OVERVIEW OF THERAPEUTIC TARGETING OF STAT5 PROPOSED FOR TREATMENT OF PROSTATE CANCER AND MYELOPROLIFERATIVE DISORDERS

Technology Description:
The present technology represents rationale-based drug design and acts by inhibiting phosphorylation and dimerization of STAT5. Significantly, the present technology inhibits both Jak2-induced and BCR-Abl (imatinib-sensitive and resistant)-induced phosphorylation and activation of STAT5. This blocks translocation of STAT5 dimer to the nucleus and thereby STAT5-driven gene transcription. It is recognized that in prostate cancer and myeloproliferative diseases, such as polycythemia vera, essential thrombocytosis, primary or idiopathic myelofibrosis and chronic myelogenous leukemia (CML), activation of STAT5 is critical for cell proliferation and viability. This is mediated through regulation of Cyclin D1 (thereby promoting advance of the tumor cell through the cell cycle and cell division) and BCL-XL (thereby preventing apoptosis) among the genes regulated by STAT5 and involved in control of cell death and proliferation. Pharmacological inhibition of STAT5 dimerization induces excessive apoptosis of prostate cancer cells and STAT5-driven leukemia cells (imatinib-sensitive and resistant).

The Src-homology 2 (SH2) domain of the STAT5a/b was targeted for the potential binding of a small molecular weight entity which would inhibit both phosphorylation and dimerization of STAT5a/b. This inhibition subsequently causes apoptosis in cancer cells susceptible to STAT5a/b regulation. Over 50,000 compounds in the NCI-chemical library were examined using a structure-based virtual screen to determine their ability to bind the SH2 domain and disrupt phosphorylation and dimerization of the STAT5a/b protein. The results of this screen identified a model compound, IST5-002, as a candidate inhibitor of STAT5a/b SH2-domain-mediated molecular interactions. The compound was demonstrated to be non-toxic in an acute Phase I study for advanced sarcomas. Based on the chemical structure of IST5-002, a family of compounds has been designed and synthesized. The members of the IST5-family of Stat5 inhibitors all inhibit Jak2/BCR-Abl-induced phosphorylation and dimerization of Stat5 and induce rapid apoptotic death of prostate cancer cells, leukemia cells and tumors in vivo.

In vitro and in vivo assays were established with which the predicted resultant interactions could be assessed. IST5-002 was tested for its ability to:
- Inhibit the phosphorylation of STAT5a/b (Jak2-and BCR-Abl induced)
- Inhibit the dimerization of STAT5a/b
- Inhibit the ability of STAT5 to translocate into the nucleus
- Inhibit the ability of STAT5 to bind and interact with DNA
- Inhibit the STAT5 mediated transcription of Cyclin D and BCL-XL
- Induce cell apoptosis and reduce the number of viable prostate cancer cells and imatinib-sensitive/resistant leukemia cells
- Decrease prostate cancer xenograph tumor growth in nude mice (effective at 25 mg/kg)

Depending on the specific assay, IST5-002 was effective in cell based in vitro assays at IC_{50} concentrations between 800 nM to 25 µM.
A group of analogs was synthesized and tested, and one compound, IST5-003, when tested in these assays proved to be more potent suggesting that compounds with improved potency and specificity can be discovered.

**Commercial Opportunity:**
Oncology targets which are STAT5 dependent would be appropriate. These include:
- Prostate cancer and
- Myeloproliferative diseases:
  - Polycythemia vera,
  - Essential thrombocytosis,
  - Myelofibrosis and
  - Chronic myelogenous leukemia (CML)

Because STAT5 mediates the biological effects of human growth hormone (GH) in acromegaly, therapeutics targeted at the actions mediated by STAT5 may also be useful in the management of acromegaly as well.

**Intellectual Property:**
Three provisional patent applications have been filed for compounds IST5-002, IST5-003, IST5-004, IST5-005, IST5-006 for the treatment of prostate cancer and hematologic neoplasms.

**What is on offer:**
This technology offers Stat5-inhibitor compounds IST5-002, IST5-003, IST5-004, IST5-005, IST5-006.

In addition, in vitro validation assays are available to assist in proposing development candidates, as well as animal models for in vivo testing. Also on offer is expertise which could assist in developing a screening assay suitable for automated robotic screening.

**Business Opportunity:** The technology is available for exclusive licensing.

**Follow-up:** Please contact Michael Caggiano at michael.caggiano@jefferson.edu or +1-215-955-6862 in The Office of Technology Transfer and Business Development at Thomas Jefferson University, citing Jefferson docket number NEV_MAR.005.