Sirpiglenastat (DRP-104), a novel broad acting glutamine antagonist, has therapeutic potential in targeting *KEAP1*-mutant lung cancer

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Disclosures

Thales Papagiannakopoulos

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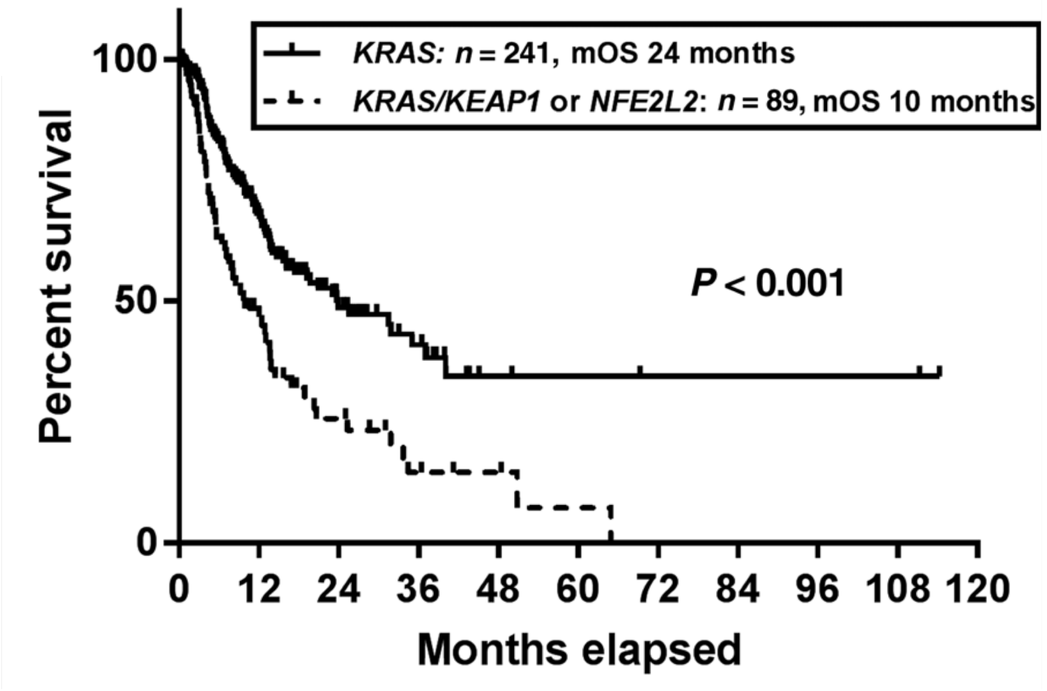
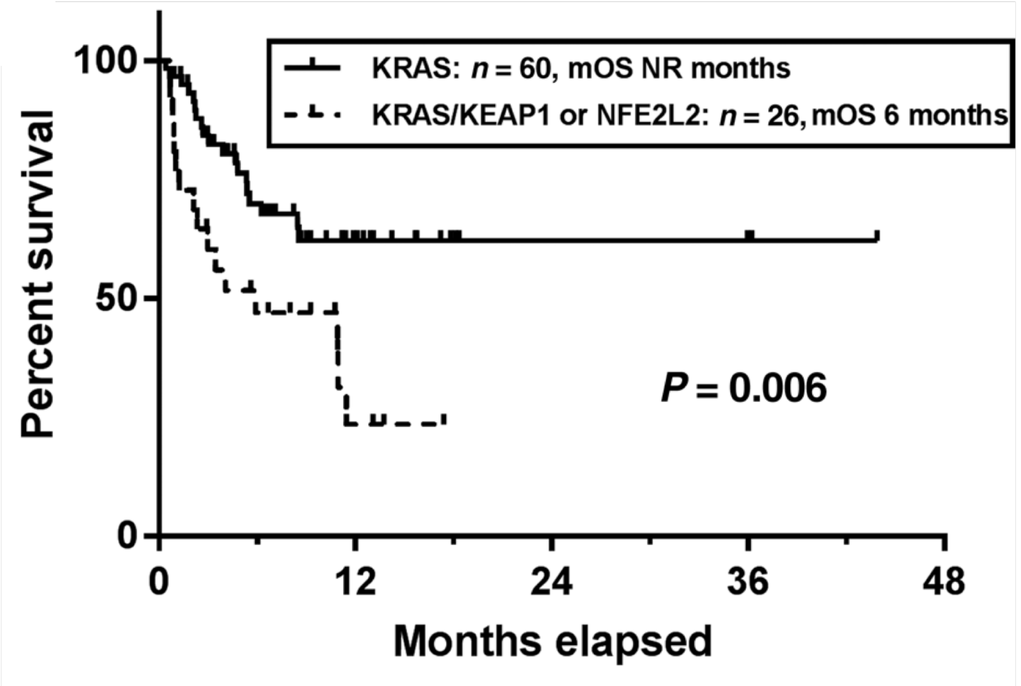
KEAP1 mutant patients do not respond to chemo, radiation or immunotherapy



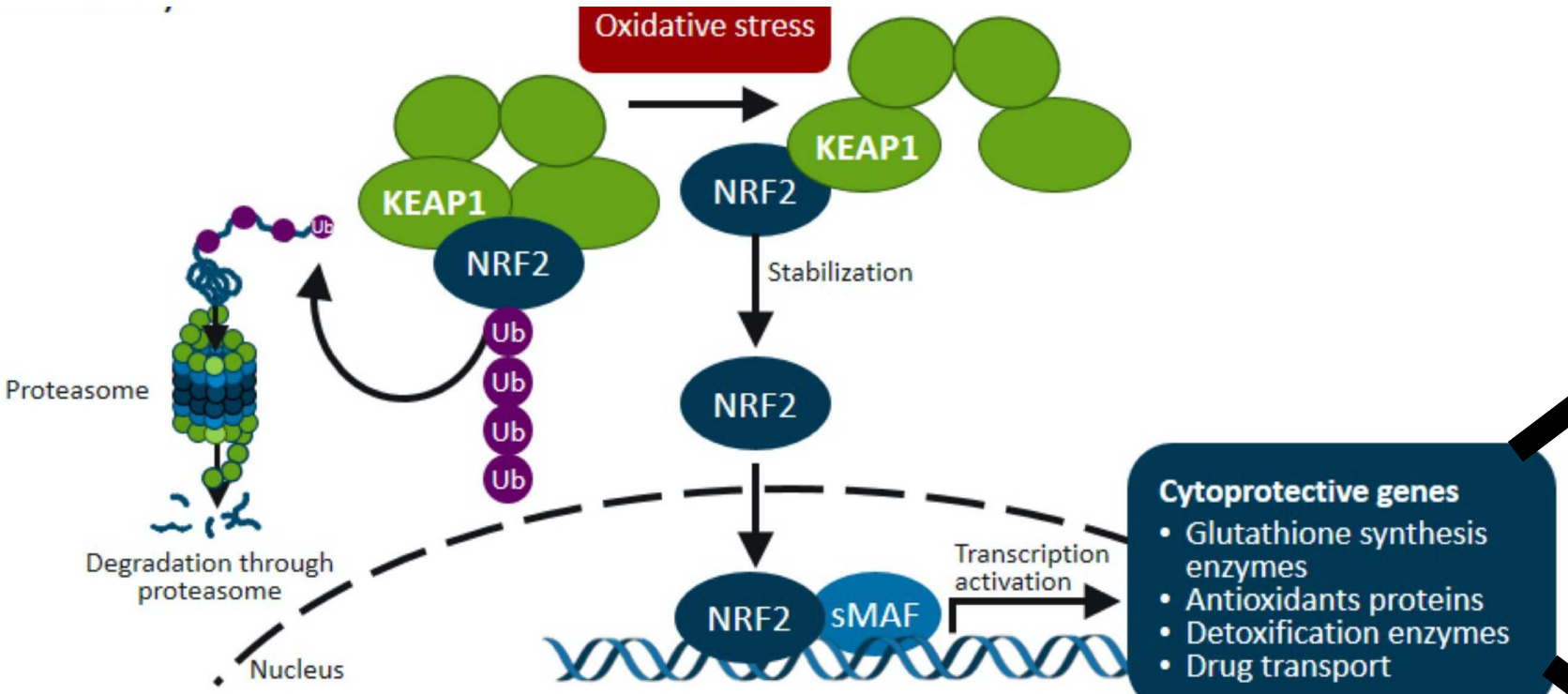
Patients receiving checkpoint inhibitors



Arbour et al; *Clinical Cancer Research 2018*

KEAP1/NRF2 pathway mutant NSCLC resistant to chemotherapy, radiation, G12C inhibitors and checkpoint (Skoulidis et al., NEJM, 2021; Jeong et al., Clin Can Res, 2020; Arbour et al., Clin Can Res, 2018; Binkley et al., Cancer Disc 2020)

