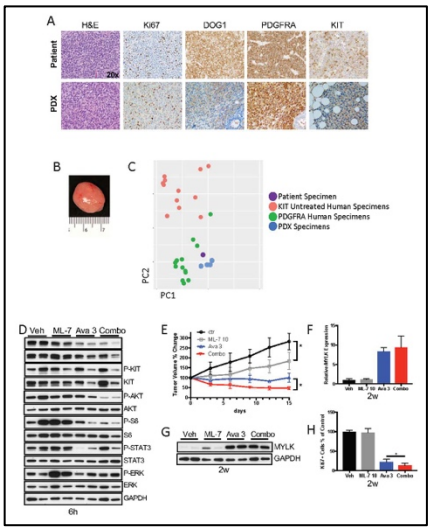
Immune and Molecular Therapy of Gastrointestinal Stromal Tumor
DeMatteo Lab 2024

Background

Gastrointestinal stromal tumor is the most common human sarcoma and is mostly driven by activating mutations in *KIT* or *PDGFRA* genes. While tyrosine kinase inhibitors (TKIs) like imatinib target both gene products and are effective in nearly 80% of patients with GIST, the *PDGFRA D842V* mutation is resistant to imatinib and most other TKIs. While TKI have revolutionized GIST treatment, they are not curative and many GISTs that originally respond to TKIs tend to develop resistance due to secondary and tertiary mutations in *KIT* or *PDGFRA* genes. Therefore, it is important to develop new therapeutic approaches. Our lab focuses on combination therapies with the goal to increase the efficacy of these tyrosine kinase inhibitors.

Current Focus and Future Directions



We have recently developed the first patient-derived xenograft of *PDGFRA D842V*-mutant GIST, the most common *PDGFRA* mutation that is also resistant to imatinib and most other TKIs. This in vivo model was used to study the effect of avapritinib, a drug developed for this mutation, but with limited use due to its dose-dependent cognitive side effects. We found that while avapritinib reduced tumor volume and PDGFRA oncogenic signaling, it also caused upregulation of myosin light chain kinase (MYLK), a protein mostly known to play a role in muscle contraction, but recently shown to play other functions and involved in a multicomponent signaling pathway with several other protein kinases. We found that while the specific MYLK inhibitor ML-7 slowed tumor growth, it substantially improved the anti-tumor effects of low dose avapritinib in vivo. We showed that MYLK inhibition resulted in increased apoptosis. By interrogating our vast RNAseq data on human GISTs we were able to confirm that MYLK is not only expressed in *PDGFRA*-mutant GISTs but also in *KIT*-mutant GISTs. Using GIST T1 cells that harbor a KIT mutation, we showed that imatinib induced MYLK expression in a dose-dependent manner and had additive effects with ML-7 in reducing cell viability. MYLK induced expression by a TKI seems to depend on their anti-tumor effect. Our results suggest that in *PDGFRA D842V*-mutant GISTs, the simultaneous inhibition of MYLK with low doses of avapritinib could result in tumor regression while minimizing avapritinib side effects. They also indicate MYLK as a potential target candidate in *KIT*-mutant GISTs.

In addition, we have been using our immunocompetent, genetically engineered Kit $^{V558\Delta/+}$ mouse model which develops a cecal GIST that is biologically similar to human GIST to investigate the function of intratumoral regulatory T cells. We are also studying various immune targets to block or activate in conjunction with imatinib to enhance imatinib's anti-tumoral effect, especially ICOS blockade, but we also are investigating CD40.

We also performed scRNAseq data of human GIST samples to look at how tumor and immune cell population change upon treatment. We are currently focused on a T cell subset.

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

6. 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.

7. 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.

8. Taylor Hartlein MD is a postdoctoral fellow from Kaweah Health and is studying a novel pathway in GIST.

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

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