**Background**

There is a strong demand for identification and validation of new druggable oncology targets. Mitosis is a unique window of opportunity for anti-cancer therapy. Aberrant mitosis in tumor cells often arrests cell proliferation and causes cell death. Consequently, inducing perturbation of mitosis through anti-mitotic therapies that target tubulin (e.g. taxanes and vinca alkloids) is a widely used approach in the treatment of cancer. However, there are severe limitations in anti-tubulin therapy because of the prominent functions of tubulin in normal cells beyond mitosis. For example, proper function of tubulin is required for vesicle transport and cell signaling in non-dividing neuronal cells; indeed, perturbation of tubulin function is often associated with neurotoxicity. Furthermore, a high frequency of resistance to anti-tubulin drugs limits the clinical usefulness to only about half of breast or ovarian cancer patients. To overcome these deficiencies drugs must selectively target proliferating mitotic cells.

**Technology**

Xuedong Liu of the University of Colorado recently solved the crystal structure of the TTK/Mps1 kinase domain and elucidated some of the major regulatory mechanisms governing this protein's function in mitosis. Using an approach that combines compound library screening, structural analysis, and rational drug design, Dr. Liu has developed small molecule compounds useful for modulating TTK/Mps1 activity, and therefore altering cellular activities such as signal transduction, cell proliferation, cell survival and cytokine secretion.

Additionally, Liu’s group has discovered that combination of an HDAC inhibitor with a TTK/Mps1 inhibitor results in robust tumor inhibition with minimal cytotoxicity; dual inhibitors that combine HDAC inhibitory activity with TTK/Mps1 inhibitory active were shown to be especially effective in tumor growth inhibition *in vivo* (data available under CDA).

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**Key Documents**

- "Novel TTK/Mps1 Kinase Inhibitors and Methods to Improve Therapeutic Windows of TTK/Mps1 Kinase Inhibitors." Provisional patent application filed May 10, 2013; available under CDA.


**Structural and mechanistic insights into Mps1 kinase activation.** J Cell Mol Med. 2009 Aug;13(8B):1679-94. PDF available upon request.