KEAP1/NRF2 Pathway



Tumor Growth

Romero et al. Nat. Med. 2017

Metastasis

Lignitto et al. Cell. 2019

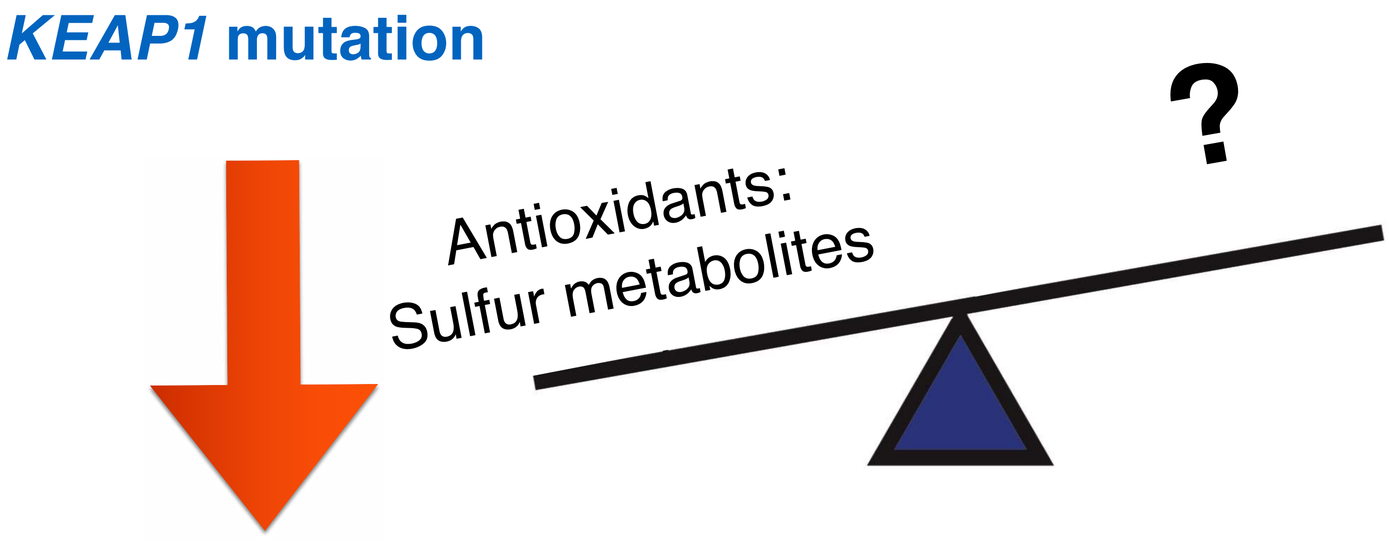
Radiation

Immunotherapy

Chemotherapy

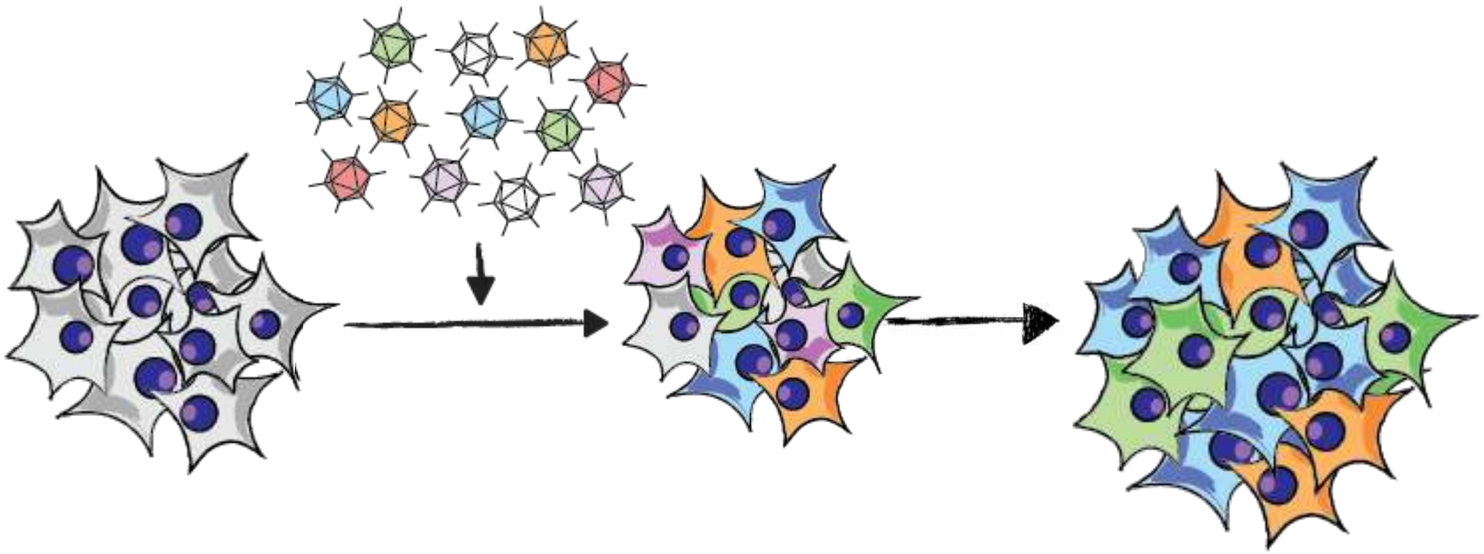
KRASG12C inhibitors

Are there druggable imbalances that arise with high antioxidant production?



CRISPR screens to identify synthetic lethal targets in *KEAP1* mutant tumors

Metabolism focused CRISPR/Cas9 libraries



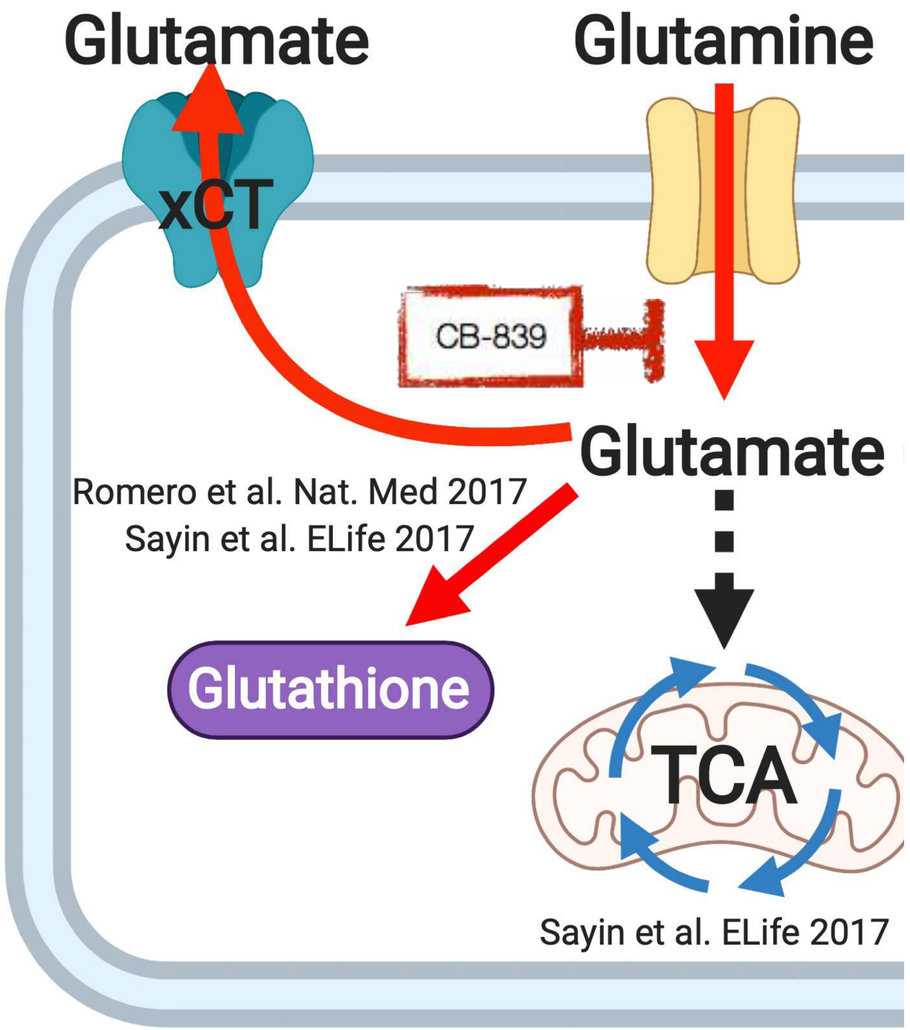
Glutamine Metabolism
Romero et al., Nature Medicine, 2017
Sayin et al., Elife, 2017

