CT161

First-in-Human Study of ENPP1 Inhibitor, SR-8541A, for the Treatment of Solid Tumors

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Abstract

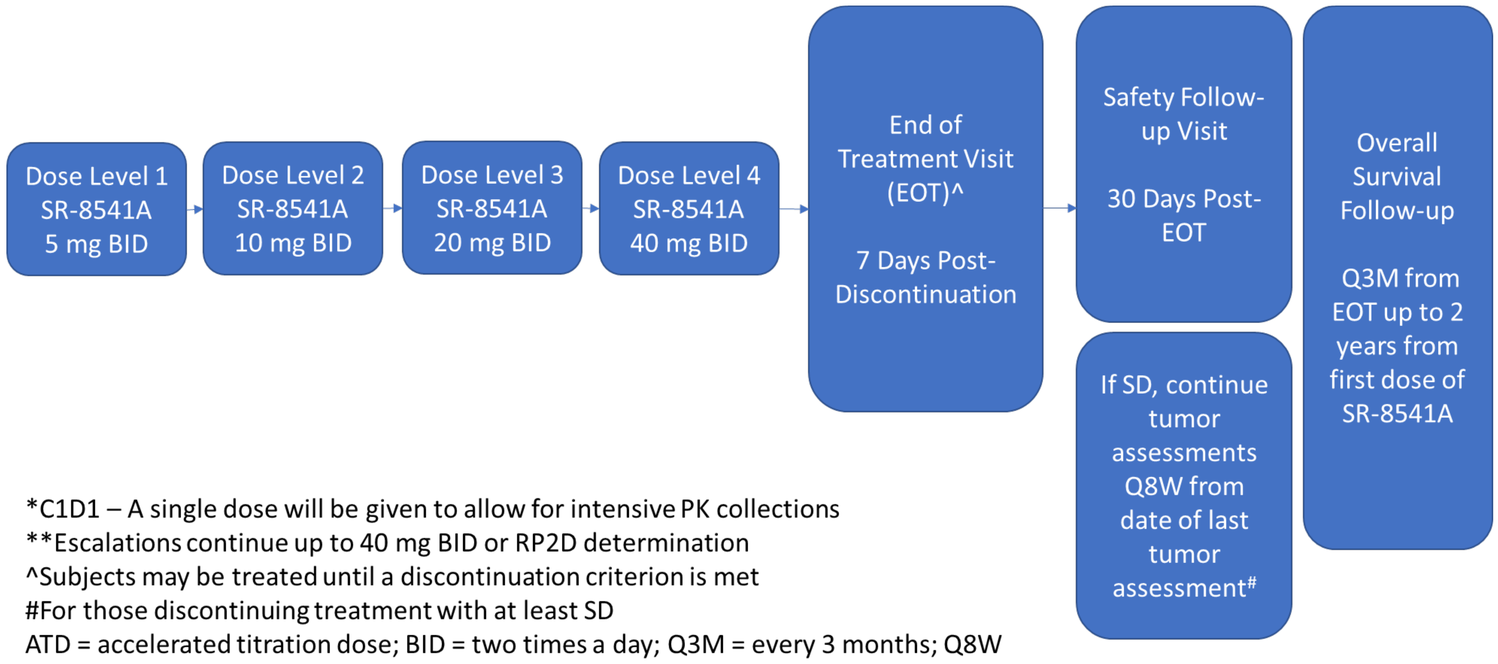
Purpose: Ectonucleotide Pyrophosphatase/Phosphodiesterase-1 (ENPP1) is the direct negative regulator of the STING pathway that hydrolyzes 2'3' cGAMP, the direct activator of STING. Compelling evidence suggests that careful and therapeutically relevant activation of the STING (STimulator of INterferon Genes) pathway is vital to elicit potent anti-cancer innate immune responses. STING is widely expressed and targeting it directly poses many challenges, including systemic activation of interferon. Therefore, alternative approaches to activate STING in a controlled manner may generate a better therapeutic response in cancer patients. Highest levels of 2'3' cGAMP can be found in tumors and recent evidence suggests that 2'3' cGAMP acts locally, as a paracrine immune transmitter. Recent studies have also reported elevated ENPP1 expression in metastatic tumors. We hypothesize that inhibiting ENPP1 with a small molecule inhibitor may produce superior outcomes by activating STING in the tumor microenvironment. We have developed SR-8541A, a highly selective and potent inhibitor of ENPP1. Our initial work to support the development of SR-8541A consisted of pharmacodynamics studies, bioanalytical development, pharmacokinetics (PK) and non-GLP toxicology studies in three species, a GLP repeat dose dog telemetry study, and 28-day GLP toxicology studies in rats and dogs including toxicokinetic (TK) analyses. Here we report initial findings from our ongoing first in human, phase I trial of SR-8541A in advanced metastatic solid tumors.

