"Mechanism of tumor progression in mouse and human familial GIST"

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Abstract: The Kit receptor tyrosine kinase has critical functions in organogenesis during embryogenesis and in the postnatal animal in gametogenesis, hematopoiesis, melanogenesis and interstitial cells of Cajal in the gastrointestinal tract (Besmer 1991; Besmer et al. 1993; Besmer 1997). In human neoplasia oncogenic activation of Kit is thought to have roles in gastrointestinal stromal tumors (GIST), mastocytosis/mast cell leukemia, acute myelogenous leukemia, seminoma and mucosal and anal melanoma.
Activating Kit mutations are found in all of these neoplasms. Based on the finding of germline Kit gene mutations in familial GIST syndrome we have developed a mouse model for familial GIST syndrome by targeted mutation of the Kit receptor tyrosine kinase gene using a knock-in strategy (Sommer et al. 2003). In KitV558D/+ mice at the time of birth myenteric plexus hyperplasia is evident in the cecum, esophagus and stomach. Neoplastic lesions in the cecum are invariably seen at 3-4 weeks of age and thereafter tumor size increases with age. It is therefore reasonable to assume that age should be an excellent milestone in investigating the mechanism of tumor progression. We now propose to investigate mechanisms of GIST tumor development and progression in our mouse GIST model and in human familial GIST.