Non-essential Amino acids
LeBoeuf et al., Cell Metabolism, 2019

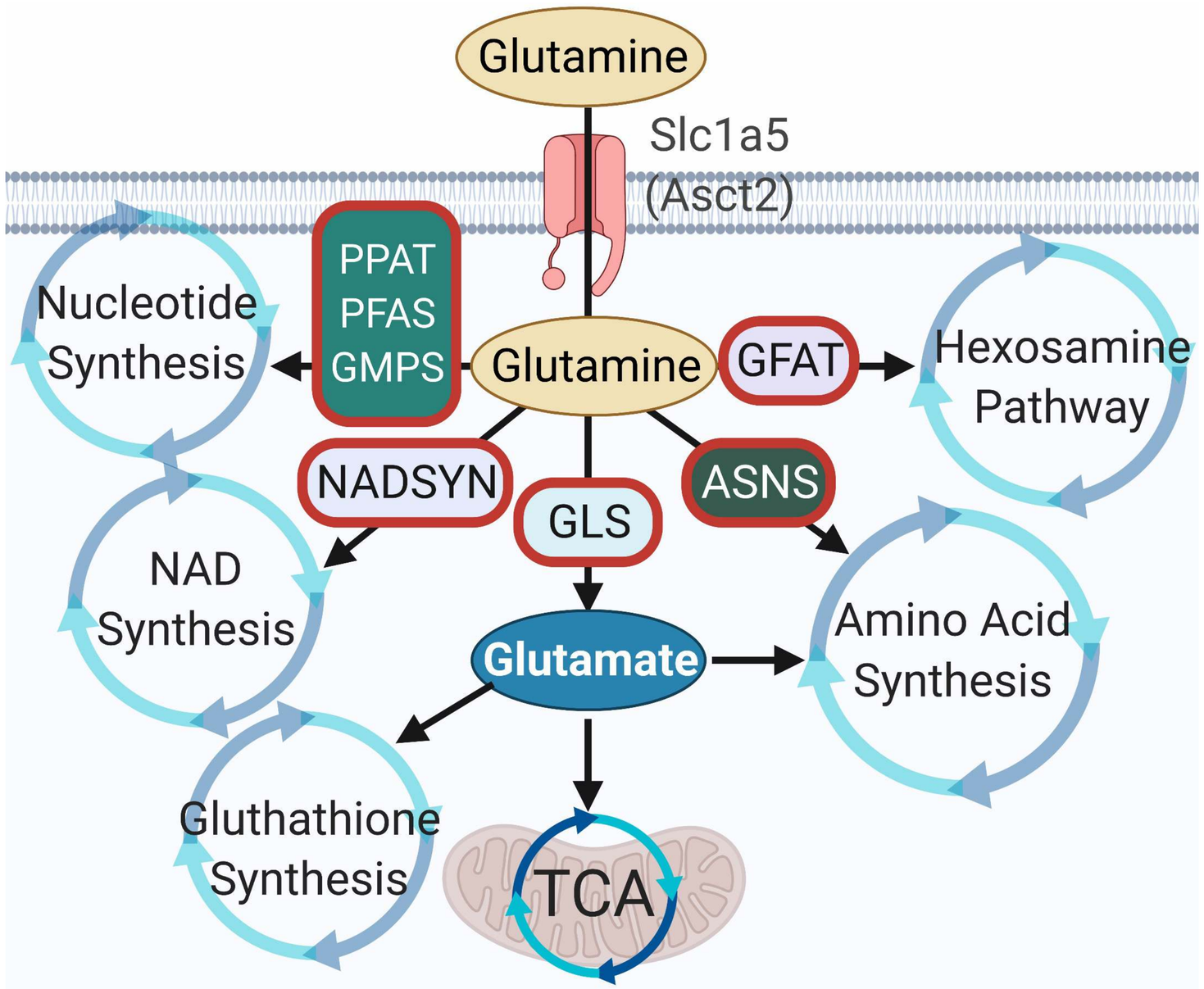
Pentose Phosphate Pathway
Ding et al., Science Advances, 2021

Heme Synthesis
Wu et al., In preparation

Low glutamate levels are a major bottleneck in *KEAP1* mutant tumors

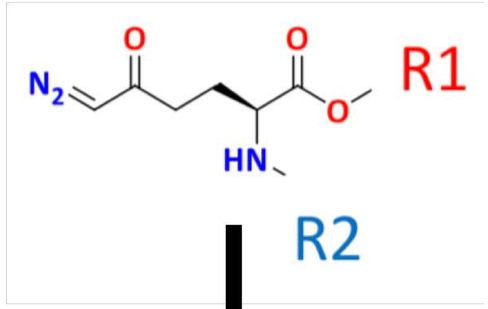


Glutaminase is only one of many glutamine-dependent metabolic enzymes



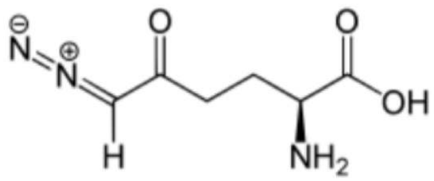
Novel glutamine antagonist (DRP-104) can inhibit all glutamine-dependent enzymes

