Development of novel therapies for chronic colitis-associated colorectal cancer

Currently, colorectal cancer is the third most common malignant neoplasm worldwide and the third leading cause of cancer deaths in the United States. One of the paradigm shifts in colorectal cancer research describes that colonic inflammation may contribute to tumorigenesis and progression of colorectal cancer. However the mechanisms that might underlie the association between colonic inflammation and colorectal cancer remain unclear.

In addition to its function as a carrier protein, insulin-like growth factor binding protein-3 (IGFBP-3) appears to have direct antitumor and anti-inflammatory properties through activation of a specific receptor, IGFBP-3R. However, IGFBP-3 appears to be degraded (proteolyzed) into smaller fragments in chronic inflammatory conditions that may contribute to colorectal cancer development in patients with Inflammatory Bowel Diseases. Through a combination of integrated laboratory and animal experiments, this research proposal will systematically characterize the specific role of certain degratory enzymes (NSPs, neutrophil serine proteases) in particular, the NSP/IGFBP-3/IGFBP-3R axis in colitis-associated colorectal cancer and allow us to initiate immediate Phase II clinical trial of NSP inhibitors to colitis-associated colorectal cancer patients and further investigations of role of the axis as therapeutic targets.