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Applying MCI-062, a Novel Pan-RAS Inhibitor, to Treat *KRAS*-Mutant Lung Cancer

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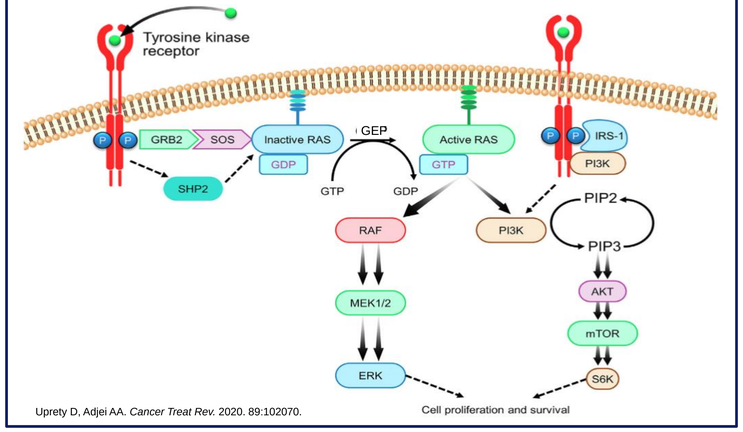
College: Honors College, Pat Capps Covey College of Allied Health Professions; **Major:** Biomedical Sciences; **Lab:** Drug Discovery, Mitchell Cancer Institute

ABSTRACT

RAS, one of the most prevalent oncogenes, is mutated in 27% of human cancers. Gain-of-function *RAS* mutations activate multiple downstream pathways, including the RAS-RAF-MEK-ERK and PI3K/AKT/mTOR pathways, which are critical in tumorigenesis and cancer cell proliferation. The RAS proteins KRAS, HRAS, and NRAS along with their downstream effectors are attractive targets for cancer therapy since they act as frequent drivers in lung, colorectal, and pancreatic cancers. However, RAS proteins have relatively smooth surfaces that lack traditional binding pockets, making inhibitors specific to RAS difficult to create. Recently, a novel small molecule pan-RAS inhibitor named MCI-062 was developed in Dr. Gary Piazza's Drug Discovery Research Center at the Mitchell Cancer Institute. As a pan-RAS inhibitor, MCI-062 is hypothesized to serve as a targeted therapy for *RAS*-mutant cancers regardless of mutation isoform, including all types of *KRAS*-mutant lung cancers. The inhibitory effects of MCI-062 were tested on the growth and proliferation of two non-small cell lung cancer cell lines, A549 and H358, using colony formation assays. The cells were plated onto 12-well plates, treated with varying concentrations of MCI-062 in duplicate, and then digitally imaged and analyzed. A549 cells have a $KRAS^{G13D}$ mutation, while H358 cells have a $KRAS^{G12C}$ mutation. The results indicate that MCI-062 effectively suppresses the growth and proliferation of both A549 and H358 cells despite their differing mutation isoforms, suggesting that MCI-062 successfully functions as a pan-RAS inhibitor.

INTRODUCTION

- Cancer is characterized by uncontrolled growth of malignant cancer cells.
- *RAS* genes were the first mutated genes identified in cancer, and their discovery ushered in the era of molecularly-targeted anticancer drug discovery.
- The three *RAS* genes *KRAS*, *HRAS,* and *NRAS* constitute the most frequently mutated oncogenes in cancer, as they are found in ~25% of human tumors.
- *RAS* mutations are most common in the top three deadliest cancers: pancreatic cancer, colorectal cancer, and lung cancer.



Uprety D, Adjei AA. *Cancer Treat Rev.* 2020. 89:102070.

HYPOTHESIS and AIMS

Pan-RAS inhibitor MCI-062 treatment inhibits proliferation of *KRAS*-mutant A549 and H358 lung cancer cells.

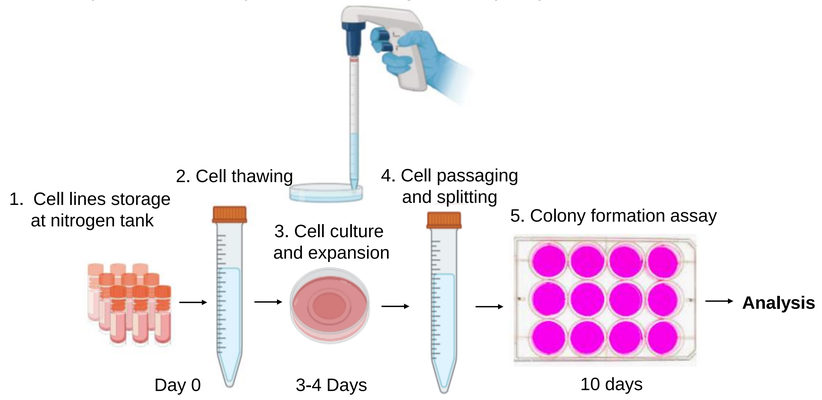
1. Determine if there are optimal conditions for colony formation in A549 and H358 cell lines.
2. Determine if MCI-062 has an optimal concentration for inhibition of colony formation for A549 and H358 cells.
3. Compare whether the therapeutic efficacy of MCI-062 is equal to or better than AMG 510 in lung cancer cells.

