

## Discovery and Validation of Tumor Suppressor Genes in Colorectal Cancer Using a Novel Cross Species Approach

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**Abstract:** Colorectal cancer (CRC) is the third most common malignancy in developed countries and, despite improvements in screening and early detection, it remains the second leading cause of cancer-related death. Understanding the molecular drivers of this disease is key to identifying effective targeted therapies. To decipher which of the many genomic alterations functionally contribute to cancer initiation and progression requires an *in vivo* system that recapitulates the biology of human disease, yet is amenable to high-throughput genetic analysis. Our team has previously employed focused RNAi screens in combination with orthotopic transplantation-based mouse models to define key tumor suppressor genes (TSGs) in hematopoietic (lymphoma and leukemia) and solid (liver) malignancies. However, similar approaches for CRC have been hampered by the lack of suitable models for high-throughput driver identification. Here, we propose a three-tiered cross-species analysis involving: 1. filtering human genomic data to define potential CRC TSGs; 2. exploiting the flexibility and speed of *Drosophila* genetics to screen those candidates in relevant gut tumor models; and 3, using orthotopic transplantation and a unique embryonic stem cell (ESC)-based mouse-modeling approach we have pioneered to investigate the role of high priority candidates in CRC initiation and progression. Altogether, this work will improve our understanding of the biology of CRC and define pipeline for the discovery and evaluation of novel cancer-associated genes. While the focus of this application is on TSGs, it can readily be applied to study amplified or mutationally-activated genes in cancer.