Pancreatic clonal replica tumors display functional heterogeneity in response to KRAS inhibition and reveal epigenetic vulnerabilities to overcome resistance

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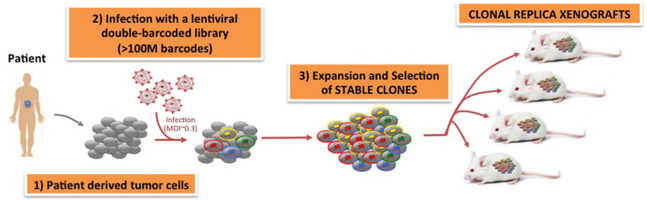
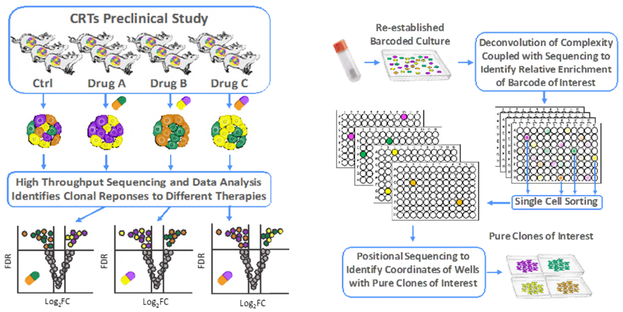
INTRODUCTION

- Pre-existing tumor heterogeneity may allow tumors to escape treatment via selection and expansion of drug-resistant clones. Recent discovery of KRAS targeted therapies (*e.g.,* SOS1i, $KRAS^{G12C}$i, etc.) has dramatically changed the clinical outlook for patients with KRAS mutant tumors.
- Here, we generated and utilized pancreatic clonal replica tumors (CRTs) to identify drug-resistant clones of KRAS inhibitors. Our CRT platform combines high-complexity *in vivo* lineage tracing with quantitative assessments of adaptive responses to therapeutics to understand tumor heterogeneity and drug resistance.



- In this study we generated a $KRAS^{G12D}$-driven CRT xenograft model of PDAC and treated the CRTs with MEKi, SOSi, and MEKi + SOSi. Upon comprehensive analysis of the clonal composition associated with each drug treatment, we identified, isolated, and validated a collection of clones with differential response to MEKi + SOS1i or $KRAS^{G12D}$i.



- Deep molecular characterization of sensitive and resistance clones revealed a novel epigenetic vulnerability which may inform on unbiased combination strategies to prolong responses to KRAS and MAPK inhibition for pancreatic cancer patients.

ACKNOWLEDGEMENT AND REFERENCES

This work is funded by Boehringer Ingelheim RCV GmbH & Co KG.

Seth S. et al Pre-existing functional heterogeneity of tumorigenic compartment as the origin of chemoresistance in pancreatic tumors. *Cell Rep*. 2019;26(6)

Differential response to SOS1i + MEKi and molecular profiling of 15 PDAC CRT clones

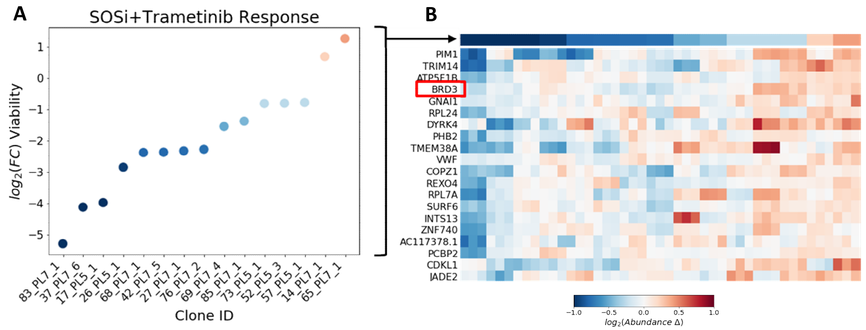
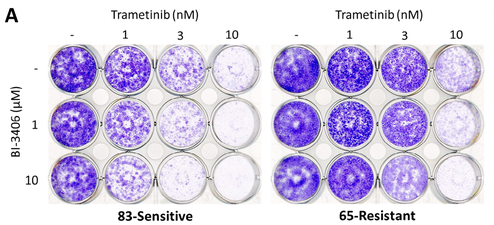


Figure 1. A. CRT study showed a range of differential clonal responses to trametinib (MEKi) and BI-3406 (SOS1i) combination *in vivo*. **B.** Correlation of mRNA profiles from individual CRT clones upon barcode-guided isolation with CRT combo response identified gene expression differentiating clonal response to trametinib + BI-3406 (*e.g.,* BRD3).

