In contrast to some hematopoietic malignancies, for which molecular therapies can induce long-lasting tumor remissions, clinical experiences over the past couple of years have revealed that in most common types of solid tumors, acquired therapy resistance against molecular therapies is inevitable. Hepatocellular carcinoma (HCC) can be seen as a prototype of a therapy resistant tumor, and it represents a major health problem, causing more than 700,000 deaths annually worldwide. HCC shows intrinsic resistance to cytotoxics, and although the multikinase inhibitor sorafenib was recently approved as the first systemic treatment for patients with advanced HCC, the survival advantage conferred to these patients from sorafenib therapy averages only 2.8 months. In my talk I will give examples how innovative mosaic cancer mouse models can be combined with stable in vivo shRNA technology to identify new cancer genes and therapeutic targets in liver carcinomas. Taking advantage of a recently developed system for transposon-mediated in vivo delivery of miRNA-based short hairpin RNAs (shRNAs) (Wuestefeld et al., Cell 2013, Kang et al., Nature 2011) we developed a platform that can be used to conduct negative-selection shRNA screens directly in mouse liver carcinomas in vivo. In my talk I will discuss the results of two recently conducted in vivo shRNA drop-out screens.