Methods: This study is evaluating the safety, tolerability, and pharmacokinetics (PK) of SR-8541A administered orally as a monotherapy in subjects with solid tumors which are refractory to standard therapeutic options, or for which there are no standard therapeutic options (NCT06063681). The primary objective of the study is to characterize the safety, tolerability, dose limiting toxicities (DLTs) and recommended phase 2 dose (RP2D) of SR-8541A. Secondarily, the study aims to evaluate the PK and efficacy per RECIST of SR-8541A. SR-8541A is administered orally in 28-day cycles and is following an accelerated titration dose (ATD) escalation. Blood samples are being collected for PK assessment, target engagement, and biomarker assessment.

Results: Sample analysis from subjects treated with SR-8541A (5 mg or 10 mg) is ongoing. No treatment-related adverse events have been reported. No dose-limiting toxicities have occurred during the 28-day DLT period. Plasma drug levels collected for the PK show Cmax concentrations in the projected therapeutic dose range. Biomarker assessment is ongoing and will be included in the presentation.

Conclusions: Patients treated at 5 mg and 10 mg with SR-8541A has shown to be safe and well tolerated. Pharmacokinetic data shows strong oral bioavailability and supports continued assessment of SR-8541A in the clinic.

Phase 1A: SR-8541A Study Schema



*C1D1 – A single dose will be given to allow for intensive PK collections
**Escalations continue up to 40 mg BID or RP2D determination
^Subjects may be treated until a discontinuation criterion is met
#For those discontinuing treatment with at least SD
ATD = accelerated titration dose; BID = two times a day; Q3M = every 3 months; Q8W = every 8 weeks; SD = stable disease

ENPP1: An Innate Immune Checkpoint

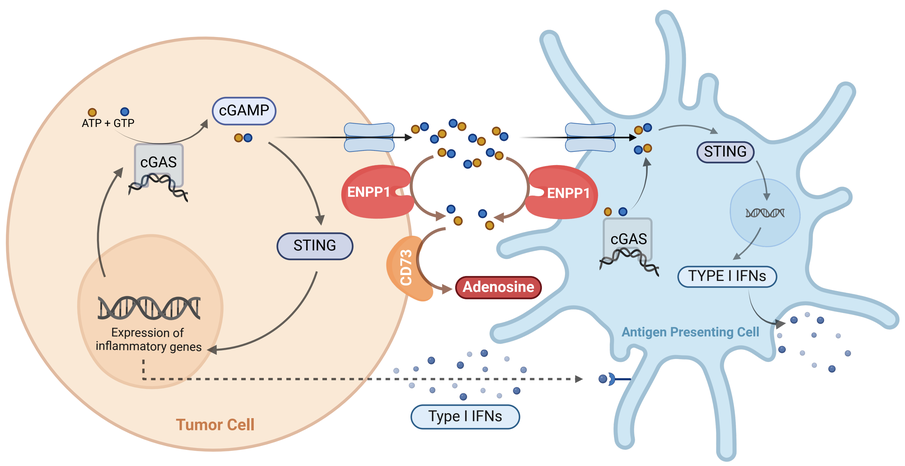


Figure 1. The cGAS-STING signaling pathway and its inhibition by ENPP1 through hydrolysis of 2'3'-cGAMP.

