



## Seung Kim, M.D. Ph.D.

Dr. Seung Kim is developing new mouse model of intestinal carcinoid and neuroendocrine tumors, something that has not previously been achieved. Dr. Kim's strategy will allow the targeted expression of specific genes in the precursor cells of carcinoid tumors in mice. Additionally, Dr. Kim's model will allow him to control the timing and level of expression of these specific genes using small molecule drugs that can be administered to the mouse. This model provides powerful tools to study developing carcinoid tumors in mice.

The first element of this model involves the conditional targeting of a specific gene to cells that express the tryptophan hydroxylase protein. Since tryptophan hydroxylase is involved in serotonin synthesis, specific gene expression can be restricted to serotonin-producing cells, such as carcinoid precursors. Targeted expression in these cells can be triggered by two approaches using the Cre recombinase protein. One technique involves the administration of the drug tamoxifen, and another technique involves delivery of Cre recombinase by viral infection of intestinal cells.

The second element of Dr. Kim's model adds an additional level of control by allowing a specific gene of interest to be turned on and off in serotonin-producing intestinal cells by administration of the drug doxycycline. This strategy involves placing a gene of interest under the control of a doxycycline-regulated expression element. Gene expression will turn off when no drug is given, and will turn on when doxycycline is administered to the mice. Moreover, the level of gene expression will depend on the dose of doxycycline given. Therefore, by combining these two elements, Dr. Kim can target expression of a particular gene to serotonin-producing intestinal cells, and can turn that gene's expression on and off at will in a single mouse model.

Clearly, this system will offer researchers a powerful tool to manipulate and study the effects of specific genes on carcinoid development. Dr. Kim's initial studies will involve expression of the Large T-antigen gene, which inactivates several key tumor suppressor genes, and can cause tumor growth in many systems. Expression of Large T-antigen in carcinoid precursors can also facilitate the development of carcinoid cell lines that could be important tools for studying this disease.

### Recent Publications:

Karnik SK, Hughes CM, Gu X, Rozenblatt-Rosen O, McLean GW, Xiong Y, Meyerson M, Kim SK. Menin regulates pancreatic islet growth by promoting histone methylation and expression of genes encoding p27Kip1 and p18INK4c. *Proc Natl Acad Sci U S A*. 2005 Oct 11;102(41):14659-64.