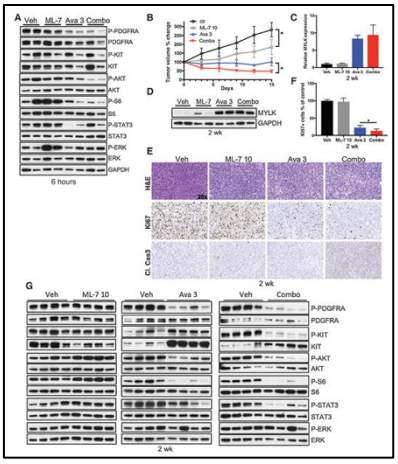
Immune and Molecular Therapy of Gastrointestinal Stromal Tumor
DeMatteo Lab 2023

Background

GIST is the most common human sarcoma, and approximately 85% of these tumors are attributable to a mutation in either *KIT* or *PDGFRA* genes. Imatinib mesylate is a tyrosine kinase inhibitor (TKI) that targets both of these genes and is effective in nearly 80% of patients with GIST. The advent of tyrosine kinase inhibitors has increased the median survival from 1 year to over 5 years. Despite this success, imatinib and the other tyrosine kinase inhibitors are not curative even in patients who respond, and many GISTs develop resistance to these drugs, necessitating further therapeutic approaches. Our lab has recently focused on discovering alternative approaches that may increase the efficacy of these tyrosine kinase inhibitors with combination therapy.

Current Focus and Future Directions



We have been using our immunocompetent, genetically engineered Kit $^{V558\Delta/+}$ mouse model which develops a cecal GIST with similar histology, Kit signaling, response to tyrosine kinase inhibitors, and immune response as seen in human GIST. We recently published work on Kit ligand, the natural ligand for the Kit receptor and showed that tumor cells as well as endothelia and smooth muscle cells produce Kit ligand in our mouse model, even after imatinib therapy. Kit ligand remains an important therapeutic target. In addition, we also recently published details of an in vivo model that was developed to study a particular *PDGFRA* mutation and the mechanism of tumor persistence following treatment with avapritinib, a drug used after patients develop resistance to imatinib. We found that resistance to avapritinib can be caused by upregulation of myosin light-chain kinase (MYLK) inhibition and suggest that concomitant MYLK inhibition may enable the use of a lower dose of avapritinib to avoid cognitive side effects.

In addition to the above mechanisms, we are also studying various immune targets to block or activate in conjunction with imatinib to enhance imatinib's anti-tumoral effect. These targets include ICOS, CD40, and VISTA. We are also utilizing recently acquired scRNAseq data of human GIST samples in order to categorize different immune cell populations and their gene expression to correlate to treatment response.

Summary

Our lab continues to search for new therapies to enhance the activity of tyrosine kinase inhibition in the treatment of GIST. We will be working to better understand TAMs in order to recruit and activate these immune cells to enhance the immune response to GIST. We will then be using combination therapy focusing on CD40 with the goal of activating the immune system to work in tandem with imatinib. We are so grateful for your continued support as we work toward these goals of combating human GIST.

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. Drew Tieniber MD is a postdoctoral fellow from the University of Pennsylvania and is using bioinformatics to study the CD8 T cell response to GIST.

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

6. Katherine Tardy MD is a postdoctoral fellow from Lankenau Medical Center and is studying ICOS blockade to enhance imatinib's anti-tumoral effect.

7. Alina Mangold MD is a postdoctoral fellow from Germany and is studying the role of regulatory T cells in the GIST tumor microenviroment and immune response.

8. Juan Esteban Perez MD is a postdoctoral fellow from the University of Pennsylvania and is working to classify the subtypes of Tumor Associated Macrophages (TAMs) and their role in GIST.

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