37. Small Molecule for Treatment-Resistant Lung Cancer

(Emory University)

Asset Overview

Product Type	Small Molecule
Disease Area	Oncology
Indication	Lung cancer
Current Stage	Lead Optimization
Target	KRAS
MoA	KRA-533 activates KRAS by preventing the cleavage of GTP into GDP, leading to the accumulation of GTP-KRAS, an active form of KRAS. Treatment of human lung cancer cells with KRA-533 resulted in increased KRAS activity and suppression of cell growth.
Brief Description	• Lung cancer patients with KRAS mutation(s) have a poor prognosis due in part to the development of resistance to currently available therapeutic interventions. Currently, there are no effective targeted therapies for patients with the KRAS mutation. • Overcoming these hurdles, Emory researchers have identified a small molecule KRAS agonist that specifically binds the protein and induces cell death in mutant KRAS lung cancer cells. Lung cancer cell lines with KRAS mutation were relatively more sensitive to the small molecule than cell lines without KRAS mutation. Additionally, this molecule suppresses malignant growth without significant toxicity to normal tissues.
Intellectual Property	US20210137953A1
Publication	Small Molecule KRAS Agonist for Mutant KRAS Cancer Therapy. Molecular Cancer (2019)
Inventors	Xingming Deng

Highlights

A small molecule KRAS agonist, KRA-533

- KRA-533 binds the GTP/GDP-binding pocket of KRAS.
- In vitro GDP/GTP exchange assay reveals that KRA-533 activates KRAS by preventing the cleavage of GTP into GDP, leading to the accumulation of GTP-KRAS, an active form of KRAS.
- Treatment of human lung cancer cells with KRA-533 resulted in increased KRAS activity and suppression of cell growth. Lung cancer cell lines with KRAS mutation were relatively more sensitive to KRA-533 than cell lines without KRAS mutation.
- Mutating one of the hydrogen-bonds among the KRA-533 binding amino acids in KRAS (mutant K117A) resulted in failure of KRAS to bind KRA-533. KRA-533 had no effect on the activity of K117A mutant KRAS, suggesting that KRA-533 binding to K117 is required for KRA-533 to enhance KRAS activity.
- Intriguingly, KRA-533-mediated KRAS activation not only promoted apoptosis but also autophagic cell death. In mutant KRAS lung cancer xenografts and genetically engineered mutant KRAS-driven lung cancer models, KRA-533 suppressed malignant growth without significant toxicity to normal tissues.

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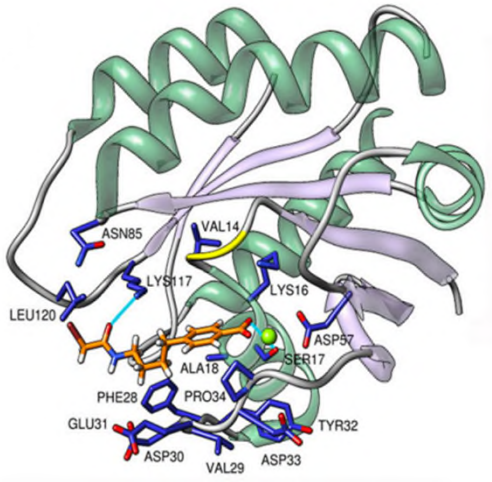
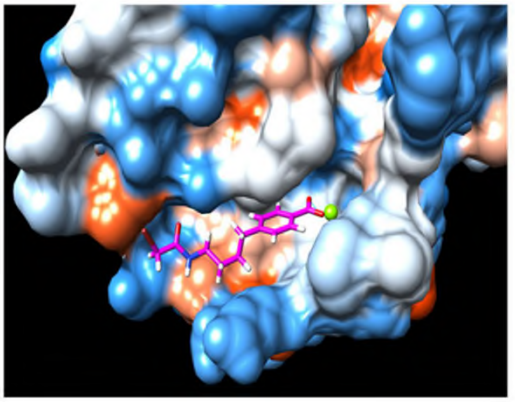
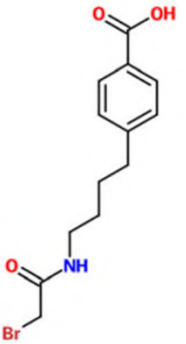
Key Data

