General Summary of Division of Genetics

In the past three years (2006-2008), we have established gastric cancer mouse model (*K19-Wnt1/C2mE: Gan* mice) thorough simultaneous activation of Wnt and PGE_2 signaling pathways in gastric mucosa. Using *Gan* mouse model, we have investigated the role of host inflammatory response and angiogenesis in gastric tumorigenesis. We have also evaluated the chemopreventive or anti-cancer effects of several compounds on gastric tumorigenesis of *Gan* mice in collaboration with pharmaceutical companies. To investigate the effects of PGE_2 in other tissues, we constructed another transgenic mice expressing PGE_2 in pancreatic islets and examined the relationship between PGE_2-induced responses and diabetes.

A) *Gan* mice develop gastric tumors that recapitulate human gastric cancer.

It has been established that induction of COX-2 and mPGES-1 is found in variety of cancer tissues including gastrointestinal cancer. COX-2 and mPGES-1 cooperate to biosynthase PGE_2. On the other hand, Wnt/β-catenin activation is one of the major causes for gastrointestinal development. *Gan* mice that express COX-2, mPGES-1, and Wnt1 simultaneously in gastric mucosa develop gastric adenocarcinoma. Microarray analyses indicate that gene expression profile of *Gan* mouse tumor is similar to that found in human gastric cancer.

Gan mice are thus unique model that recapitulates human gastric cancer, and useful for clinical as well as basic research on gastric tumorigenesis.

B) Inflammation promotes gastrointestinal tumorigenesis through Wnt activation.

Accumulating evidence has indicated that inflammatory responses play a key role in tumor development. We investigated the role of macrophages in gastrointestinal tumorigenesis, and found that depletion of macrophages results in suppression of intestinal tumor growth. Moreover, TNF-α secreted from activated macrophages promotes Wnt/β-catenin signaling in gastric tumor cells. These results suggest that inflammation promotes tumor cell growth by activation of Wnt/β-catenin signaling.

C) Gastric tumors stimulate stromal fibroblasts resulting in activation of angiogenesis.

In the *Gan* mouse tumor tissues, angiogenesis is significantly enhanced. Using *Gan* mice and other transgenic strains expressing only PGE_2 or Wnt1 in the stomach, we found that tumor epithelial cells stimulate stromal fibroblasts to be myofibroblasts. Activated myofibroblasts express angiogenic factors including VEGF, which causes enhancement of angiogenesis.