TARGETING RAS PATHWAYS IN CANCER

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K-*Ras* oncogenes have been implicated in about one fifth of all human cancers including those with the worse prognosis, such as non-small cell lung carcinoma (NSCLC), pancreatic ductal adenocarcinoma (PDA) and colorectal carcinoma (CRC). Our laboratory is interested in using genetic engeneering strategies to develop mouse tumor models that closely recapitulate the natural history of these human tumours.

To this end, we have engineered a mouse strain that expresses an endogenous K-Ras oncogene in a temporally and spatially controlled manner. Expression of this oncogene in lungs of adult mice results in the immediate onset of unscheduled cell proliferation, leading to the formation of adenomas and malignant adenocarcinomas. In contrast, expression of the same K-*Ras* oncogene in the pancreas of adult mice does not induce tumour development unless mice undergo chronic or episodic pancreatitis. Thus, suggesting that chronic inflammation plays a key role in the development of PDA.

We have used these tumour models to validate targeted therapies using molecular genetics followed by classical pharmacological approaches. Briefly, we have crossed K-Ras driven NSCLC and PDA model strains with mice carrying germ line or conditional knock out mutations in loci encoding for potential therapeutic targets. This basic experimental approach has led us to uncovered unsuspected synthetic lethal interactions between K-Ras oncogenic signalling and ablation/inhibition of selected targets. Thus, providing rational approaches for future therapeutic intervention.