#221394: Impact of Novel Pan-RAS Inhibitors on Efficacy and Resistance to AMG-510 and MRTX-1133 in Pancreatic Cancer Cell Lines.

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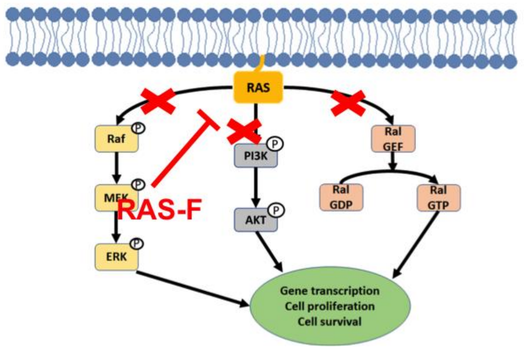
Background/Methods:

- Activating mutations in RAS are a very common driver in many solid tumors, including pancreatic cancer. Currently clinical agents exist for the KRASG12C and for the KRASG12D mutant form, with others in development.
- Current studies suggest that the development of resistance to these drugs as single agents may result in limited durability of efficacy becoming a serious obstacle to their effectiveness.
- We have developed a pan-RAS inhibitor ("RAS-F") that binds all three main isoforms of RAS: KRAS, HRAS and NRAS. We find it is active against all mutant forms of RAS tested and we have shown it is active against pancreatic cancer cell lines and in pancreatic cancer PDX *in vivo* models.
- We have now tested this family of compounds in combination with AMG-510 (KRAS G12C specific) and MRTX1133 (KRAS G12D specific) agents. We find that it can co-operate with these drugs to suppress 3D soft agar growth.
- Moreover, we have generated an MTRX1133 resistant Panc1 cell line and found that co-treatment with our agent reverses the resistance.

Figure 1.

Mechanism of action of Qualigen pan-RAS compound



Methods:

We used Molecular Modeling followed by in silico library screening, 3D bioassay and biophysical assays to identify direct pan-RAS inhibitors molecules. Medicinal Chemistry was then used to optimize the compounds in an iterative process. In vivo activity of RAS-F was confirmed in xenograft experiments with cell lines and PDX models.

Main Takeaways:

- We have developed a platform of Pan-RAS binding compounds that act as inhibitors against multiple mutant and wild type RAS driven cell lines.
- The agents can co-operate with AMG-510 (sotorasib) and MRTX1133. The agents can also suppress resistance to MRTX1133 *in vitro*.
- These Pan-RAS compounds may overcome resistance to AMG-510 and MRTX1133 *in vivo*.

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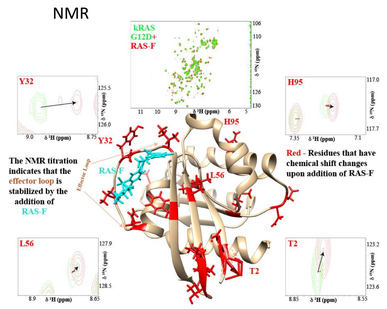
Results

- RAS-F binds KRAS directly and interferes with the structure of the effector loop.

Figure 2.

NMR analysis confirms RAS-F binds KRAS and alters the structure of the effector binding Domain (Residues 32-40).



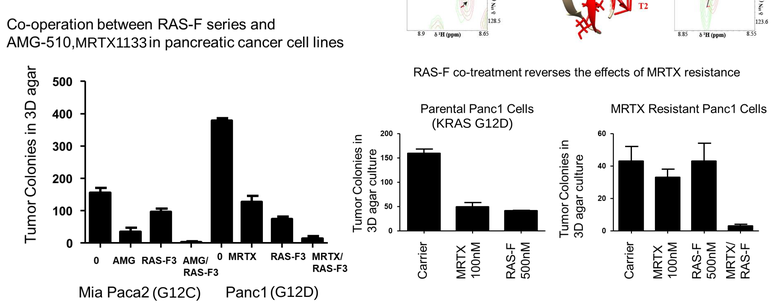


Figure 3.

Left: RAS-F compounds co-operate with AMG-510 and MRTX1133 in soft agar assays to suppress tumor colony growth.
Center: RAS-F and MRTX1133 suppress the soft agar growth of Panc1 cells.
Right. Panc1 cells conditioned to be resistant to MRTX1133 are re-sensitized by the addition of RAS-F.

- RAS-F compounds co-operate with AMG-510 and MRTX113.
- RAS-F compounds overcome MRTX resistance in a conditioned cell line.

Future Directions for Research:

- Similar studies addressing AMG-510 resistance are ongoing.
- Medicinal Chemistry optimization is ongoing. We have already identified compounds with enhanced *in vitro* binding activity (<0.1 um).
- *In vivo* studies will follow.