Structural modeling of KRA-533 in the GTP/GDP-binding pocket of KRAS protein

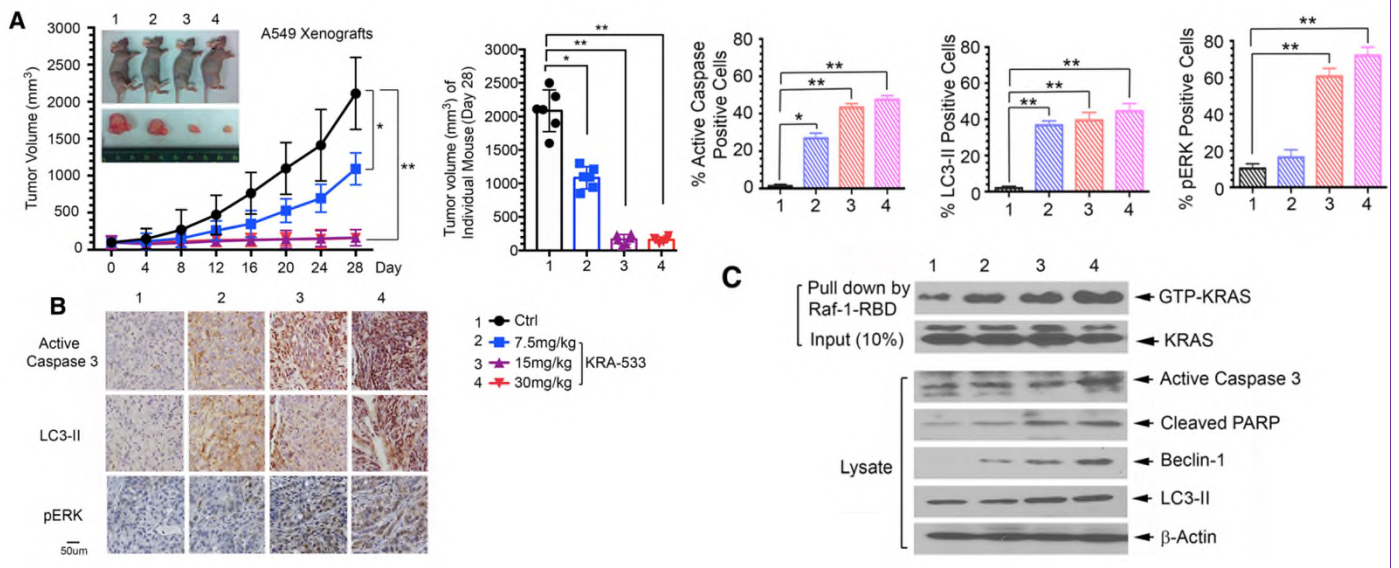






KRA-533
MW: 314.17

In vivo imaging and antitumor results of RT&X-PDT



(a) Nu/Nu nude mice with A549 xenografts bearing mutant KRAS were treated with increasing doses of KRA-533 (0, 7.5, 15, and 30 mg/kg/d) for 28 days (n = 6). Tumor volume was measured once every 2 days (left panel). Tumor volumes of 6 individual mice in each group were compared on day 28 (right panel). After 28 days, the mice were sacrificed, and the tumors were removed and analyzed. Data represent mean ± SD, n = 6 per group. *P < 0.05, **P < 0.01, by 2-tailed t test. **(b)** Active caspase-3, LC3-II and p-ERK were analyzed by IHC staining in tumor tissues at the end of experiments and quantified. Data represent mean ± SD, n = 6 per group. *P < 0.05, **P < 0.01, by 2-tailed t test. **(c)** KRAS-GTP (active form of KRAS) was pulled down by Raf-1-RBD from tumor tissue lysates, followed by Western blot using KRAS antibody. Expression levels of active caspase-3, cleaved PARP, Beclin-1 and LC3-II in tumor tissues were analyzed by Western blot