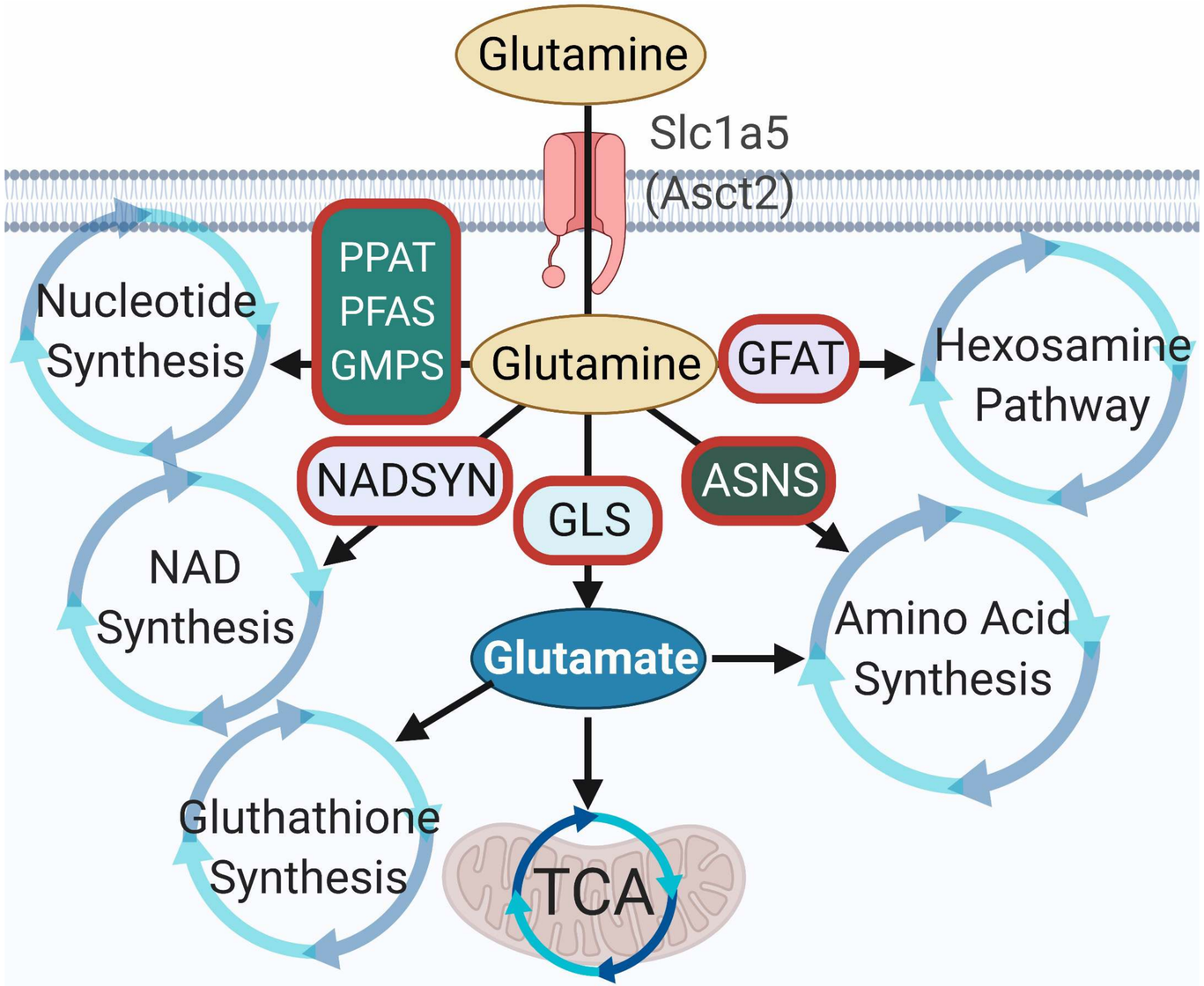
DRP-104



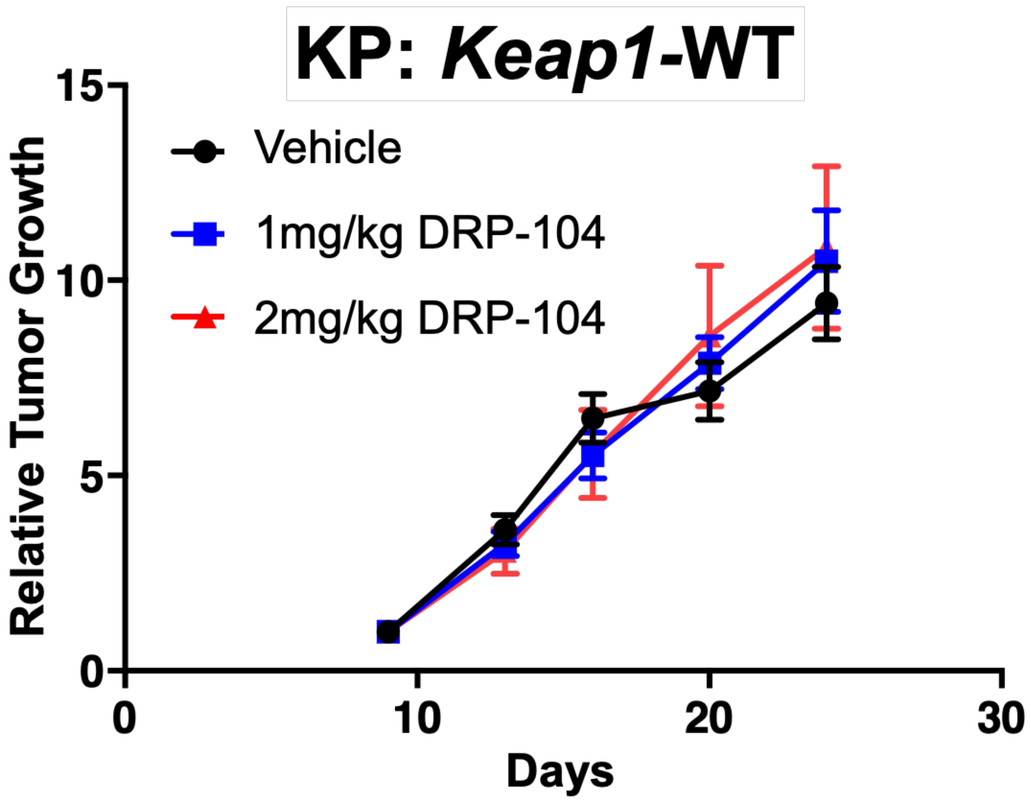
DRP-104 pro-drug stable in GI and plasma, preferential conversion to **DON** in tumors by enzymatic cleavage

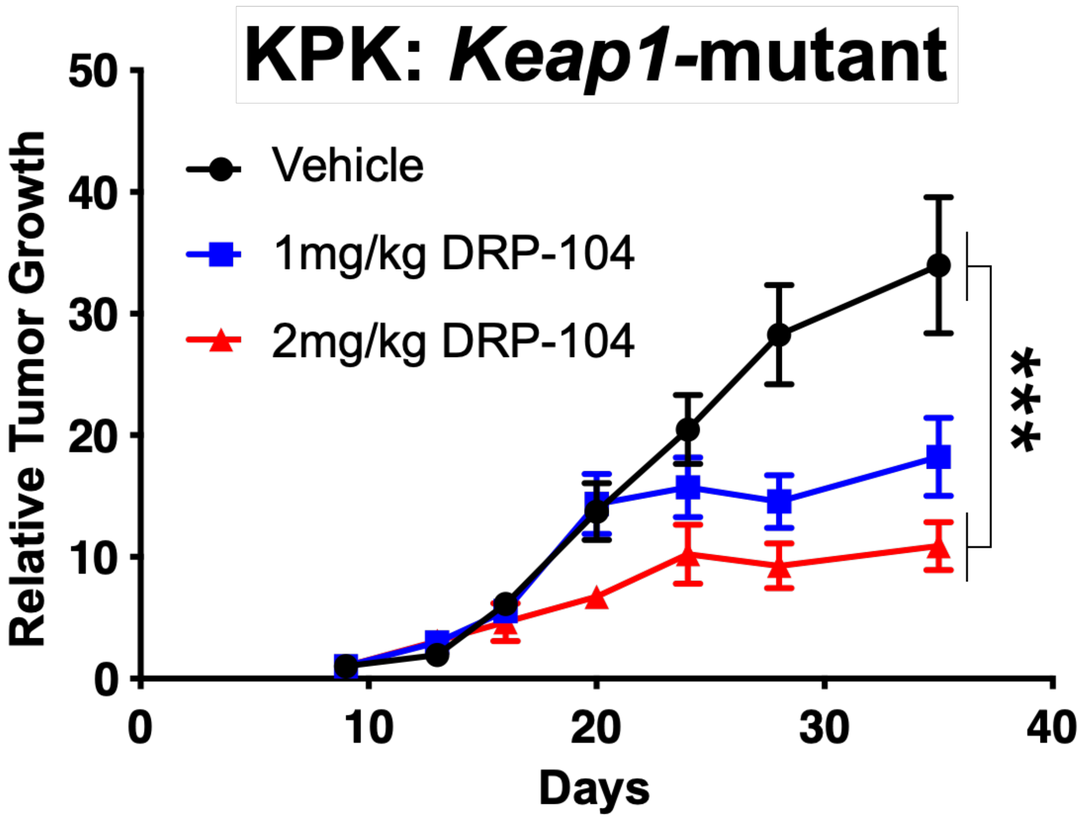
DON





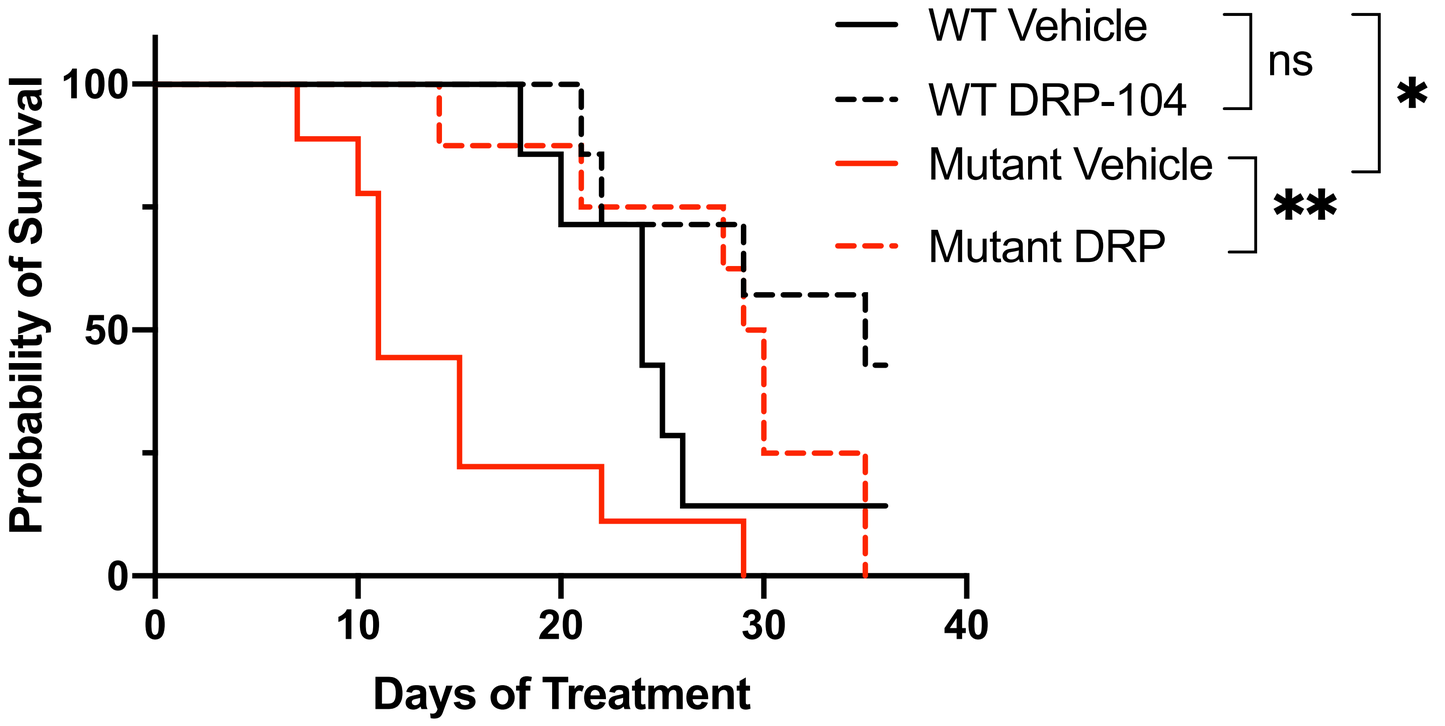
DRP-104 demonstrates anti-tumor activity in *KEAP1* mutant Lung Adenocarcinoma mouse models

