GIST Cancer Research at Fox Chase Cancer Center

Prepared for Tania and Robert Stutman

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Contents

The GIST Cancer Research Fund at Fox Chase Cancer Center

The GIST Cancer Research Fund generously supports the groundbreaking work of Margaret von Mehren, MD, and Lori Rink, PhD, who lead a laboratory dedicated to Gastrointestinal Stromal Tumors (GIST) research. Thanks to your support, their team is advancing understanding of this rare cancer and driving the development of novel therapies that bring hope to patients at Fox Chase Cancer Center (FCCC) and beyond.

The GIST Translational Laboratory

Lori Rink, PhD, Associate Professor

Lori Rink, PhD

Dr. Lori Rink leads the GIST Laboratory, which includes three graduate students—**Gulnaz Alebaeva, Delia Zumpano, and Adam Chatoff**—with the support of **Jane Koshy**, Scientific Technician. Throughout the year, the lab also welcomed several rotating students, including **Elissa Kouemeni** (Empower Fellow, University of Delaware) and **Kexin Zhu** (FCB2P Fellow, Wuhan University). We look forward to welcoming **Sergio Abramov** in September 2025. In October 2024, **Dr. Rink and Dr. von Mehren**, along with students **Delia Zumpano and Adam Chatoff**, traveled to the **GIST Summit meeting in Essen, Germany.** Thanks to the generosity of the GIST Cancer Research Fund, Delia and Adam were able to participate in this important international meeting and share their work with the broader GIST research community.

Your continued support has helped advance research in five distinct areas:

1. Characterization of Persistent GIST Cells Receiving Targeted Therapy. RESEARCHERS: Nazeretian, Dr. Rink, Dr. Greco, and Dr. von Mehren

Ashot Nazaretian, Graduate Student

The tyrosine kinase inhibitors (TKIs) imatinib mesylate (IM) and avapritinib (AVA) are first-line therapies in advanced *KIT* and *PDGFRA* exon 18-mutated GIST, respectively, with initial tumor response observed in >80% of patients. Despite this, most patients progress within two years. Responses to post-IM lines of TKIs (sunitinib, regorafenib, and ripretinib) are brief (3-9 months), and no approved second-line therapy exists for patients with acquired resistance to AVA. Once all approved TKI therapies are ineffective, patients with advanced GIST are left without further treatment options.

Despite the success of IM and AVA, complete response to therapy is rare (~5%). Most GIST patients with advanced disease demonstrate either partial response (40-68%) or stable disease (14-32%) following TKI treatment. Therapeutic benefit is observed by decrease in tumor density and volume on

CT imaging, with the maximum tumor shrinkage typically occurring after ≥ six months of treatment. Similarly, *in vivo* studies performed in our laboratory using TKI-sensitive patient-derived GIST xenograft (PDX) models have recapitulated the clinical experience. TKI treatment in these sensitive PDX models leads to significant tumor shrinkage as early as 1-2 weeks into treatment, yet compete response is never achieved, and ultimately these tumors will exhibit resistance following ~5-6 weeks of therapy. Histologic examination of these responding "remnant" tumors (PDX and patient samples) revealed the presence of viable, KIT-positive GIST cells.

We hypothesize that these non-cycling or "senescence-like" residual tumor cells that remain after the bulk of the tumor has been eliminated by therapy may represent a form of tumor dormancy that may play an important early role in TKI resistance. In collaboration with **Dr. Stephanie Greco**, (Department of Surgical Oncology at FCCC) who has studied senescence in colon cancer, we are currently using innovative single cell-RNA sequencing of treated tumors to characterize the surviving cells and non-tumoral components (immune cells, cancer-associated fibroblasts). These studies have identified markers of interest that we are interrogating to determine if they may be involved in contributing to this dormant phenotype. Dr. Greco and Dr. Rink currently have a novel feasibility study open to isolate disseminated tumor cells (DTCs) from liver and blood in patients undergoing surgery for GIST. We believe these studies will allow us to develop future studies to investigate the biology of cancer dormancy and recurrence in GIST and to potentially identify novel vulnerabilities to target these surviving cells before they can re-emerge, potentially with polyclonal acquired drug-resistant mutations.

