The Fletcher GIST research group and my colleagues at Mass General Brigham and Dana-Farber in Boston are so grateful for the ongoing support from GIST Cancer Research Fund donors, which has allowed us to develop an unparalled research infrastructure of GIST cell lines and related mouse models. This strong infrastructure has allowed our research group, in close collaboration with many others, to do the work leading to the FDA approvals of the available effective drugs for GIST. With the research funding from GCRF this past year and the progress we summarize below, we know additional effective therapies will be made possible in the near future. At a time when NIH funding sources are increasingly limited, we so appreciate GCRF's tireless efforts to continue enabling new effective GIST therapies and – ultimately – succeed in our mission of curing metastatic GIST.

The KIT and PDGFRA proteins which cause most GISTs belong to a group of proteins known as kinases. Kinases transfer energy to other proteins in the form of phosphorylation, and this causes GIST cells to grow uncontrollably. The great success of imatinib and other KIT/PDGFRA kinase inhibitors is that they shut down the kinase activity, and therefore GIST growth ceases. In many patients, this also results in a certain level of GIST cell death, but virtually always, a subset of the original GIST cells survive and can develop resistance to the KIT/PDGFRA-inhibitor drugs.

Therefore, our efforts supported by GCRF funding in the past year have been to develop drug approaches that change GIST therapies from drugs that stop growth to drugs that outright kill the GIST cells. In this work we have discovered ways in which other activated kinase proteins in GIST (beyond KIT and PDGFRA) support GIST growth and survival. In the case of these other kinases, activation does not result, as it does in KIT, from mutations. Our GCRF research support has also enabled us to identify the mechanisms by which these kinases are activated and, thereby, opened the door to new strategies to shut these companion kinases down.

Our GCRF research advances in the past year are relevant in both typical KIT (or PDGFRA) mutant GISTs in adults and to the SDH-deficient GISTs which are often found in younger individuals. The details are different in these GISTs, but in both cases multiple kinases play a “divide and conquer” role in causing GIST cells to grow and survive. Through a combined drug attack on these several kinases we are able not only to block GIST growth but also maximize cell death. These are strategies we will continue to work hard on in the next year, particularly identifying the least toxic drug strategies that silence several important kinases concurrently. The immediate goal of these studies is to provide the strongest possible evidence for approaches that should be tested in clinical trials. Our overarching GIST research goal, which has moved forward substantially with GCRF support in the past year, is to advance these approaches quickly for the benefit of GIST patients. We are mindful that novel drug approaches to treating GIST are needed urgently, to achieve our goal of curing metastatic GIST.