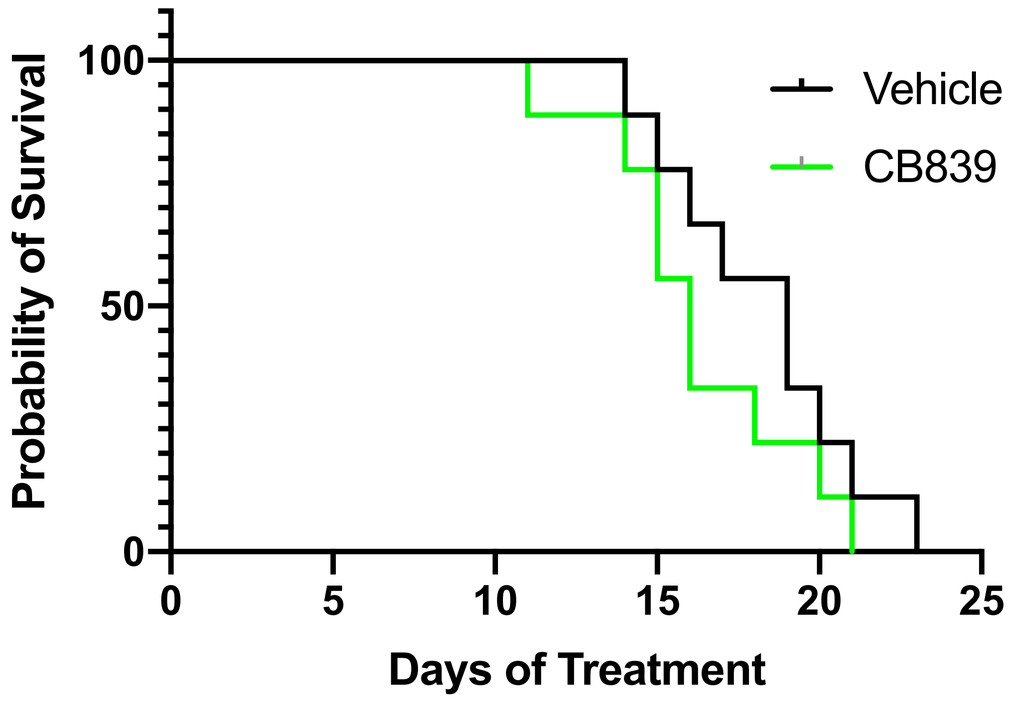




Collaboration with Dracen Pharmaceuticals

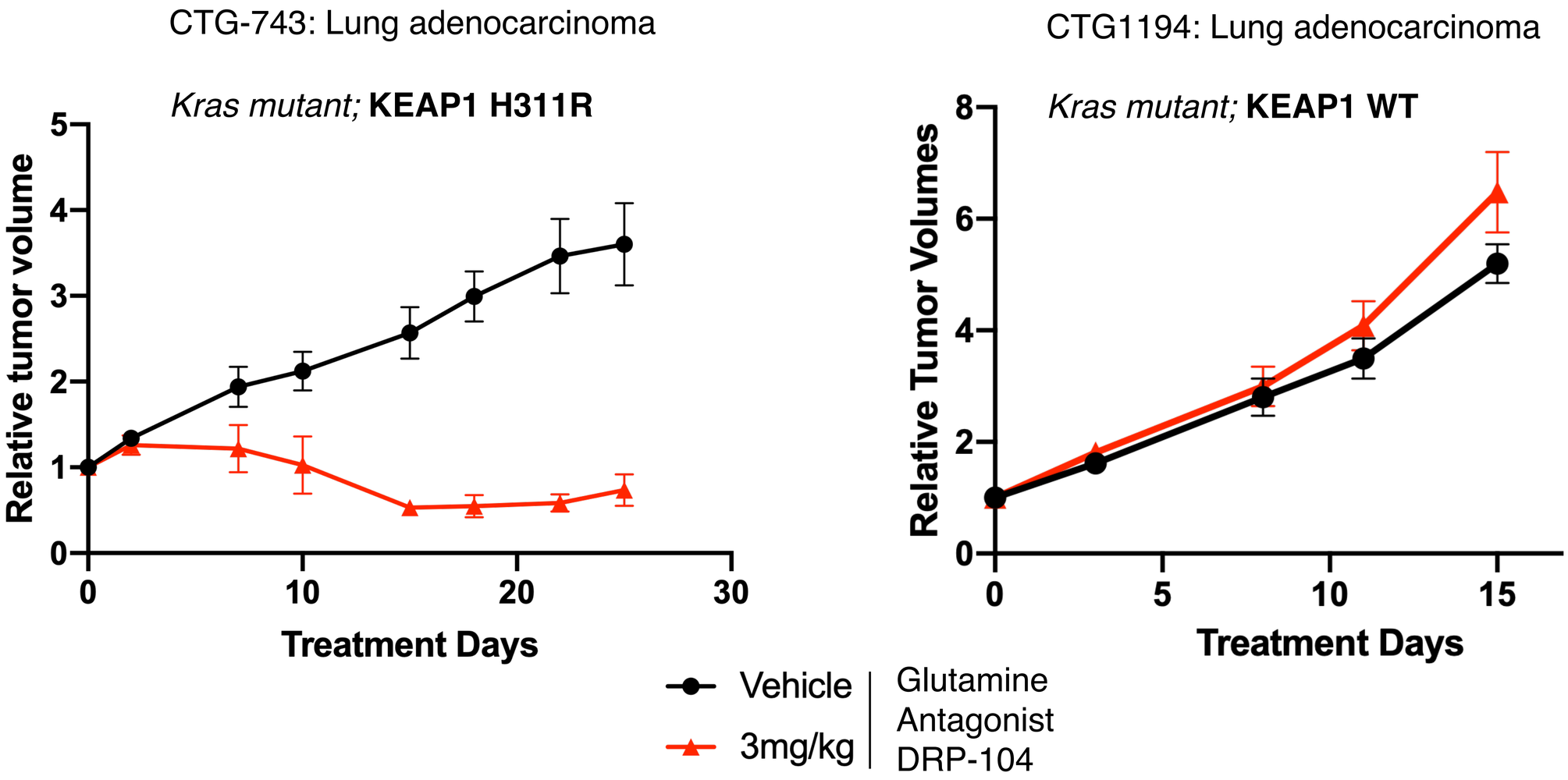
DRP-104 extends survival in *KEAP1* mutant Lung Adenocarcinoma mouse models





Collaboration with Dracen Pharmaceuticals

DRP-104 demonstrates anti-tumor activity in *KEAP1* mutant Lung Adenocarcinoma PDX models



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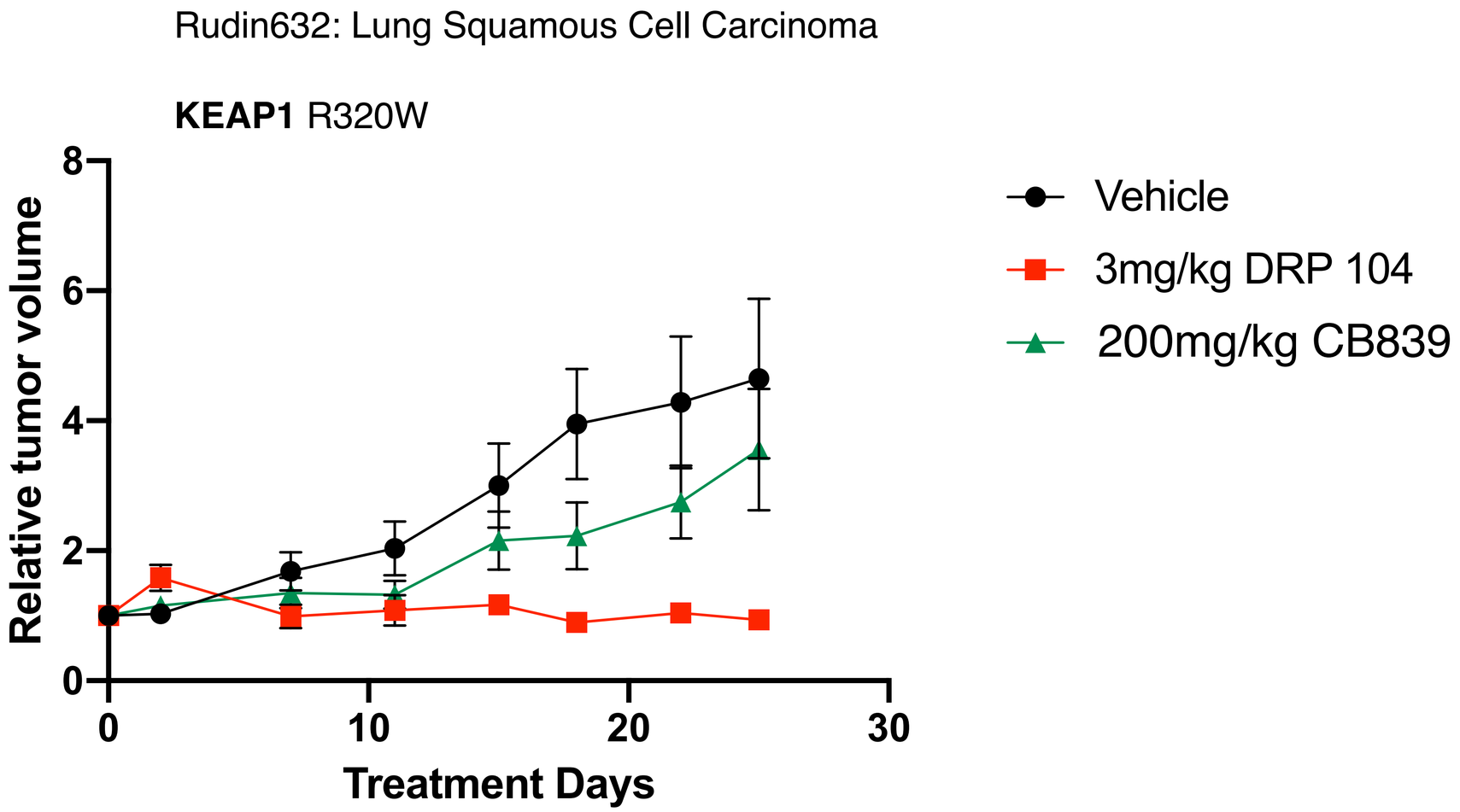
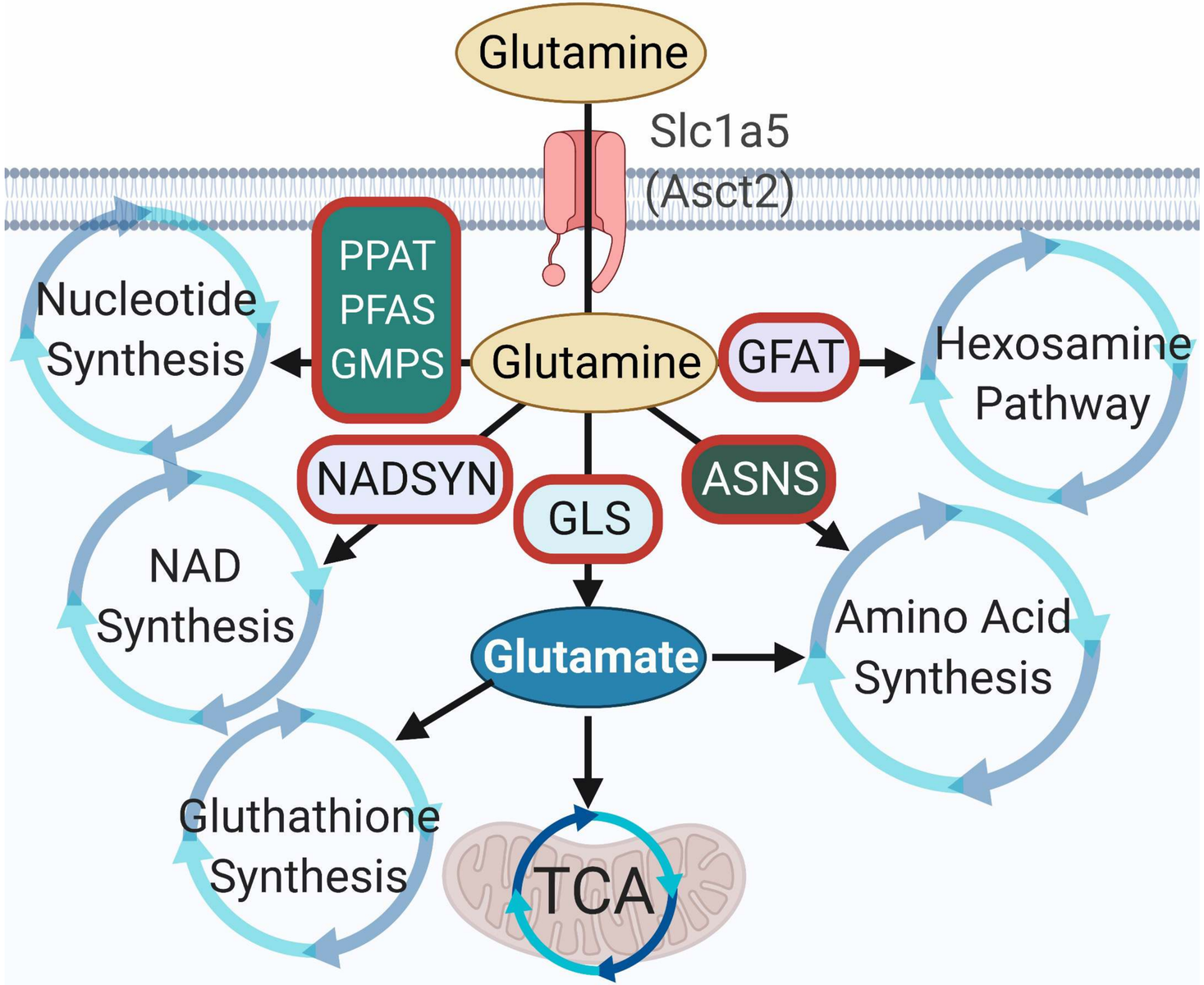
DRP-104 demonstrates superior anti-tumor activity compared to GLS1 inhibition in *KEAP1* mutant Squamous Cell Carcinoma PDX models

