Perhaps because of its rarity, GIST has not received the same level of attention and research funding as other more common cancers. As a result, research in this field has attracted fewer investigators, and progress has been less rapid than needed. In addition, few hospitals and cancer centers have been able to develop the multidisciplinary treatment and research programs necessary to develop new therapies for GIST. Philanthropic support provides needed start-up funds for promising new research and support for educational programs, as well as building new patient care and research facilities.

Our hope is to make a difference for current and future GIST patients. A single donor can make a world of difference for GIST research. A gift of any amount would have an immediate, significant impact on developing better care for GIST patients at The University of Miami, Sylvester Comprehensive Cancer Center and throughout the world. Any gift is 100% directed to GIST Cancer Research.

At Sylvester, we have several active GIST research projects which would advance at a much faster rate with additional support. These trials are summarized below.

**Project 1: Inhibition Of Autophagy Sensitizes Gastrointestinal Stromal Tumor Cells To imatinib and Bcl-2 Inhibitor-Induced Apoptosis.** Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the GI tract. Most GISTs are driven by mutations in KIT or platelet-derived growth factor receptor-α (PDGFRA), which responds well to imatinib, a tyrosine kinase inhibitor (TKI) that blocks KIT and PDGFR-α signaling. Bcl-2 family plays a critical role in promoting tumor cell survival in GISTs. ABT-737 as an inhibitor of Bcl-2/Bcl-xL can result in a time and dose-dependent induction of cell death. Autophagy is another key mechanism to promote tumor cells survival, inhibition of which can induce the cell death in GISTs. Chloroquine, an antimalarial drug, has been also identified as an autophagy inhibitor. In this study, we propose to assess the combinational effects of imatinib, ABT-737 and chloroquine in GIST cells. Human GIST cell lines, GIST-T1 and GIST-882, will be employed in our study. Cells will be treated with imatinib, ABT-737 and chloroquine either separately or in different combinations. Cell viability will be tested by means of a color change assay and additive/synergistic effects will be analyzed by isobologram software. The levels of related proteins of apoptosis (PARP, Caspase-3) and autophagy (LC3-II, beclin-1) will be measured by western blot. Cell apoptosis and cell cycle will be tested by flow cytometry. GISTs will be grown in mice as tumor explants or using the cell lines. Tumor bearing mice will be treated with single agent, double combinations and the three-drug therapy. Tumors
will be harvested from mice and analyzed for the activity and mechanism of action of the 3 drugs as outlined above. We believe the combination of imatinib, ABT-737 and chloroquine will have collaborative effects on the treatment of GISTs in vitro. The combined strategy may enhance the clinical efficacy with acceptable toxicity. Once mouse experiments are completed, we plan to advance this regimen to a phase I clinical trial. (PI: Jon Trent, MD, PhD)

Project 2: This project is an open label, non-randomized, parallel-arm phase II study in patients with locally advanced or metastatic GIST where ctDNA will be used to guide the patient’s treatment of either sunitinib or regorafenib. This project will use circulating tumor DNA (ctDNA) from patients blood obtained by simple phlebotomy. Then, next generation sequencing (NGS, performed by Guardant Health) of ctDNA will be performed to determine whether a patient has a KIT exon 13/14 or exon 17/18 resistance mutation. Patients with KIT exon 13/14 mutation will be treated with sunitinib 37.5 mg orally (PO) once daily (QD) 28 days per cycle. Patients with KIT exon 17/18 mutation will be treated with regorafenib 120 mg orally (PO) once daily (QD) 28 days per cycle. Patients will be assessed for progression of disease (PD) every 56 days and will be allowed to continue until PD. Upon PD, patients will crossover to the alternative treatment and be treated until PD.

The primary objective is to determine the effect of ctDNA stratification on objective response rate (ORR) determined by modified Response Evaluation Criteria in Solid Tumors (mRECIST), version 1.1 in patients with advanced GIST treated with sunitinib or regorafenib. A secondary objective is to evaluate clinical benefit rate (CBR) determined by modified Response Evaluation Criteria in Solid Tumors (mRECIST), version 1.1 in patients with advanced GIST treated with sunitinib or regorafenib. A last objective is to evaluate the safety and tolerability of assigned treatment (sunitinib and regorafenib). This study population will include 48 GIST patients with metastatic or unresectable disease after progressing on imatinib over a 3-year (2 accruing/1 follow up) period.

Based on the estimated number of potentially eligible patients seen at University of Miami, a total of 48 patients, 24 patients per year, will be enrolled over a period of 2 years. To gather data on disease relapse/progression and survival, all patients will be under follow up for a minimum of 1 year unless they withdraw consent or are removed from the study for any reason. Thus, the expected study duration is 3 years.

This non-randomized, parallel-arm study will use a Bayesian predictive probability design that minimizes the number of patients enrolled to test the hypothesis. The design will be applied separately and based on the same assumptions in each of two treatment groups. We expected that 24 patients would be enrolled in each group. The primary endpoint is ORR based on mRECISTv1.1. We assume that ORR of historic control is 5% (p0). Thus, we consider this rate as uninteresting. The target ORR using either Sunitinib or Regorafenib is 25% (p1). The trial will monitor the number of observed responses continuously after evaluating the first 10 patients in each group. We use 10% significance level and 90% statistical power for monitoring. In conclusion, this study will determine
whether patient outcome can be improved by using ctDNA to determine secondary resistance mutation and treat patients with the most effective therapy. (PI: Jon Trent, MD, PhD)

Project 3:

