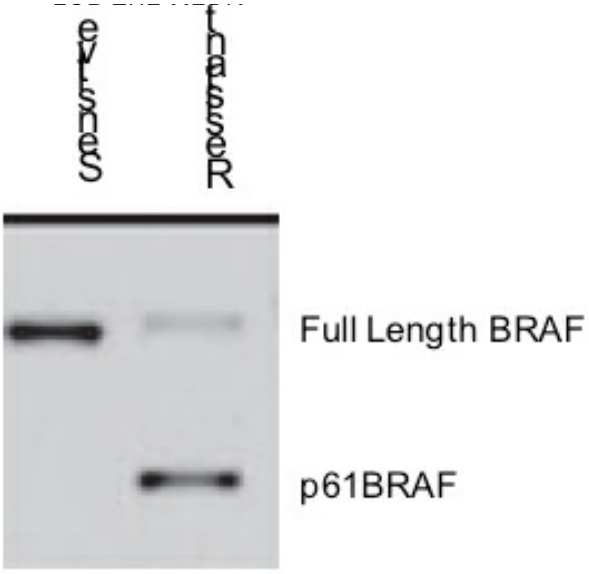

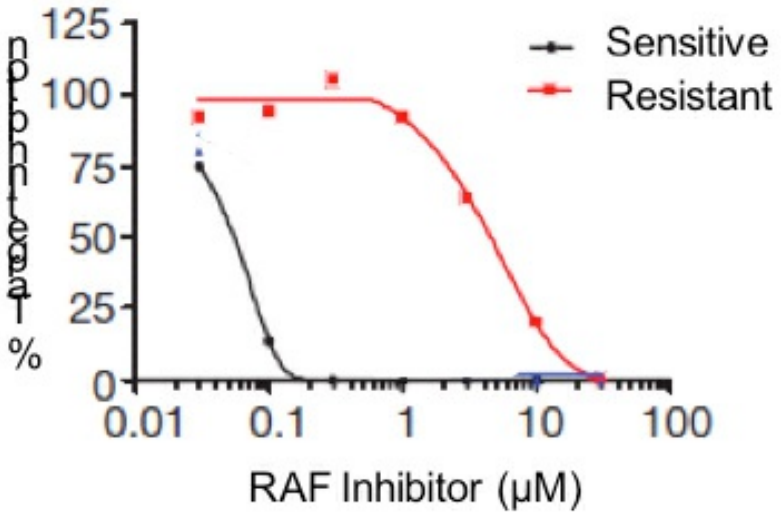

Over 60% of melanoma tumors harbor activating mutations in the BRAF oncogene and patients with such tumors are suitable candidates for therapeutic intervention with RAF inhibitors such as Zelboraf. Upwards of 80% of patients treated with RAF inhibitors develop resistance to therapy, however, and eventually suffer tumor progression. There remains a need for suitable biomarkers to monitor development of such resistance prior to relapse so that more effective therapies can be pursued.

Dr. Neal Rosen and colleagues have identified a novel splice variant of activated BRAF that predicts resistance to continued treatment with RAF inhibitors. Using a cell-line model, the inventors demonstrated that exposure to a RAF inhibitor resulted in the formation of a novel 1.7kb splice variant encoding constitutively active BRAF lacking exons 4-8, which they refer to as p61BRAF. This splice variant was shown to drive resistance to treatment with RAF inhibitors and such inhibition could be overcome by

combination treatment with a MEK inhibitor. Retrospective analysis of melanoma patient samples demonstrated that 30% of patients that developed resistance to Zelboraf harbored the p61BRAF splice variant, indicating the clinical relevance of these findings. Further, the inventors have developed reagents and assays useful for identifying novel therapeutics that can overcome RAF-inhibitor resistance.

Advantages

Provides clinically actionable results prior to measureable tumor progression

Stage of Development

Validated in retrospective analysis of patient samples

Publication

Poulikakos, Poulikos (2011) *RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF (V600E).* Nature. 480:387-390.

Lou, Kai-Jye (2011) *Splicing out BRAF's resistance.* SciBx. Volume 4/Number 48: 1-3.

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Intellectual Property Status

U.S. Basic Patent issued 9,481,910, in November 2016

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Stage of Development

In vitro

Indications

Cancer › Melanoma

Types

Diagnostics › Biomarkers

Research Tools

Connect