INTRODUCTION. A major challenge in the discovery of new oncology therapies is the identification of key molecular targets which modulate critical tumor suppressor and oncogene signaling pathways. Model organisms such as C. elegans and Drosophila provide a genetic platform where these key pathways can be rapidly screened to discover new molecular targets (1, 2). To this end, we have engineered these model organisms to mimic the genetic alterations observed within the key cancer signaling pathways in human tumors such as p53, PTEN, Rb, or β-catenin. The resulting phenotypes of these transgenic models were utilized to perform genome-wide functional screens that identified new genes which regulate these critical pathways.

Figure 1. Genetic inactivation of a novel kinase, kin-a, reverts an oncogenic β-catenin pathway phenotype in C. elegans.
RESULTS. Genome-wide screening of key cancer pathways led to the identification of genes whose inactivation dramatically suppressed these oncogenic phenotypes (see Figure 1). To further validate these gene products as therapeutic targets, the corresponding human orthologues were isolated and characterized across a platform of tumor biology assays. The endpoints used in this validation analysis integrated human tumor/normal tissue expression profiling, target inactivation effects on multi-parameter high content signal transduction-phenotypic assays, and target activation phenotypes in cell-based and animal models. Several novel kinases identified as strong modifiers of an oncogenic β-catenin phenotype in C. elegans registered strong mammalian oncology target validation effects across these assays. Of particular note was that the inactivation of these kinases led to apoptosis and modulation of key signal transduction events over a number of human tumor cell lines dependent upon constitutive activation of the β-catenin pathway. Importantly, small molecule inhibitors directed against these targets were able to recapitulate many of the biological effects observed for inactivating the target with small inhibitory RNAs.

DISCUSSION. The completion of the sequence of the human genome has provided researchers with a daunting choice of molecular targets which may play a causative role in tumor biology (3). We have applied phenotypic screens in model organisms to identify new gene products which regulate major oncogenic (β-catenin) and tumor suppressor pathways (p53, Rb) in human cancer. This approach has led to the identification of novel molecular targets whose genetic and chemical modulation similarly regulates these pathways in human tumor cells. Interestingly, such large scale genetic screening of these key pathways has also unmasked novel regulatory themes of cancer signal transduction. Our results highlight the use of pathway-based genetic screens in model organisms integrated with mammalian oncology target validation as a promising approach to discover new oncology therapeutic targets within these historically intractable cancer signaling pathways.

REFERENCES