Combination benefit of adding BET bromodomain degrader to MEKi + SOS1i



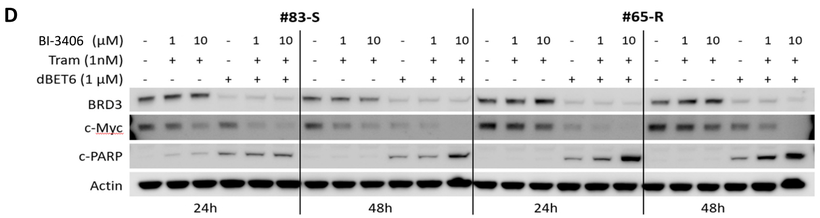
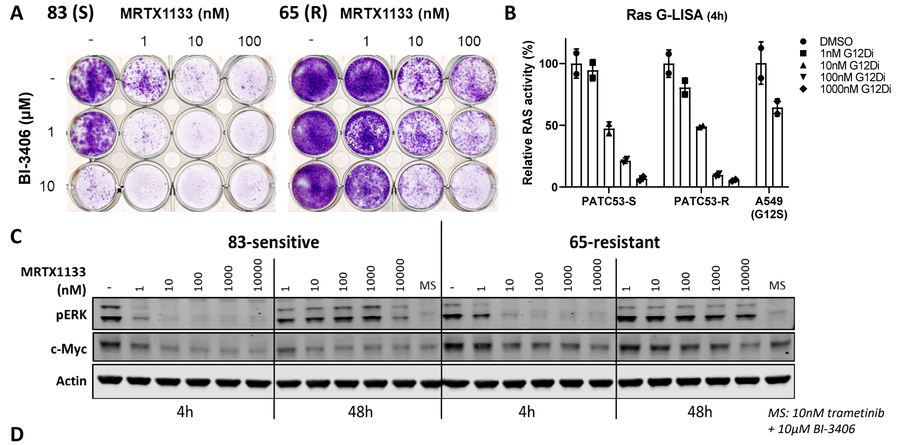
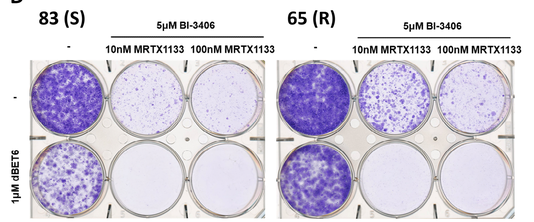


Figure 2. A. Confirmation of the response of sensitive and resistant clones to MEKi + SOS1i. **B.** p-ERK was suppressed by MEKi + SOS1i in both clones while clone 65 (resistant) showed higher levels of BRD3 and c-Myc.
C-D. Combination benefit of adding BET degrader dBET6 to MEKi + SOS1i in both clones suppressing cell proliferation and c-Myc expression and inducing apoptotic response.

CRT clones also showed differential response to $KRAS^{G12D}$i and sensitivity to BET degrader





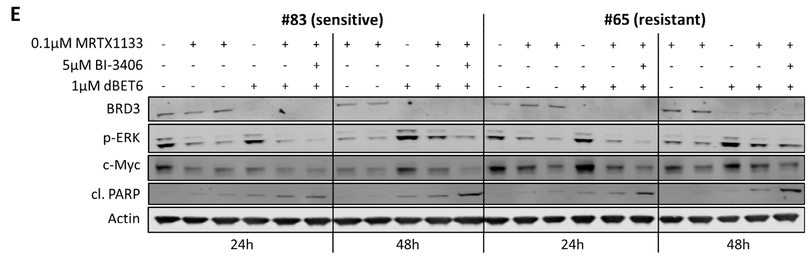


Figure 3. A. Differential clonal response to MRTX1133 ($KRAS^{G12D}$i) and BI-3406 combination. **B.** MRTX1133 reduced RAS-GTP loading similarly in both clones in a dose-dependent manner. **C.** Resistant clone showed elevated levels of c-Myc following MRTX1133 treatment. **D-E.** Combination benefit of adding BET degrader dBET6 to MRTX1133 + BI-3406, suppressing cell proliferation and c-Myc expression and inducing apoptotic response.

SUMMARY

- Our study revealed pre-existing heterogeneous subclones with differential response to KRAS and/or MAPK inhibition. Transcriptomic profiling of clonal diversity further revealed a BRD3-driven epigenetic plasticity in resistant clones that may contribute to escaping direct KRAS inhibition in pancreatic cancer.
- Pharmacological combination of MEKi (trametinib) + SOS1i (BI-3406) or $KRAS^{G12D}$i (MRTX1133) with BETi (dBET6) exhibited combination benefits in preclinical pancreatic cancer models, which provides a new avenue to overcome such resistance by combining KRAS inhibitors with BET inhibitors.

SC-US-74202