2. Identification of Wee1 as a Target in GIST by Kinome Profiling.
RESEARCHERS: Zumpano, Dr. Duncan, Dr. Rink and Dr. von Mehren

Delia Zumpano, BS
Graduate Student

GIST has three major genotypic subtypes: *KIT* mutant, *PDGFRA* mutant and SDH deficient GIST. Mutational subsets confer different natural histories and primary response to Gleevec. Limited options exist for those patients whose disease is refractory to primary treatment. Therefore, there is an urgent need to identify novel targets to provide additional therapeutic options and combinations for refractory GIST. Inhibition of cancer-promoting cell signaling pathways by targeting additional protein kinases active in GIST may provide these options.

In collaboration with **Dr. James Duncan** (Cancer Biology Program, FCCC), we have obtained kinome profiles for these subsets using an innovative mass spectrometry-based technique that allows us to analyze the majority of the human kinome simultaneously. We have successfully profiled the kinome using primary tumors from each of the three major GIST subtypes and have demonstrated that the basal activation state of the kinome in these distinct GIST subtypes cluster separately from each other and from normal gastric tissue. We have identified uniquely activated kinases in each group, as well as kinases which are overexpressed

in both *KIT* and *PDGFRA*-mutant GIST. We showed that GIST cells are exquisitely dependent on the cell cycle-related kinase, WEE1, identified in our kinome profiling study. WEE1 is the main controller of the G2/M checkpoint in the cell cycle. Further studies have suggested a role for WEE1 in other non-canonical functions, such as maintaining replication fork stability and safeguarding against replication stress. Furthermore, we demonstrated that targeting WEE1 in combination with avapritinib, both in cell lines and in mouse models revealed significant efficacy. This work was published in JCI Insight (https://insight.jci.org/articles/view/143474). We have been awarded a 5-year NCI R01 grant to elucidate the critical role of WEE1 in GIST with a specific focus on the protein's non-canonical roles. Recent studies have identified that GIST cell lines treated with WEE1 inhibitors in combination with TKIs show decreased replication fork speed and delays the cell cycle. Pausing the cell cycle could lead to errors in DNA replication and DNA damage, leading to cell death. In the past year, we have completed preclinical studies utilizing TKI-refractory patient derived GIST xenograft models which revealed significant efficacy of Wee1 inhibition in combination with TKIs.

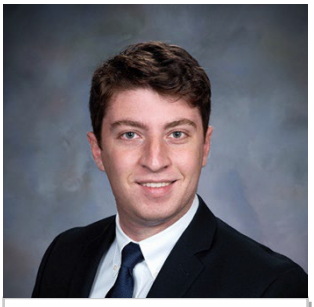
While GIST tumors are generally resistant to standard chemotherapy, we hypothesized that WEE1 inhibitors could make GIST cells more sensitive to DNA-damaging agents, regardless of mutation status. In preliminary studies of TKI-refractory GIST, we found that combining doxorubicin (a topoisomerase II inhibitor) with a WEE1 inhibitor increased apoptosis and reduced cell viability. Mechanistically, doxorubicin induces DNA damage, while WEE1 inhibition prevents repair by forcing damaged cells through the G2/M checkpoint, leading to replication fork stalling, mitotic catastrophe, and ultimately cell death. Encouragingly, in animal studies using both xenograft and PDX models, the combination of doxorubicin + WEE1 inhibitor significantly reduced tumor volume and improved survival compared to vehicle or single-agent treatments. This work is ongoing and holds promise for a new therapeutic strategy in resistant GIST.

3. *Development of Novel Patient-Derived Xenograft (PDX) Models of GIST.*
***RESEARCHERS:** Nazaretian, Dr. Rink and Dr. von Mehren*

A major limitation in GIST research is the lack of reliable laboratory models. Only a few GIST cell lines exist, and creating new ones has proven extremely challenging. To overcome this barrier, our team has partnered with surgical oncology colleagues to develop patient-derived xenograft (PDX) models. This approach involves implanting tumor tissue obtained during surgery directly into mice, allowing us to study tumors in a living system. To date, we have successfully established 14 PDX models representing a range of KIT/PDGFRA mutations and TKI sensitivities, including a novel avapritinib-resistant model. These models are a powerful tool for testing new drugs and drug combinations—such as those described in Section #2—in preclinical settings that closely mirror the diversity of patient tumors.

