Serine Protease Inhibitors- Cancer Treatment and Prevention Technology

**Background:** In cancer cells, the MET and RON pathways are frequently dysregulated leading to changes that are required for tumor progression and metastasis, including cell migration, invasion, proliferation, differentiation, survival, and angiogenesis. Targeting these pathways with small molecule kinase inhibitors has been developed as a therapeutic strategy for metastatic cancer. However, these kinase inhibitors lack selectivity and sustained efficacy in the clinic due to rapid onset of resistance in patients, largely by upregulating their extracellular activating ligands. Hepatocyte growth factor (HGF) is the activating ligand for MET while macrophage stimulating protein (MSP) activates the RON pathway. Researchers at Washington University in St. Louis have developed dual function inhibitors that effectively block the production of HGF and MSP to inhibit both the MET and RON signaling pathways.

**Technology Description:** Both HGF and MSP are secreted as inactive forms and depend on HGFA (HGF Activator), matriptase and hepsin serine proteases, for their activation. Hence, triplex inhibitors of HGFA, matriptase and hepsin will block cell signaling through MET and RON pathways. Dr. James W. Janetka and his team have developed an array of inhibitors consisting of small peptide ketobenzothiazoles (kbt), cyclic peptides and non-peptidyl benzamidines. The benzamidine series are competitive small molecule inhibitors while the kbt series are mechanism-based covalent reversible inhibitors. The Janetka team has identified seven compound subsets with excellent potency and selectivity against one, two, or all three of HGFA, matriptase, and hepsin. Lead compounds exhibit good selectivity for HGFA, matriptase and hepsin over thrombin and Factor Xa. To date, compounds have been shown to have potent anticancer effects in breast, lung, prostate, and glioma cancer cell lines. Therefore, the inhibitors are promising new therapeutics for the prevention of tumor progression and treatment of metastatic cancers driven by MET and/or RON cell signaling.

**Key Advantages:**
- New drug for prevention of tumor progression and treatment of cancer metastasis
- Demonstrated efficacy in multiple cancers (breast/lung/prostate/glioma)
- Overcoming resistance to targeted therapies (e.g. MET and EGFR kinase inhibitors)
- Increased specificity may lead to a favorable toxicity profile
- Targets multiple pathways implicated in cancer oncogenic dependence


**Patents:** Patent pending

**Lead Inventor:** James W. Janetka, PhD; Associate Professor, Dept. of Biochemistry & Molecular Biophysics, and Adjunct Professor, Dept. of Chemistry at Washington University in St. Louis.

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