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 research efforts of Margaret von Mehren, MD and Lori Rink, PhD, who manage a lab devoted to GIST research. With your support, Dr. von Mehren, Dr. Rink and their team continue to focus on advancing our understanding of GIST in pursuit of novel therapies.

The GIST Translational Laboratory
Lori Rink, PhD
Associate Professor

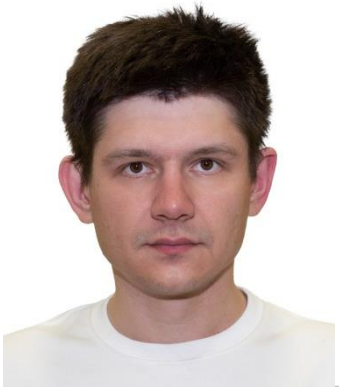
Lori Rink, PhD

Dr. Rink leads the GIST laboratory which includes three graduate students, Gulnaz Alebaeva, Delia Zumpano and Adam Chatoff, with the assistance of Jane Koshy, a Scientific Technician. Visiting scientist, Sergio Abramov, joined the group in October of 2025. Throughout the year, several students have rotated in the lab including (Elissa Kouemeni- Empower Fellow, University of Delaware; Elizabeth Brown- Undergraduate, Villanova University).

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

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

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.



Sergei Abramov,
Visiting Scientist

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

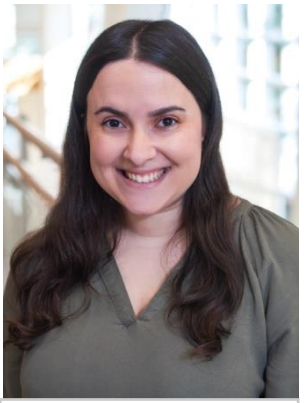
and volume on CT imaging, with the maximum tumor shrinkage typically occurring after ≥ six months of treatment. Similarly, *in vivo* studies performed in our laboratory using TKI-sensitive patient-derived GIST xenograft (PDX) models have recapitulated the clinical experience.

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 Fox Chase Cancer Center (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. During the last year, we enrolled the first patient on this study and have completed processing and analysis of samples. We hope to enroll the remainder of (n=9) participants in the upcoming year. 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 reemerge, 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. We have completed multiple preclinical studies using TKI-refractory patient-derived GIST xenograft (PDX) models that demonstrated significant antitumor activity with the combination of Wee1 inhibition and TKIs. All of the forementioned studies utilized the first-generation Wee1 inhibitor adavosertib, which showed promising efficacy but whose clinical development was discontinued due to dose-limiting toxicities and an unfavorable safety profile. To address this limitation, we recently initiated a collaboration with a clinical-stage biopharmaceutical company to evaluate a next-generation Wee1 inhibitor with substantially improved selectivity relative to adavosertib. Importantly, this agent has demonstrated favorable tolerability and has been safely administered at higher doses in Phase I clinical studies. We have already completed *in vitro* combination studies across a panel of GIST cell lines and found that this next-generation Wee1 inhibitor exhibits greater synergistic activity with TKIs than adavosertib. Ongoing *in vivo* preclinical studies have generated encouraging preliminary results, further supporting the potential of this combination strategy as a therapeutic approach for treatment-refractory GIST. This work is currently ongoing and a manuscript describing this work is in progress.

3. Development of Novel Patient-Derived Xenograft (PDX) Models of GIST.

RESEARCHERS: Dr. Rink and Dr. von Mehren

A limitation to the study of GIST is the lack of available models to study in the laboratory. There are limited cell lines that have been developed and attempts at developing them have been very challenging. One method to overcome this difficulty has been to implant tumor tissue removed at the time of surgery and directly implant the tissue into mice. This approach, called PDX models, is one that we have been taking in collaboration with our surgical oncology colleagues. To date we have successfully developed sixteen models with a variety of *KIT*/*PDGFRA* mutations and TKI sensitivities, including a novel avapritinib-resistant PDX model. Once developed, this approach allows for testing of novel drugs and drug combinations, including those described in Section #2, in animal models representing different genotypes to expand the available models for further preclinical testing of novel agents and or combinations of agents. Our manuscript describing our established PDX models and comprehensive genomic characterizations of these models, entitled "Establishment and Genomic Validation of Novel Patient-Derived Xenograft Models for Drug Discovery in Gastrointestinal Stromal Tumor" was recently accepted for publication in *BMC Cancer.*