Our manuscript, *"Establishment and Genomic Validation of Novel Patient-Derived Xenograft Models for Drug Discovery in Gastrointestinal Stromal Tumor,"* which details these models and their genomic characterization, is currently under revision.

4. *Metabolic profiling of SDH-Deficient GIST*
RESEARCHERS: Chatoff, Dr. Snyder, Dr. Rink and Dr. von Mehren



Adam Chatoff, BS
Graduate Student

There is currently no first-line therapeutic option for SDH-deficient GIST, in stark contrast to the front-line tyrosine kinase inhibitors (imatinib and avapritinib) that have transformed treatment for advanced KIT/PDGFRA-mutant GIST.

In collaboration with **Dr. Nathaniel Snyder** (Center for Metabolic Disease Research, Lewis Katz School of Medicine at Temple University), we are investigating the metabolome of SDH-deficient GIST using cell lines, clinical samples, and genetic models. Our hypothesis is that SDH deficiency drives a broader network of metabolic rewiring and changes in enzyme activity, which may reveal new therapeutic vulnerabilities unique to this GIST subtype. These studies are ongoing and hold promise for uncovering novel treatment strategies.

In addition, our team recently published a review article, "Metabolic Effects of Succinate Dehydrogenase Loss in Cancer" in the *Journal of Cellular Physiology* (*https://doi.org/10.1002/jcp.70066*).

5. *Testing and evaluating new therapies in GIST*
Margaret von Mehren, MD
Chief, Division of Sarcoma Medical Oncology
Physician Director, Clinical Trials Office
Associate Director, Clinical Research
Professor, Department of Hematology/Oncology

Margaret von Mehren, MD

The primary goal of Dr. von Mehren's work is the testing and evaluation of new therapies for soft tissue sarcomas. Each year, approximately 7,000 new cases of are diagnosed in the U.S., with only about 50 percent of patients surviving their disease. For those whose sarcoma recurs, the limitations of current treatments lead to even lower survival rates. Dr. von Mehren has a particular interest in developing novel therapies for GIST, the most common sarcoma of the intestinal tract. GIST is characterized by the presence of a growth factor called KIT on the surface of tumor cells. In most cases, mutations in the KIT gene – and in rarer cases, in PDGFRA, BRAF, or SDH – activate the protein, driving tumor cells to continuously grow and divide.

Dr. von Mehren and the GIST laboratory have long focused on understanding and treating tumors that *do not* respond well to standard targeted therapies. These include subset of GIST without activating mutations (SDH deficient, NF-1 mutated or quadruple negative GIST), as well as tumors that have developed resistance to approved treatments.

Over the past year, the clinical trial program has centered on managing GIST resistant to available therapies:

- We completed patient enrollment in the **PEAK Phase 3 trial** (CGT9486 + sunitinib vs. sunitinib alone) and eagerly await results anticipated in late summer/early fall.
- We contributed to the **Phase 1/2 Study of DCCC-3116 in combination with ripretinib**, exploring new approaches for patients with advanced disease.
- Through a collaboration with **SARC**, we are conducting a **Phase 2 trial of bezuclastinib + sunitinib** to better understand mechanisms of resistance and identify which patients benefit most.
- The **first-in-human trial of IDRX-42** for metastatic and/or unresectable GIST continues to enroll patient, with plans to study this agent in earlier lines of therapy.
- We are preparing to join a **Phase 1a/1b trial of ziftomenib + imatinib**, testing a novel treatment strategy after imatinib failure.

These studies reflect our commitment to pushing the boundaries of GIST research—bringing forward new therapies, deepening our understanding of resistance, and offering patients access to innovative treatments.

Dr. von Mehren, Dr. Rink and their laboratory colleagues are deeply grateful for the generous and enduring support of the GIST Cancer Research Fund. For more than 22 years, your commitment has fueled our progress, with contributions totaling over $1.5 million. We are profoundly thankful for your partnership and the hope it brings to patients, families and the research community!