Lay abstract

Of all recent advances in the treatment of human cancers, the ability to re-engage the immune system in anti-tumor cell killing and control holds the most promise. While there have been great strides in immune-mediated treatment of certain cancers such as melanoma, which are known as immunologically recognized cancers, the response of breast cancers has been dismal, which are typically immune stealthy and not well recognized by the immune system. Anti-tumor immune therapies such as antibodies to the immune masking factor PD-1 act in large part by blocking a specific type of immune cell known as the T regulatory cell (Treg), whose function is to suppress immune responses and thereby prevent autoimmunity. Breast cancers more than most other types of cancer co-opt Tregs and the PD-1 system, and use them to prevent recognition of breast cancers by the immune response. Consequently, in breast cancer there has been only modest progress in the application of immunotherapies such as anti-PD-1 antibodies, and clinical trials have resulted in significant responses in only a very small subset of women with metastatic disease. Based on our research, we have found a way to specifically block immune suppressing Tregs at the molecular level which is highly specific and enhances anti-tumor immune responses by αPD-1 antibody therapy. We have found that there is a specific signal that regulates the protein synthesis program within T cells that turns them into immune-suppressing, pro-tumor Tregs, promotes their development and their pro-tumor immune suppressing functions, and which is a highly druggable target. Notably, we are separately funded to develop a small molecule inhibitor to this target. Moreover, I have a long track record of successful drug discovery, development and clinical introduction of new therapeutics in metastatic breast cancer derived from my own research. Therefore, the potential to actually develop novel therapeutics from this advanced preclinical research is real. Our work is clinically relevant and significant because it seeks to both better understand which molecular signals we need to block to prevent pro-metastatic immune suppression by Tregs, and provides a path forward to exploit this understanding for the development of new small molecular inhibitors of Treg function for treatment of metastatic breast cancer.