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"Inhibiting Liver Cancer Stem Cells to Improve Response to Thermal Ablation"

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SCIENTIFIC ABSTRACT
Gastrointestinal stromal tumor (GIST) is an orphan disease with mutant succinate dehydrogenase (mSDH) tumors comprising <7.5% of GIST cases (i.e., 150-200 cases annually). These mSDH GIST occur in the setting of Familial Paraganglioma-GIST Syndrome, which affects adolescents and young adults and lack effective therapies, including tyrosine kinase inhibitors (TKIs). But, in a small clinical study of paraganglioma patients, only mSDH, but not wild-type SDH, tumors responded to the DNA damaging agent, temozolomide (TMZ). Currently, the major impediment to advancing mSDH GIST research has been a lack of human cell lines. Our group has now developed the first patient-derived mSDH GIST cell lines, which are TKI-resistant, but TMZ-sensitive. Moreover, a small cohort of our TKI-refractory mSDH GIST patients have had objective radiographic responses to TMZ. Thus, we hypothesize that mSDH GIST patients will respond to TMZ in a prospective clinical trial. We will evaluate the efficacy of TMZ in a Phase II, single arm study in advanced mSDH GIST patients with the objectives of determining ORR at 6 months (primary objective), PFS and OS, as well as evaluating serum metabolites as biomarkers of TMZ response. Overall, this represents a novel approach for repurposing an FDA-approved drug, TMZ, to treat an orphan disease without current effective therapy. We anticipate these studies will: 1) identify the first efficacious therapy for mSDH GIST; and 2) yield new insights into monitoring mSDH GIST treatment responses. These studies have the potential for immediate clinical impact for treating mSDH GIST patients.

LAY ABSTRACT
Gastrointestinal stromal tumor (GIST) caused by mutations in succinate dehydrogenase (SDH) genes that control sugar metabolism is a rare form of cancer that affects 150-200 patients annually. Making the situation worse, these tumors are inherited, and mostly affect teenagers and young adults. There no effective therapies for treating this cancer, nor are there available research models for studying drugs. However, our group has grown the first human GIST cells that have defects in these sugar genes in order to study this deadly cancer. We have identified temozolomide, a chemotherapy drug taken in pill form, as effective for killing these cells in the laboratory. Furthermore, we successfully treated a small group of UC San Diego GIST patients with temozolomide after they failed traditional GIST treatments. We now aim to perform a clinical trial to scientifically test the effectiveness of this drug in patients with GIST caused by these sugar metabolism defects. We will

also check blood levels of sugar breakdown products to determine if these are useful for following treatment responses. Overall, this represents a novel, homegrown, translation from bench-to-bedside using the FDA-approved drug temozolomide to treat a lethal form of cancer that has no effective treatment. We anticipate these studies will: 1) identify the first successful therapy for these GIST patients; and 2) yield new insights into monitoring their drug treatment responses. These studies have the potential for immediately changing clinical care of GIST patients in the prime of life.