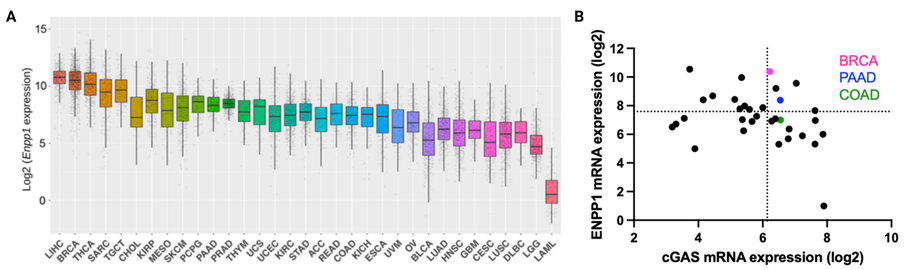


Figure 2. A) ENPP1 mRNA levels across 33 human cancer types found in the TCGA database. **B)** TGCA analysis of 33 different tumor types showing ENPP1 and cGAS expression. BRCA, COAD, and PAAD are highlighted as tumor types of interest. PMID

Single Dose PK Readout Shows Strong Bioavailability

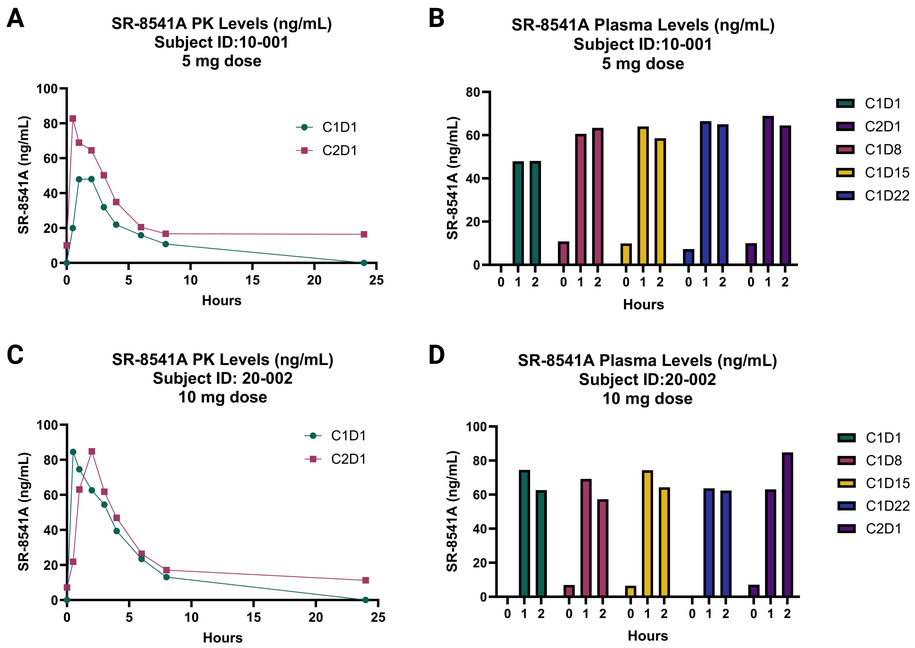


Figure 3. PK drug levels in plasma after a single oral dose of **A)** 5 mg or **C)** 10 mg of SR-8541A and PD drug levels measured weekly during 28 days of BID, oral dosing of **B)** 5 mg or **D)** 10 mg of SR-8541A.

Inhibition of ENPP1 Enzymatic Activity in Patient Serum

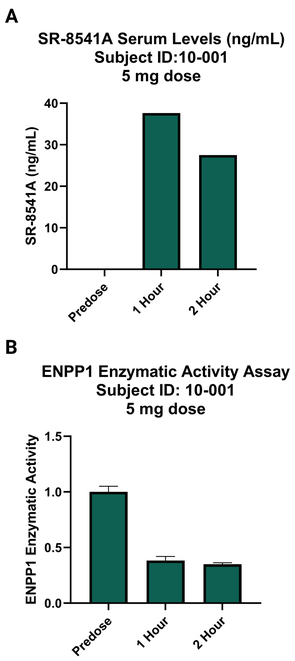


Figure 4. A) Serum drug levels measured weekly during 28 days of BID, oral dosing of 5 mg of SR-8541A. **B)** Measurement of ENPP1 activity in serum at baseline, 1 hr, and 2 hr post dose.

Conclusions & Next Steps

- To date, 6 patients have been enrolled in this Phase 1 A
- No treatment related adverse events, no SAEs, and no DLTs have been observed.
- Early PK data shows evidence of high bioavailability with both the 5 mg and 10 mg cohorts in the projected therapeutic range.
- PD studies conducted in patient serum show >60% inhibition of ENPP1 enzymatic activity in the 5 mg cohort.
- Additional patients are being enrolled to determine RP2D for future combination studies.

Contact Information & Funding

Reach out to Alexis Weston
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