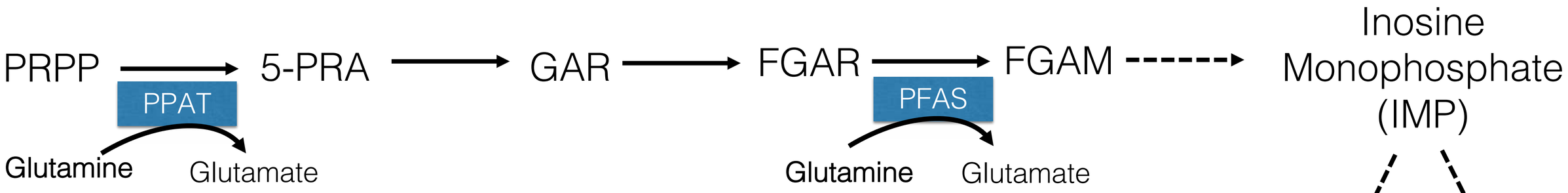


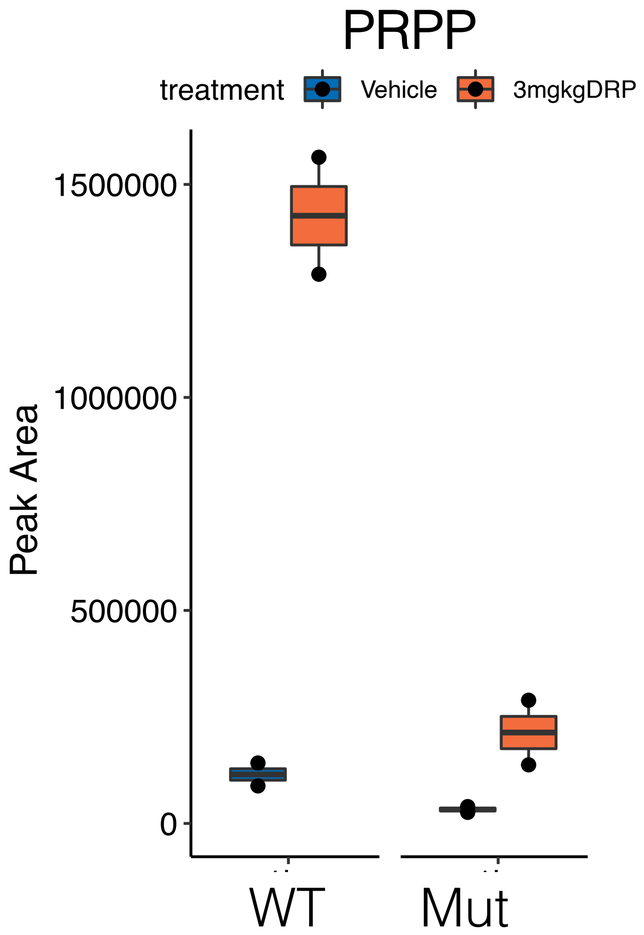
Collaboration with Dracen Pharmaceuticals

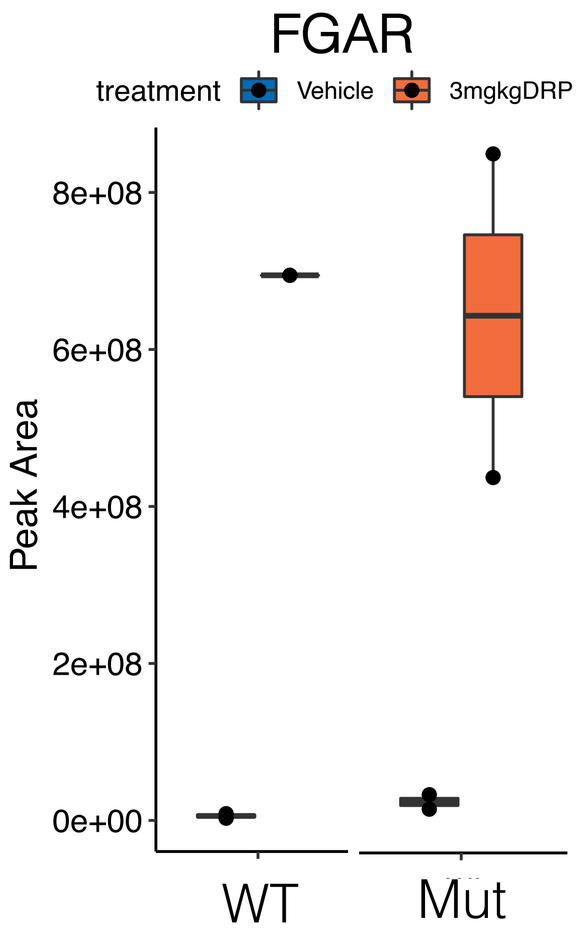
Which glutamine-dependent reactions are inhibited by DRP-104?



