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Integrated platform enables KRAS-targeted drugs discovery

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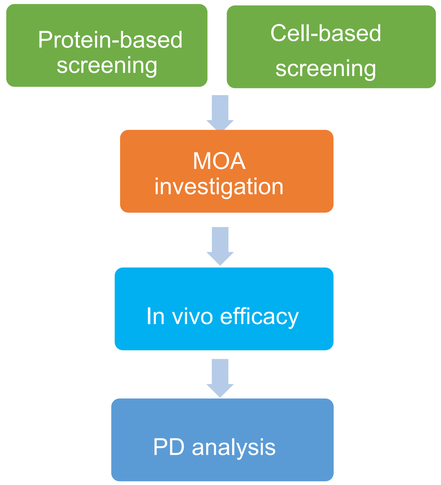
Introduction

The Kirsten rat sarcoma viral oncogene homolog (KRAS) is mutated in approximately 25% of all human cancers and is known to be a major player promoting and maintaining tumorigenesis through the RAS-MAPK pathway. KRAS inhibitors, such as AMG510 and MRTX849, show promising results in patients with tumors harboring KRAS G12C mutation. While the approval of AMG510 was a major breakthrough for those patients harboring KRAS G12C mutations, G12C only accounts for a fraction of those with KRAS mutations and eventual resistance to G12C inhibitors is unavoidable. Therefore, developing new drugs directed against various KRAS mutants and combination strategies that target resistance mechanisms have become vital in the war against KRAS-mutant tumors.

To enable the discovery of novel KRAS inhibitors, we established a one-stop service platform. Our platform provides assays on nearly all the current mainstream mutants of KRAS, such as G12C/G12D/G12R/G12S/G13D, and engineered cell lines harboring single or double KRAS mutations. In addition, we developed a panel of resistant models to KRAS G12C inhibitors that bring a better understanding of the biological basis of drug resistance, serving as a new tool to optimize KRAS-G12C inhibitor regimens and combinatory strategies. The comprehensive KRAS-targeted drug discovery platform is empowering new drug research and development.

One-stop service platform



Results

Protein-based screening

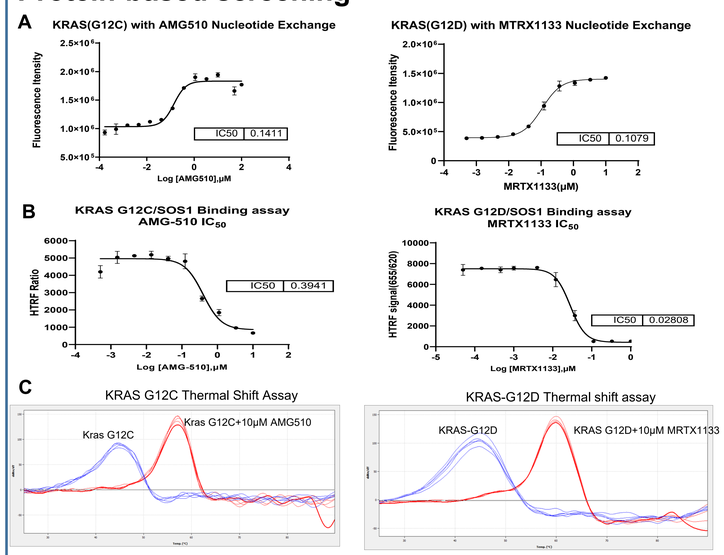


Figure 1. Screening and profiling of KRAS inhibitors based on protein detection. A) The screening and profiling of KRAS (G12C,G12D) antagonists/inhibitors was detected by Nucleotide Exchange Assay. B) KRAS upstream and downstream protein-protein (SOS1 or RAF1) interaction was detected by HTRF Assay. C) Thermal Shift Assay was employed to test the binding of AMG510 or MRTX1133 to KRAS G12C/G12D.

Cell-based screening

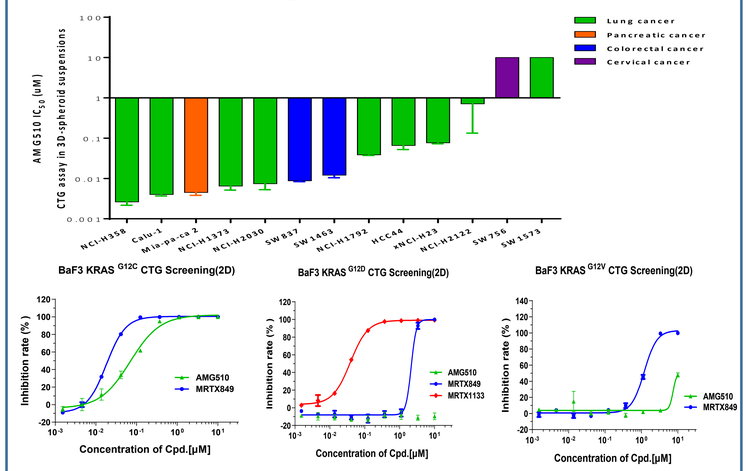


Figure 2. The inhibitory effect of KRAS inhibitors on KRAS G12C mutant human cancer cell lines and KRAS mutant Ba/F3 engineered cell lines was detected by 2D&3D CellTiter-Glo (CTG).