Materials and Methods

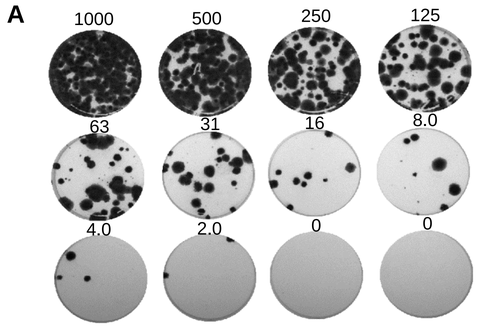
- **Cells:** A549 and H358 lung cancer cell lines
- **Novel cancer therapy drug:** MCI-062, pan-RAS inhibitor
- **Experiments:**

✓ Cell culturing and passaging

✓ Colony formation assay to evaluate the growth capacity of cancer cells



Results



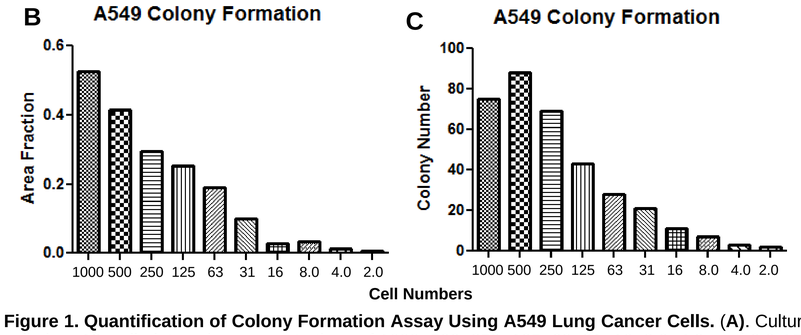


Figure 1. Quantification of Colony Formation Assay Using A549 Lung Cancer Cells. (**A**). Cultured cells in a 12-well plate using concentrations of 1000, 500, 250, 125, 63, 31, 16, 8.0, 4.0, and 2.0 A549 cells per well. Cells were incubated and monitored for 10 days. Colony formation was analyzed using a crystal violet dye. The area fraction **(B)** and the colony number (**C)** were calculated using a custom macro developed at the Mitchell Cancer institute for NIS-Elements.

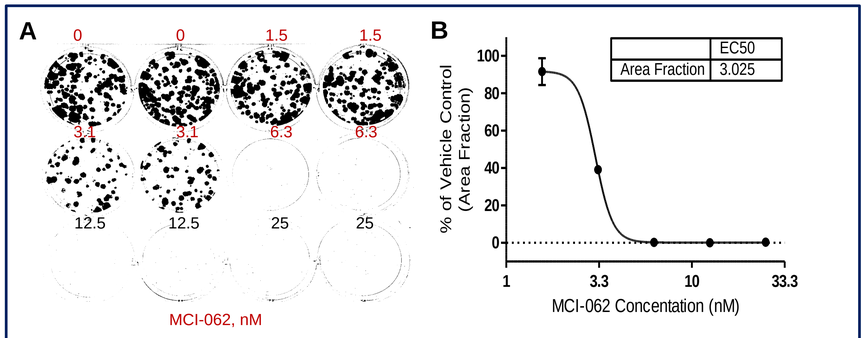


Figure 2. Quantification of pan-RAS inhibitor MCI-062 in Suppressing Cell Growth of A549 Cells. (A). Colony formation assay was performed in presence of 80 cells of A549 per well in the treatment with 25, 12.5, 6.3, 3.1, 1.5 or 0 nM of MCI-062 for 10 days. **(B).** Area fraction vs. MCI-062 concentration graph was created in GraphPad Prism, and EC50 of MCI-062 for A549 cells was calculated.

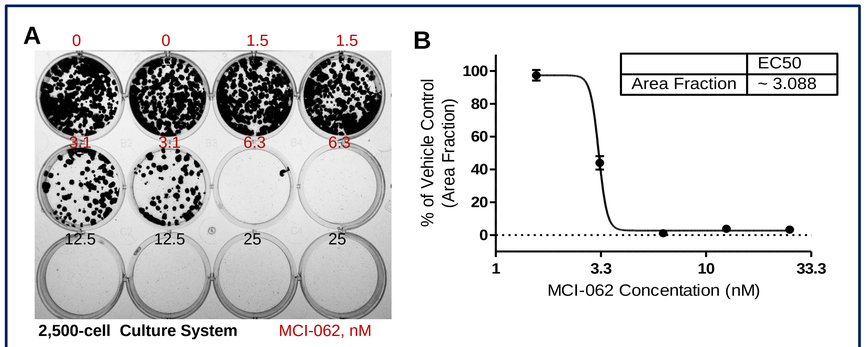


Figure 3. Colony Formation Assays with H358 Lung Cancer Cells. (A). Colony formation assay was performed in presence of 2,500 cells of H358 per well in a treatment with 25, 12.5, 6.3, 3.1, 1.5 or 0 nM of MCI-062 for 10 days. **(B).** Area fraction vs. MCI-062 concentration graph was created in GraphPad Prism, and EC50 of MCI-062 for H358 cells was calculated.

Conclusions and Perspectives

1. MCI-062 inhibits the growth of A549 cells with $KRAS^{G13D}$ mutation and H358 cells with $KRAS^{G12C}$ mutation.
   - ✓ Potentially extends beyond AMG 510, which solely inhibits $KRAS^{G12C}$.
2. These studies implied MCI-062 exhibits therapeutic action against lung cancer driven by mutant *KRAS*.
3. This research project may help advance targeted treatment of patients with lung cancer involving *KRAS* mutations.

- ➢ Comparing therapeutic efficacies of MCI-062 and AMG 510
  - ✓ Using other cell lines with different *RAS* mutations
- ➢ Studying MCI-062's interaction with developed EGFR, RAF, and MEK kinase inhibitors
- ➢ Testing MCI-062's therapeutic efficacy with cancer immunotherapy
- ➢ MCI-062 may serve as a useful probe for developing optimal cancer therapies.

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