Immune and Molecular Therapy of Gastrointestinal Stromal Tumor
DeMatteo Lab 2026

Gastrointestinal stromal tumor is the most common human sarcoma and largely driven by activating mutations in *KIT* or *PDGFRA* genes. While tyrosine kinase inhibitors (TKIs) like imatinib have revolutionized therapy for GIST, 10-20% of patients present with GISTs that are resistant to TKI therapy. Furthermore, TKIs are not usually curative, and most patients develop resistance with a few years. Therefore, the development of improved and novel therapies remains essential. Our lab focuses on immune and molecular combination therapies that aim to augment the efficacy of these tyrosine kinase inhibitors.

An important tool in systemic cancer treatment is immunotherapy, which stimulates the T cells of the immune system to target and destroy cancer cells. Unfortunately, conventional immunotherapy treatments, which leverage the most commonly studied subtypes of T cells ($\alpha\beta$ Tcells), have not shown efficacy in GIST patients, even when combined with TKIs. Based on analyzing RNA derived from tumors of GIST patients, our lab showed that a different, rarer subtype of T cell (called $\gamma\delta$ T cell) was associated with improved overall survival 5 year survival in GIST patients.

Some of our recent work has focused on characterizing the biology of $\gamma\delta$ T cells in GISTs and identifying the ways in which they can be used for novel types of immunotherapy for GISTs. We isolated these T cells from tumors of GIST patients with a technique called flow cytometry and looked at the RNA profiles at a single-cell level. Intriguingly, we found that $\gamma\delta$ T cells' function and subtypes were differentially altered in patients that had received prolonged imatinib therapy, as well as those who developed resistance to imatinib therapy. These $\gamma\delta$ T cells normally function to drive inflammatory immune responses that are associated with the killing of tumor cells. By examining RNA from isolated $\gamma\delta$ T cells in GISTs developed in our genetically engineered mouse model, we were able to identify several shifts in the cellular physiology of these cells in response to imatinib therapy, notably a response to the hypoxia generated in the tumor during imatinib therapy; this may represent a key component of the dampening effect on anti-tumoral immunity that is known to accompany imatinib therapy. These key insights open the door for development of novel $\gamma\delta$ T cell-directed therapies that seek to stimulate their inflammatory subpopulations as well as mitigate the hypoxic environment that may drive their suppression.

In contrast to $\gamma\delta$ T cells, macrophages represent the largest proportion of immune cells in the tumor microenvironment (TME). Macrophages are generally known for their ability to phagocytose (engulf & destroy) bacteria, infected cells and other debris. They typically do not have the direct cytotoxic effects that T cells or natural killer (NK) cells have. However, they also play an important role as regulatory cells for the immune system, shaping the response and recruitment of B, T and NK cells via cell signaling pathways. Their role is critical to influencing the immune environment, both in general and in the TME.

Current projects include classifying the populations of TAMs found in GIST and determining how they compare to other cancer types. Other projects involve the testing of several compounds in our mouse model known to stimulate TAMs, either to change their numbers or their signaling functions. These experiments have three aims: to block pro tumoral TAM populations, stimulate a specific TAM subset to promote a hostile environment to the tumor or modulate their metabolic activity to support the antitumoral response. New compounds discovered which modify the TAMs and TME will lay the groundwork for potential novel therapies that can be trialed in humans for the treatment of GIST.

DeMatteo Laboratory Personnel

Ronald P. DeMatteo MD is John Rhea Barton Professor and Chair of Surgery at the University of Pennsylvania. His laboratory has been funded by the NIH since 2001. His laboratory attracts trainees from throughout the country. He will supervise all aspects of the proposal. The lab is entirely focused on GIST.

Shan Zeng PhD is a molecular biologist and is primarily studying the role of gamma delta T cells in GIST.

Ferdi Rossi PhD is a molecular biologist. He previously worked with Peter Besmer for 10 years and now works in our lab. He has multiple projects in GIST.

Montana Morris MD is a postdoctoral fellow from NYU Langone Health and is working to classify the subtypes of tumor-associated macrophages (TAMs), their function, and potential therapeutic strategies.

Iulia Barbur MD is a postdoctoral fellow from the University of Pennsylvania who is working on an analysis of novel treatments. She evaluates immunohistochemistry and cell signaling pathways to determine tumor cell response in mouse models following treatment.

Charles Neff MD is a postdoctoral fellow from Lankenau Medical Center, Main Line Health who is working with Montana on the potential modification of certain subtypes of tumor-associated macrophages to promote their therapeutic efficacy.

Kevin Do is a research technician currently investigating alternative tyrosine kinase inhibitors. He will be leaving the lab to begin medical school at Cooper.

Matthew Weber is a newly hired research technician. He will be assisting in laboratory management and ongoing projects as detailed above until he develops his own research interest.