Cell-based MOA

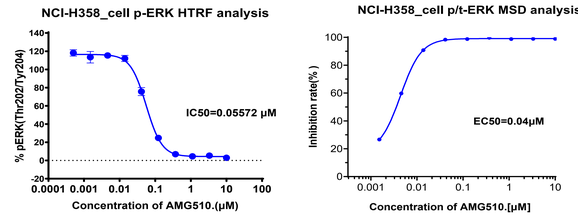


Figure 3. The mechanism of action (MOA) investigation of AMG510 on RAS-RAFMEK-ERK pathway was detected by cellular MesoScale Discovery(MSD) and HTRF analysis.

In vivo model efficacy study

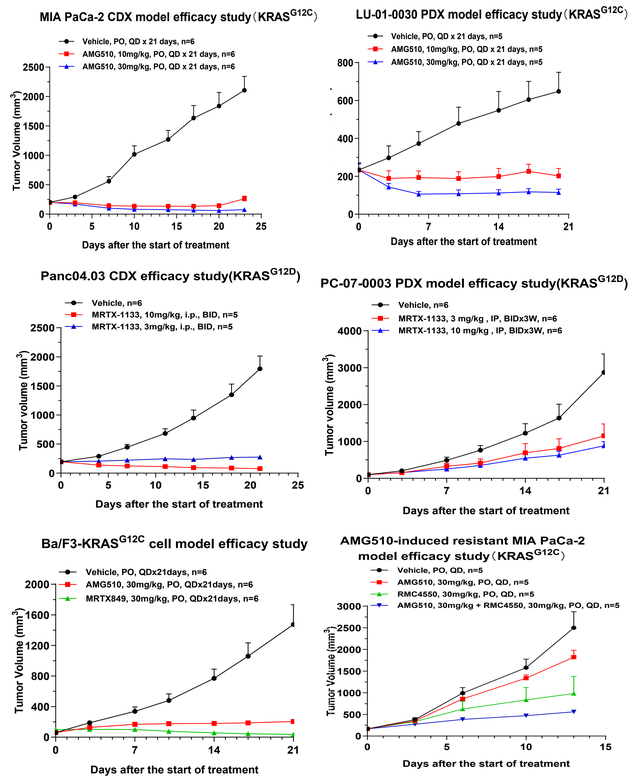


Figure 4. KRAS inhibitors *in vivo* efficacy evaluation in a panel of CDX, PDX, Ba/F3 engineered cell, and drug-induced resistant models

Ex vivo PD analysis

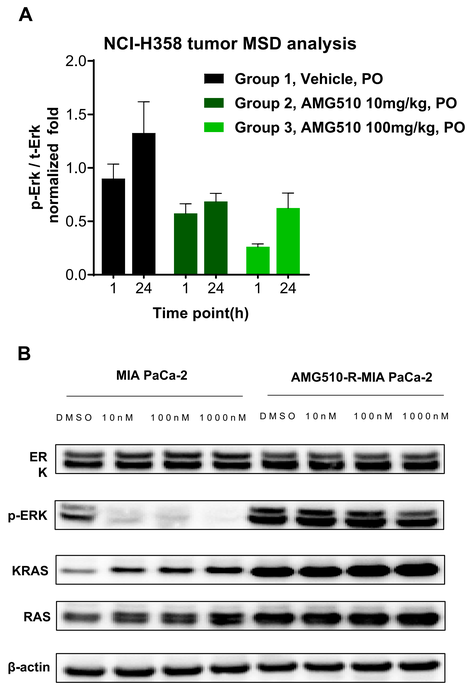


Figure 5. A) MSD detected the expression of p-ERK/ERK based on tissue samples generated by NCI-H358 in vivo model. B) MIA PaCa parental cells and AMG510-resistant cells (AMG510-R-MIA PaCa-2) were treated with different concentrations of AMG510, and the protein expression levels of ERK, p-ERK, KRAS and RAS were detected by WB.

Conclusion

We established a one-stop service platform, covering affinity detection of compounds to KRAS proteins, protein-protein interaction detection, KRAS pathway activation detection, cell proliferation assay (2D/3D culture system), and in vivo efficacy evaluation in KRAS related xenograft models. This platform can largely empower KRAS-targeted drug discovery.

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