Dr. Tamas Gonda

This proposal details a comprehensive 5-year plan for career development in the field of gastrointestinal chemoprevention research with a focus on the role of epigenetics in the tumor microenvironment. The research and career development plans are specifically aimed to explore new scientific directions and prepare me for a career as an independent physician- scientist. Dr Benjamin Tycko, with whom I have worked closely over the last four years, will serve as my primary mentor. He has a track record of successfully helping transition mentees to independent scientists and I am certain that he will support me to achieve that goal. My advisors were also selected to broaden my scientific background and along with significant departmental resources assure a successful transition to independence towards the end of the grant period. The central hypothesis of this application is that modifying DNA methylation profoundly impacts the tumor microenvironment and this leads to prevention of gastric dysplasia. In preliminary results we have established that distinct and significant changes in DNA methylation are observed in the tumor associated reactive stroma or myofibroblasts. These changes were noted in some of the earliest stages of neoplastic changes and were modifiable. Supplementation with folate, a key methyl donor, had beneficial effect on neoplastic progression and resulted in both reversal of some epigenetic marks in myofibroblasts and an effect on the tumor associated inflammatory response. Therefore, the proposal builds on these results to identify the benefit of combining epigenetic chemoprevention with anti-inflammatory interventions and to address the mechanisms of effect in stromal cells. In depth-methylation profiling, transgenic manipulation to target methylation in stromal cells and in-vitro co-culture experiments are used to dissect the direct role of stromal DNA methylation on neoplastic progression. The results will define the role of folate in gastric chemoprevention, identify whether stromal cells are primarily responsible for this effect and answer whether DNA methylation in myofibroblasts can be specifically targeted to halt early gastric neoplasia. As gastric cancer remains a major public health problem and Helicobacter eradication is not sufficient to prevent progression of pre-neoplastic lesions the clinical impact of these experiments is significant and translation of these results to human studies will be readily feasible.