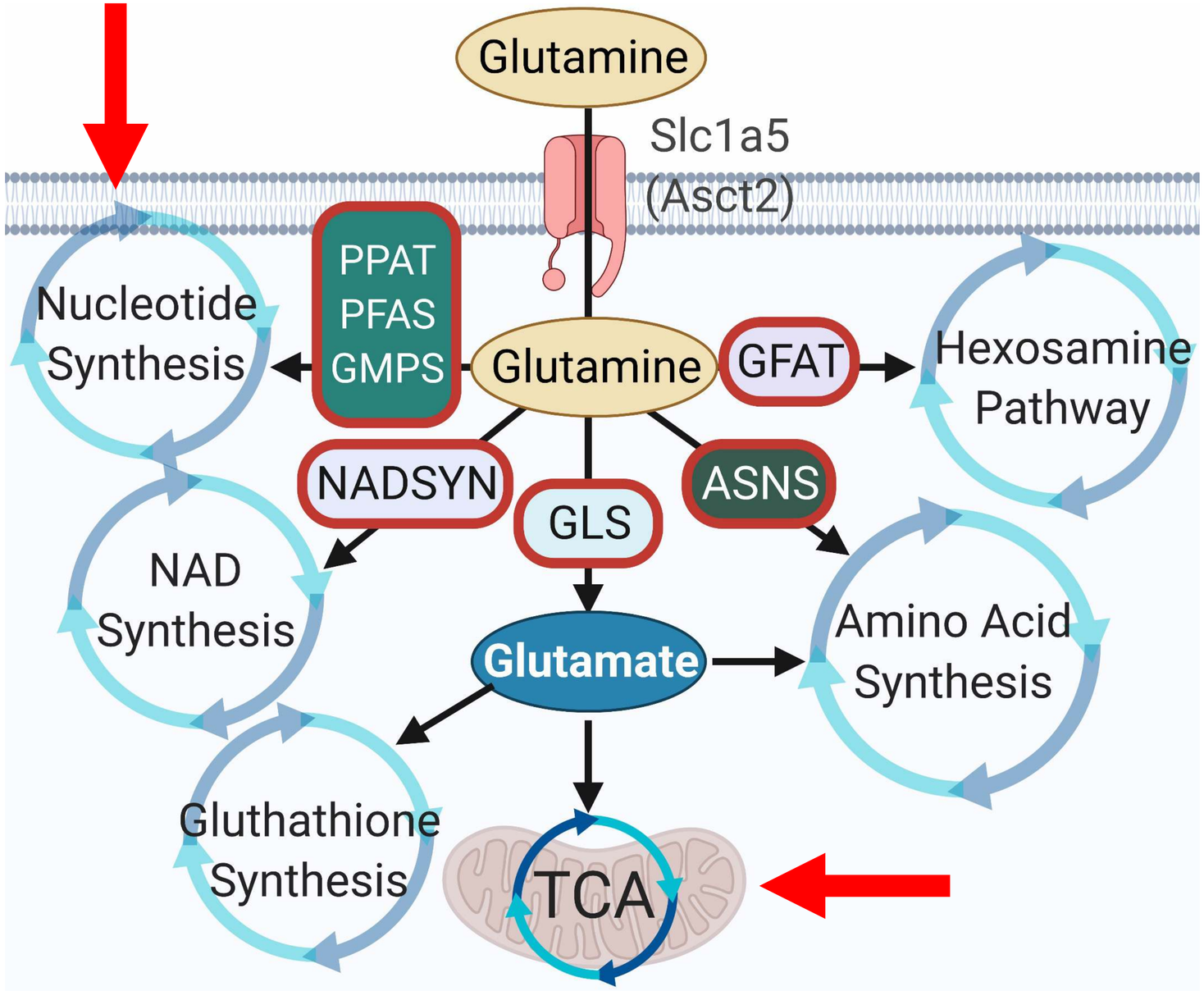
DRP-104 suppresses multiple steps of nucleotide/purine synthesis



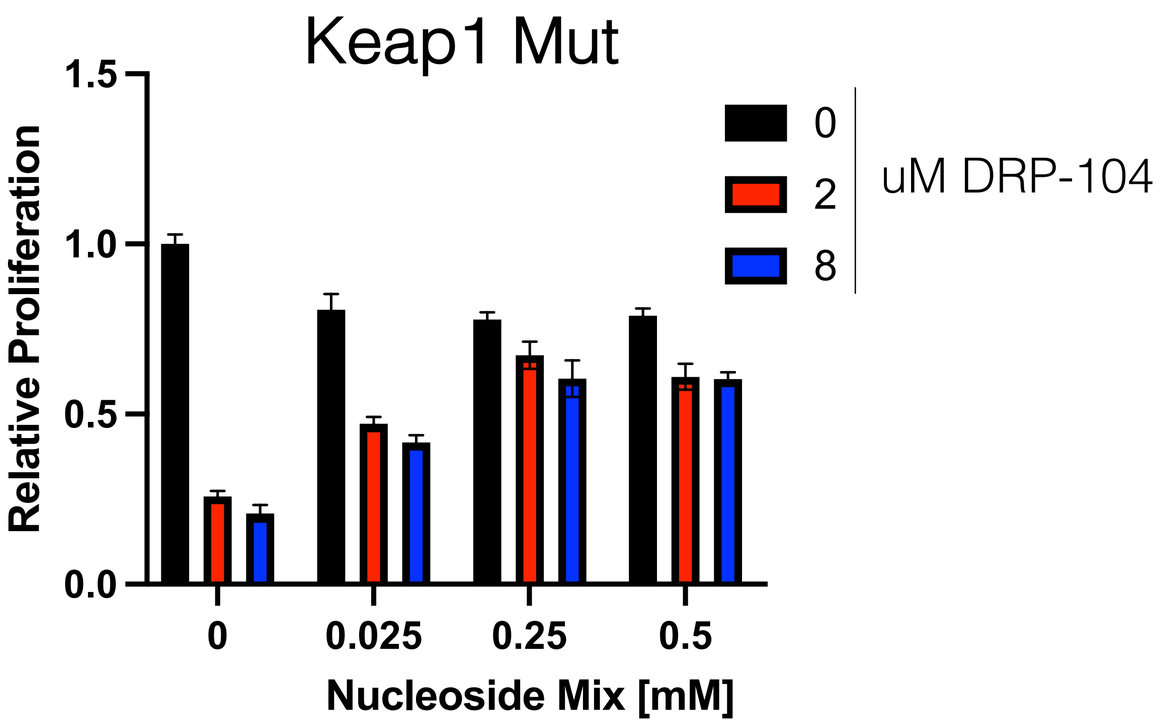


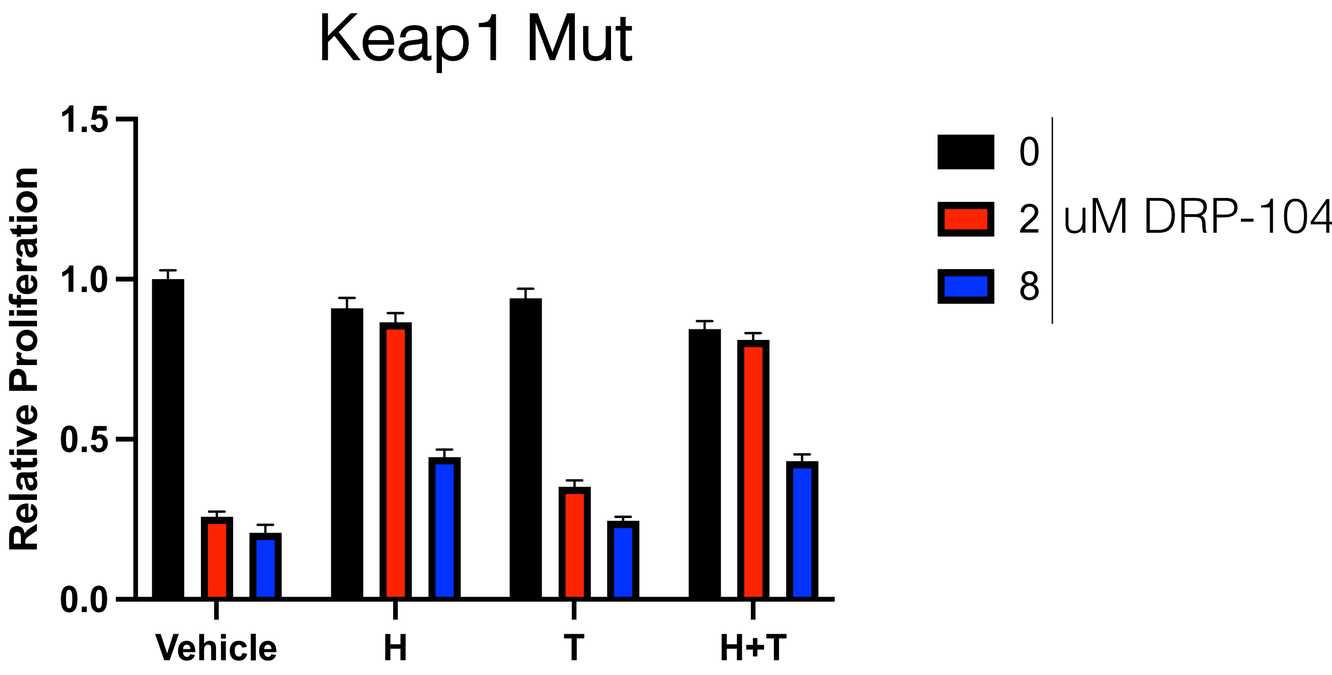


Can metabolite supplementation rescue DRP-104 sensitivity?