Project 3a: To determine whether the use of hepatic areterial embolization is safe, effective and improves GIST patient quality of life. Bland embolization is the injection of microscopic particles into a small artery feeding a tumor which then expand to block blood flow to the tumor resulting in tumor cell death. This approach has been shown to control liver metastasis that progress after the GIST becomes resistant to imatinib. While the standard technique calls for lobar embolization, this approach embolizes half the liver, has more side-effects, and has the potential of severe side effects such as death. We propose to study a sub-lobar lesion specific method where only the enlarging GIST lesion is embolized. We postulate that this will allow for shorter recovery times and less pain associated with post-embolization syndrome without diminishing efficacy. Primary endpoints focus on evaluating safety and lesion specific progression free survival. Secondary endpoints will be overall survival and size-based evaluation to guide when a lesion should be targeted. This approach may require more interventions over all however they may be better tolerated. This impact on quality of life may in itself be beneficial. (PI: Shree Venkat, MD; Felipe de Souza, MD; Jon Trent, MD, PhD)

Project 3b: To determine safety and efficacy of preoperative embolization of GISTs. GIST treatment is based in a multidisciplinary approach often with adjuvant and neoadjuvant imatinib, sunitinib, regorafenib or ripretinib. Preoperative arterial embolization of hypervascular GISTs is reported as safe and effective. We propose to use preoperative hepatic arterial embolization to facilitate tumor resection with a significant reduction of intraoperative blood loss, morbidity and even mortality. Particularly, in very hypervascular tumors, capillary devascularization provides a more efficient reduction of blood loss during surgery, mandating super-selective sub-lobar embolization of as many arterial feeders as possible. The concept of interventional embolization of GIST focuses on the precise targeting of the occlusive embolic material to arterial tumor vessels supplying either primary or metastatic hypervascular GISTs prior to surgery. We believe this will reduce potentially high blood loss during surgery and therefore improve intra-operative conditions, reducing the complication rate. Moreover, in selected cases for surgical down staging, embolization might assume a neoadjuvant role. In this study the primary endpoints focus on evaluating tumor shrinkage and compare to pro-operative radiation isolated utilizing advanced MR imaging techniques. Secondary endpoints are to evaluate the rate of post-procedure complications, organ-sparring surgeries, effects of the embolization combined to systemic therapy and overall progression of disease. This impact on quality of life will be assessed. (PI: Shree Venkat, MD; Felipe de Souza, MD; Jon Trent, MD, PhD)

Project 4:

Project 4a: To assess the use of oral water contrast to assess GIST recurrence on computed tomography (CT) studies. Computed tomography (CT) is the main imaging study used to assess GIST recurrence. It has been shown that in the oncologic population oral contrast improves delineation of bowel, and increases the ability of radiologists to establish a diagnosis based on CT. Nonetheless, iodine or barium oral contrasts, given their hyperdense appearance, can obscure bleeding or enhancing masses in the bowel. Nonetheless, CTs for GISTs are often performed without administration of oral contrast or with oral administration of iodine or barium contrast, thus limiting the ability of radiologists to diagnose recurrence of GISTs, with potential delays in treatment. We plan to assess if the oral administration of water improves the performance of CT to
diagnose recurrence compared to CT performed without oral administration of water or with administration of barium or iodine oral contrast. (PI: Francesco Alessandrino, MD; Rosa Castillo, MD; Ty Subhawong, MD; Jon Trent, MD, PhD)

**Project 4b.** Assessment of imaging studies by multidisciplinary team during sarcoma tumor board: do they differ from radiologists’ assessment? Multidisciplinary tumor boards improve survival of oncologic patients. Nonetheless, imaging studies of GISTs patients are interpreted by radiologists separately and not always re-interpreted at time of multidisciplinary tumor board. Although radiologists are proficient in interpreting imaging studies, the lack of inputs from other clinicians, such as medical oncologists, surgical oncologists, and radiation oncologists, may have a negative impact in the radiologists’ assessment. We plan to compare the assessment of imaging studies by multidisciplinary team during sarcoma tumor board with the separate assessment by radiologists with different experience. (PI: Francesco Alessandrino, MD; Rosa Castillo, MD; Ty Subhawong, MD; Jon Trent, MD, PhD)

**Project 5:** To develop a comprehensive database of GIST patients in order to improve diagnosis, identify novel therapeutic targets, and develop new effective therapeutic approaches with fewer side effects. The database will consist of GIST patients who were treated or diagnosed at the University of Miami, Sylvester Comprehensive Cancer Center and Jackson Health system from 2003 to present. The estimated number of patients will be greater than 1,300 and as such will be the largest database of GIST patients developed to date. The major components of the database will be: Patients demographics, Clinical course of the disease, including all modalities of treatment (surgical, chemotherapy, radiation, ablations, etc.), responses to treatment and outcomes, radiographic imaging, pathological features of the disease, genetics of the tumor and its evolution during the disease course. The sources of the information are: Electronic medical records of the participating institutions and institutions participating in Care Everywhere, Pathology database (CoPath), pathology slides and blocks, imaging database – PACS. The goals of the creation of the GIST Database are: 1) Revision of the existing criteria that predict disease progression (which were developed in the pre-imatinib era) including the knowledge of the outcomes of the patients who received neoadjuvant and/or adjuvant chemotherapy. 2) Develop genetic criteria that predict the risk of disease progressions. 3) Discovery of new genetic targets for existing/developing treatment with biologicals and other modalities of targeted therapy, creating personalized treatment regimen for each patient with resistant GIST. In summary, the development of an overarching database will lead to faster more accurate diagnosis, earlier determination of response or progression on therapy, identification of new treatment targets, and ultimately development of better, safer therapy for GIST patients. (PI: Andrew Rosenberg, MD; Jon Trent, MD, PhD)