat cancer with durable efficacies and high specificity, but little side-effects. Combined with other therapies, it will most likely lead to a reduction of breast cancer mortality within the next decade.