4. Metabolic profiling of SDH-Deficient GIST

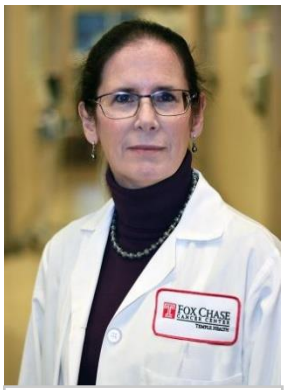
RESEARCHERS: Chatoff, Dr. Snyder, Dr. Rink and Dr. von Mehren

Adam Chatoff, BS
Graduate Student

There is no current first-line therapeutic option for SDH-deficient GIST. This is in stark contrast to therapeutic targeting with the front-line TKIs, IM and AVA, that have transformed therapy 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 profiling the metabolome in SDH-deficient GIST using SDH-deficient GIST cell lines, clinical samples, and genetic models. We hypothesize that SDH-deficiency in GIST may reveal a wider network of metabolic rewiring and changes in enzyme activity to deal with this rewiring with the potential to identify novel therapeutic vulnerabilities in this GIST subtype. In addition, to our review article entitled, "Metabolic Effects of Succinate Dehydrogenase Loss in Cancer" in the *Journal of Cellular Physiology (https://doi.org/10.1002/jcp.70066)* we are also drafting a manuscript detailing the metabolomic characterization studies that we have performed.

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. There are approximately 7,000 new cases of soft tissue sarcomas diagnosed annually with only 50% of patients surviving their disease, and with the limitations of current therapies, a far lower rate of survival if the sarcoma recurs. Dr. von Mehren has a particular interest in novel therapies for Gastrointestinal Stromal Tumors (GIST), the most common sarcoma of the intestinal tract. GIST is characterized by the presence of a growth factor, named KIT, found on the surface of the tumor cells. The gene for KIT, or in rare cases PDGFRA, BRAF, or SDH, undergoes mutations that activate the protein, causing tumor cells with these mutated genes to continuously grow and divide.

Dr. von Mehren and the GIST laboratory have long focused on understanding tumors that *do not* respond well to standard targeted directed therapy. These include the subset of tumors that don't carry activating mutations (SDH deficient, NF-1 mutated or quadruple negative GIST), and those GISTs that have become resistant to the standard therapies. Over the past year, the clinical trial efforts have focused on the management of GIST resistant to approved therapies. We completed accrual to "A Master Protocol for the Multi-cohort, Phase 1/2 Study of DCCC-3116 in Combination with Anticancer Therapies in Participants With Advanced Malignancies" where patients with advanced GIST were treated with the combination of ripretinib and DCCC-316 "A First-In-Human (FIH) Study of IDRX-42 in Participants with Metastatic and/or Unresectable Gastrointestinal Stromal Tumors (GIST)"; as well as "SARC044: A Phase II Trial of Bezuclastinib in Combination with Sunitinib in Patients with GIST Who Progressed on Sunitinib Monotherapy". The first two studies reported data at ASCO and SARC044 will be presented at CTOS this fall. We have started enrolling to several new trials. The first, "A Phase 1a/1b Study of the Safety, Pharmacokinetics, and Antitumor Activity of the Oral Menin Inhibitor Ziftomenib in Combination with Imatinib in Patients with Advanced Gastrointestinal Stromal Tumors (GIST) After Imatinib Failure" is evaluating a novel combination for GIST treatment. The second is "A Phase 3, Randomized, Multicenter, Open-

Label Study of IDRX-42 (GSK6042981) versus Sunitinib in Participants with Metastatic and/or Unresectable Gastrointestinal Stromal Tumors (GIST) after Imatinib Therapy (StrateGIST 3)" assessing the potential benefit of IDRX-42 as compared to sunitinib. We will also be enrolling patients to "A Phase 2, Multicenter, Study Evaluating the Efficacy, Safety, Tolerability, Pharmacokinetics of KQB198 in Combination with Imatinib in Participants with Advanced/Metastatic GI Stromal Tumor in 1st Line Setting" that tests if combination therapy using a KIT targeted agent as well as a SOS inhibitor leads to enhanced benefit. Lastly, we will be joining the randomized phase III trial of IDRX-42 compared with imatinib.

Ongoing Funding Efforts:

In January 2026, Drs. Rink and von Mehren joined colleagues from Dana Farber Cancer Institute, Oregon Health Sciences and University of Pennsylvania in submission of a GIST SPORE application to the National Cancer Institute. GCRF has been foundational in supporting our longstanding collaborations with these investigators, allowing such a proposal to be feasible.

Dr. von Mehren, Dr. Rink and their laboratory members are grateful for the generous support of the GIST Cancer Research Fund. Since 2002, GIST Cancer Research Fund has contributed $1.6M to Fox Chase Cancer Center research.