

**Docket #:** S17-372

# **Small molecule inhibitors to overcome chemo- and radiation therapy resistant cancer**

**Disease indication** - Chemo- and radiation therapy resistant cancer, such as ovarian cancer, head and neck cancer (HNC), lung cancer, glioblastoma multiforme and breast cancer.

**Drug format** - Small molecule, to be used alone or in combination with existing chemotherapeutic drugs.

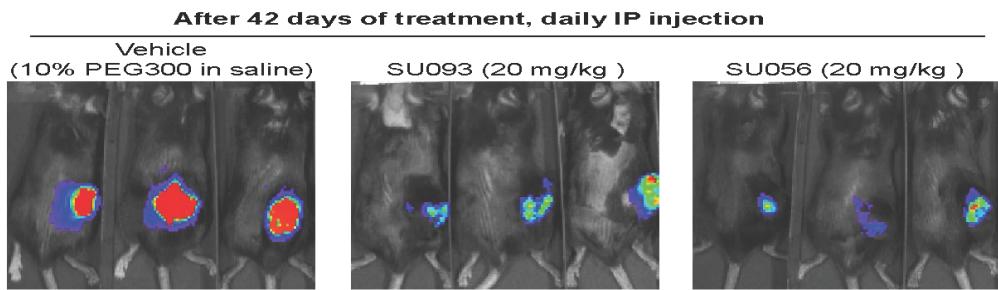
**Drug class** - First-in-class.

## **Research stage and Preliminary data:**

*In vitro*: Identified multiple small molecule inhibitors that restore radiation sensitivity and reduced hypoxia-mediated pro-survival tumor adaptation in ovarian cancer and HNC cell lines.

*PK/Safety*: Assessed the pharmacokinetics and safety profile of these compounds to prepare for clinical trial.

*In vivo*: Two compounds showed significant tumor regression in ovarian cancer model with no liver toxicity.



*Mice with an ovarian tumor xenograft were injected with GBP1 inhibitors (SU093 and SU056) or a vehicle control. The mice treated with the GBP1 inhibitors showed tumor regression after 42 days of treatment.*

**Target** - GBP1 (Guanylate-Binding Protein 1) - a large GTPase which plays a major role in cancer cells stressed by hypoxia or a low supply of nutrients.

**Background** - Resistance to radiation therapy and current chemotherapeutic agents such as paclitaxel, carboplatin and doxorubicin is a major cause of cancer treatment failure. The failure of first line chemo- and radiation therapy, particularly in ovarian cancer, emphasizes the need for new targeted drugs that can counteract resistance. GBP1 binds to pro-survival kinases such as serine/threonine-protein kinase pim-1 (PIM1) in the cytoskeleton and initiates a signaling pathway that induces resistance to taxane-based drugs and radiation therapy. GBP1 overexpression has been associated with paclitaxel and radioresistance in ovarian cancer and enhanced cell invasion in glioblastoma multiforme. GBP1 has also been implicated in resistance to radiation therapy in HNC patients. Compounds that inhibit GBP1 could close the “backdoor” of therapy resistance.

**Mode of action** - GBP1 is an upstream mediator of treatment resistance. Inhibiting the GBP1 active site disrupts GBP1:PIM1 interaction, antagonizes the pro-survival effects of PIM1 and mediates other treatment re-sensitizing effects. Overall, these compounds switch off a gateway of drug resistance and restore sensitivity to taxane and radiation therapy.

**Competitive edge** - First-in-class approach to an unmet medical need.

**Patent status** - Patent application filed

## Patents

- Published Application: [WO2019178091](#)
- Published Application: [20200375977](#)
- Issued: [11,771,692 \(USA\)](#)

## Innovators

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