Immune and Molecular Therapy of Gastrointestinal Stromal Tumor
DeMatteo Lab 2025

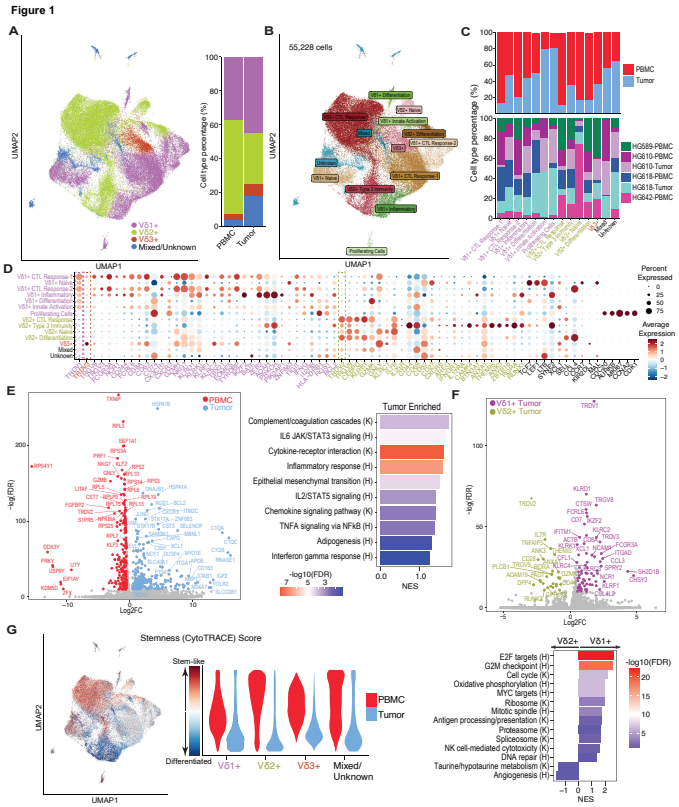
Background

Gastrointestinal stromal tumors are the most common human sarcoma and are 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 rarely curative, and the majority of patients with certain high-risk tumors have disease recurrence within 5 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.

Current Focus and Future Directions

An important tool in systemic cancer treatment is immunotherapy, which seeks to stimulate 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 ($\alpha\beta$ T cells), have not shown efficacy in GIST, even when combined with TKIs. Recently, looking at the RNA derived from tumors of GIST patients, our lab showed that a different, rarer subtype of T cell ($\gamma\delta$-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 in our biobank with a technique called flow cytometry and looked at the RNA profiles at a single-cell level. This identified even more specialized subpopulations, one of which we showed to drive inflammatory immune responses that are associated with the killing of tumor cells; we further identified aspects of tumor cell biology that can stimulate this population. 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 that developed resistance to imatinib therapy. 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 by 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.



Single Cell RNA-seq analysis γδ-T cells of cells from patients with GIST

Other current projects include exploring the testing of several compounds in our mouse model known to stimulate other cells of the immune system, such as tumor-associated macrophages (TAMs), the receptors of which have been identified as being highly expressed in GIST TAMs. Additionally, we are seeking to characterize the novel role estrogen-related receptor might play in driving the growth and survival of GIST tumor cells, and how targeting it might be leveraged for therapy.

DeMatteo Laboratory Personnel

1. 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. All of the work in the lab is now focused on GIST.

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

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

4. Hyunjee Kwak MD is a postdoctoral fellow from the University of California San Francisco – East Bay, and is studying CD40 agonism in enhancing imatinib's anti-tumoral effect.

5. Taylor Hartlein MD is a postdoctoral fellow from Kaweah Health and is studying the estrogen-related receptor pathway in GIST.

6. Montana Morris MD is a postdoctoral fellow from NYU Langone Health and is working to classify the subtypes of Tumor Associated Macrophages (TAMs), their role in GIST, and the potential therapeutic benefit of their modulation

7. Iulia Barbur MD is a surgical resident from the University of Pennsylvania who is working on an analysis of a GIST database.

8. Kevin Do is a research technician currently investigating alternative tyrosine kinase inhibitors.