A replacement for chemotherapy?

Metastasis is a process where cancer cells of primary tumors gain properties enabling them to escape from the primary tumor and move to a secondary location in the body where they develop additional tumors. This event in advanced tumor progression subsequently results in >90% of all cancer patient deaths and there are currently no effective therapies to either prevent or treat metastatic cancer. In my lab at the Washington University School of Medicine in Saint Louis, we now have developed new small molecules which potently inhibit three key proteolytic enzymes, HGFA, matriptase and hepsin, which are essential for tumor progression and metastasis.

Similar to a blocked fuel pump in a vehicle which stops a car from moving and its engine from running, these inhibitors stop cancer cell signaling by cutting off the fuel (the growth factors HGF and MSP) supply to its engines, the c-MET and RON kinase receptors. The inhibitors block the processing of both HGF and MSP by the enzymes (oil refineries) and, without the fully refined growth factors, the kinase receptors cannot turn or stay on. Depending on the cancer type, an inhibitor of one or more of these enzymes will be necessary to block signaling and metastasis. We have rationally designed a complete set of seven compound subsets encompassing all such possible combinations in hand which inhibit:

HGFA, matriptase and hepsin
HGFA and matriptase
HGFA and hepsin
matriptase and hepsin
HGFA only
matriptase only
hepsin only

These exciting compounds are a powerful toolkit of new drugs for the treatment and prevention of metastatic cancer. The inhibitors, now in preclinical testing, have potential to 1) treat tumors that are chemoresistant to targeted kinase inhibitors and 2) to replace standard adjunct chemotherapy (post-surgery) altogether with safer and more effective therapeutics without the debilitating side-effects normally encountered in current cancer therapy.

***James W. Janetka**, Ph.D.*
Associate Professor of Biochemistry & Molecular Biophysics
Adjunct Professor of Chemistry, Washington University
Saint Louis, USA

Publication

Structure-based discovery of small molecule hepsin and HGFA protease inhibitors: Evaluation of potency and selectivity derived from distinct binding pockets.
Franco FM, Jones DE, Harris PK, Han Z, Wildman SA, Jarvis CM, Janetka JW.
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