GIST Cancer Research Fund Proposal for 2023-2024
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Understanding mechanisms of resistance

Recently, two new drugs (avapritinib, ripretinib) have become approved for treatment of advanced GIST. These drugs provide new therapy options, but already we have seen clinical resistance to these new drugs. In order to continue to improve treatments, we need to understand the ways by which GIST cells can overcome these new "wonder drugs". We have established new technologies and cell lines to determine the mechanisms of resistance to these agents. Using our improved technologies, we can "fast forward" our experiments to more rapidly discover new resistance mutations. In addition to determining resistance mechanisms for these two new agents, we will also study resistance mechanisms to new drugs that will be tested in clinical studies in 2023-2024: CGT9486, THE-630, IDRX42, NB003, and the combination of CGT9486 + sunitinib. We have already completed pilot experiments with THE-630, IDRX42, NB003, and CGT9486

Developing strategies to optimize the treatment of PDGFRA-mutant GIST

Avapritinib is a recently approved drug for treatment of GIST with PDGFRA exon 18 mutations, particularly the imatinib-resistant PDGFRA D842V mutation. It is widely believed that all PDGFRA exon 18 mutant GIST are resistant to imatinib, but have developed evidence that this is not true. We are developing cell lines and prediction models that will help clinicians chose between imatinib and avapritinib for initial treatment of advanced GIST with PDGFRA exon 18 mutations. In addition, we are developing models and strategies to overcome avapritinib resistance as current there are no effective therapy.

Analysis of Succinate Dehydrogenase (SDH) Subunit Mutations in a human cell model

Mutation of various SDH subunits is seen in some cases of wild-type GIST, especially GIST arising in children or younger adults. These mutations can be sporadic or inherited as part of the Carney-Stratakis Syndrome. Recently, we have developed the first human cell lines that are deficient in SDHA, the most common type of mutation in SDH-deficient GIST. We are using these cell lines to assist in the diagnosis and genetic counseling of patients with potential inherited forms of GIST. In addition, we will use these cell lines to screen for novel treatments for SDH-deficient GIST. In collaboration with UCSD, we discovered that SDH-deficient cells are uniquely sensitive to an existing mild oral chemotherapy agent (temozolomide). As part of a consortium, we recently completed a phase 2 study of temozolomide for treatment of SDH-deficient GIST. We will continue to develop our cell line bank and study new therapeutic approaches We are now testing the efficacy of the combination of temozolomide and a DR5 agonist antibody (INBRX-109) for treatment of patients with advanced/metastatic SDH-deficient GIST.

We will provide and update on the above studies at the October 2023 GCRF patient event at OHSU.