Inhibition of tumor growth by heparins *in vivo*

Unfractionated Heparin (UFH) and its improved version LMWH are known to have poly-pharmacological activity at various levels. Earlier studies have focused on the plasma anti-Xa and anti-IIa pharmacodynamics (PD) of the different LMWH. Other important PD parameters for heparin and LMWH might explain the diverse clinical impacts of this class of agents in thrombosis and beyond. These diverse pharmacological actions include stimulation of the release of the vascular tissue factor pathway inhibitor (TFPI), inhibition of inflammation (via NFκB), inhibition of key matrix degrading enzymes, inhibition of platelet-cancer cell adhesion, and other mechanisms. There is much evidence supporting the notion that LMWH play a key role in hypercoagulation in thrombosis, cancer, angiogenesis, and inflammatory disorders. In that regard, many cancer patients reportedly have a hypercoaguable state, with recurrent thrombosis due to the impact of cancer cells and chemotherapy or radiotherapy on the coagulation cascade. Experimental studies have demonstrated that UFH or its low molecular weight fractions interfere with various processes involved in tumor growth, tumor angiogenesis, and metastasis, with different efficacy depending on the structure features of the LMWH. Evidences from our laboratory documented that various LMWH have different potency in cancer associated thrombosis and in processes involved in tumor progression as a function of its structure.

Clinical trials have suggested a clinically relevant and improved efficacy of LMWH in this regard, as compared to UFH on the survival of cancer patients when given post-tumor surgery and with chemotherapy. Studies from our laboratory demonstrated a significant role for LMWH, and LMWH releasable TFPI on the regulation of angiogenesis, tumor growth, cancer-mediated inflammation, and tumor metastasis. The anti-angiogenesis effect of LMWH was shown to be reversed by anti-TFPI.

Studies from our laboratory also showed potent inhibition of matrix degrading enzymes by LMWH, but not by TFPI. Thus, modulation of tissue factor VIIa non-coagulant activities by LMWH releasable TFPI and the inhibitory effects on matrix degrading enzymes beside the anticoagulant and anti-inflammatory efficacy might provide combined mechanisms for improved clinical outcome in cancer patients.