

# Development of Non-Metastatic and Metastatic Xenograft Models of Pancreatic Neuroendocrine Disease for Defining the Molecular Landscape Responsible for Progression and Therapeutic Outcome

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**Background:** We have generated a unique mouse model of highly metastatic islet cell carcinoma by selectively abrogating floxed alleles of p53 and Rb genes using Cre-recombinase driven by the renin promoter. Incorporation of a multi-colored fluorescent reporter, Confetti, confers the ability to observe clonality of primary tumors and metastases. This ability allows concise identification and excision of metastatic and non-metastatic primary lesions from the spontaneous model for discrete molecular profiling of each tumor as well as implantation into host xenograft animals for longitudinal drug studies.

**Methods:** Clonal color-matched expansion of the rare cells that progress to primary tumors and metastases allow for rapid identification and excision of non-metastatic and metastatic primaries from the same mouse. Primary tumors are divided into multiple xenograft animals for subsequent proposed drug intervention studies. Next-Generation Sequencing technology is used to define the molecular landscape of each tumor as a basis to stratify non-metastatic vs. metastatic as well as responder vs. non-responder phenotypes.

**Results:** Dissection of animals of appropriate genetic constitution reveals that most mice harbour multiple primary tumors of different fluorescent color. Remarkably, in the subset of animals that developed metastatic disease, all observed liver metastases are a single color suggesting they derive from only one of multiple primary tumors in each case. Preliminary xenograft experiments show that metastatic primary tumors, when implanted will seed metastases to liver, however non-metastatic primaries do not. Whole Exome Sequencing of DNA from multiple sets of metastatic and non-metastatic tumors, along with identified responses to drug treatment will offer up insight into genes responsible for metastatic progression as well as response to therapy.

**Conclusion:** Our utilization of our spontaneous neuroendocrine pancreas model combined with multiple fluorescent reporters to dissect out primary tumors for xenograft development, is providing unique insights into pancreatic islet carcinogenesis, metastasis, and feasibility for drug studies.