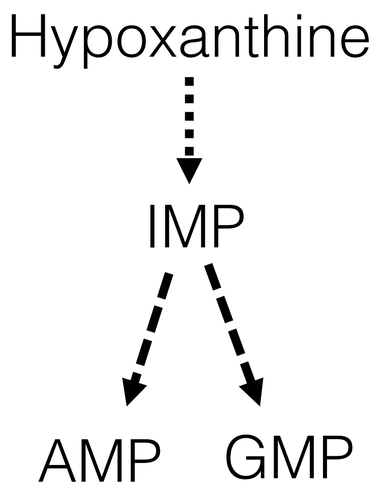
Nucleotide and purine supplementation rescues DRP-104 sensitivity



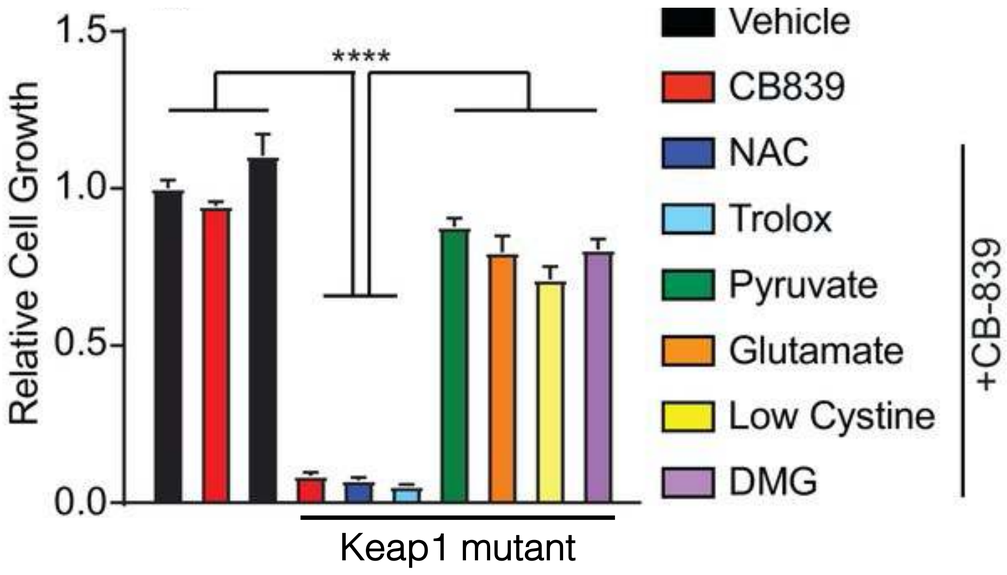


<u>Nucleoside Mix:</u>
Cytidine, Hypoxanthine,
Uridine, Thymidine,
Guanosine, Adenosine

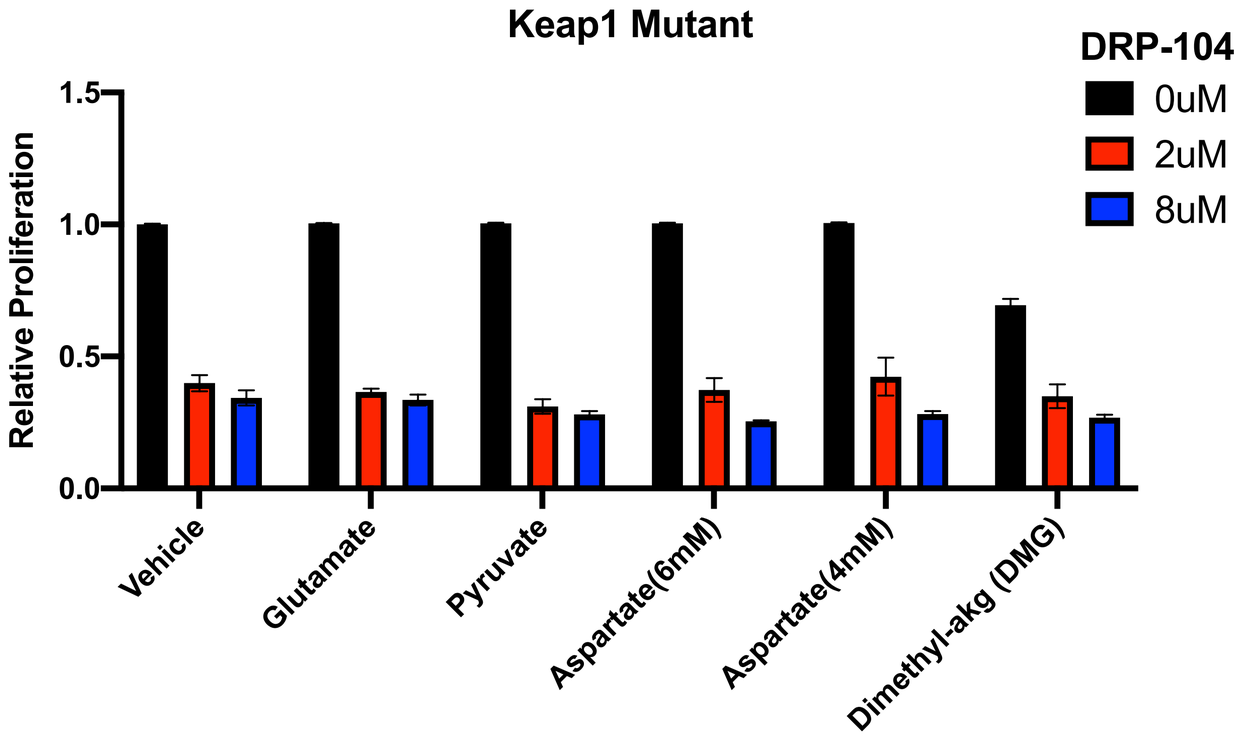
H – Hypoxanthine (20uM) fuels purines
T – Thymidine (16uM) fuels pyrimidines



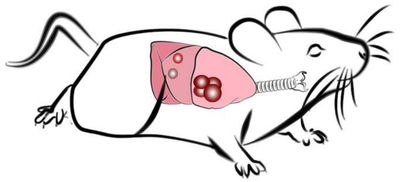
TCA cycle carbon fuels do not rescue DRP-104 sensitivity but they do rescue CB-839



Sayin VS et al., eLife 2017



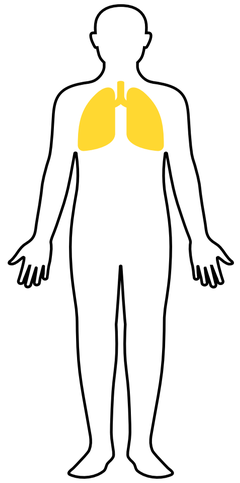
Summary and Clinical Trial



Pre-clinical studies demonstrating efficacy of DRP-104 in *KEAP1* mutant tumors:

- Validation of target in *in vivo* using multiple NSCLC PDX models and syngeneic cancer models
- DRP-104 demonstrates better efficacy than CB-839 in multiple models
- DRP-104 broadly inhibits all 10 glutamine metabolizing enzymes.
- In *KEAP1* mutant tumors, DRP-104 robustly inhibits nucleotide/purine metabolism

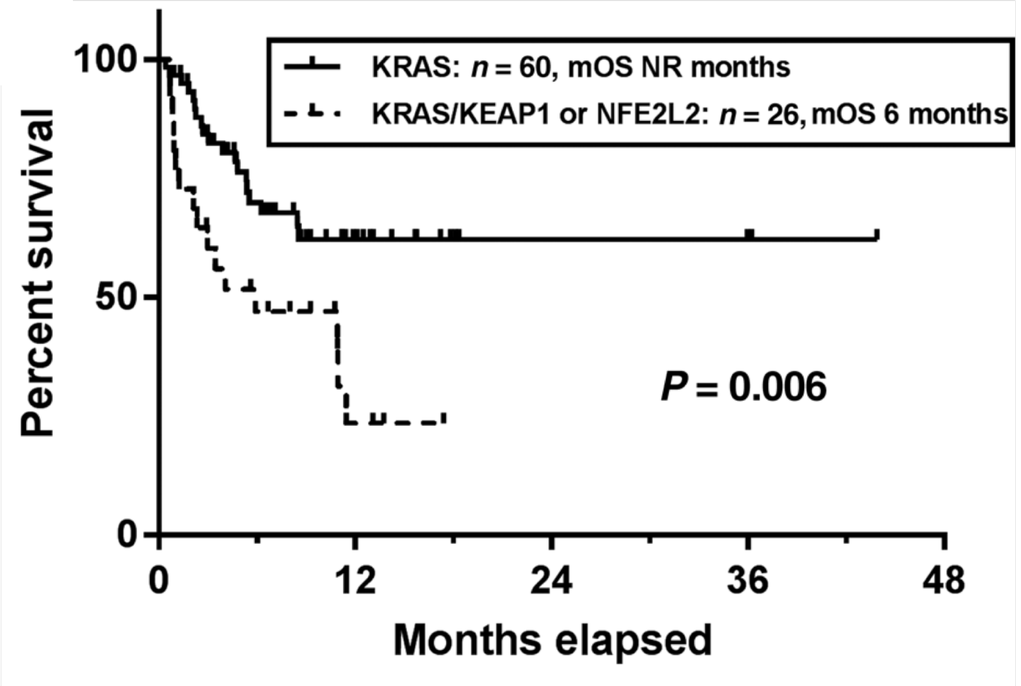
NCT04471415: First-in-human phase 1/2a Study of DRP-104 as Single Agent in KEAP1/NRF2-mutant NSCLC is ongoing



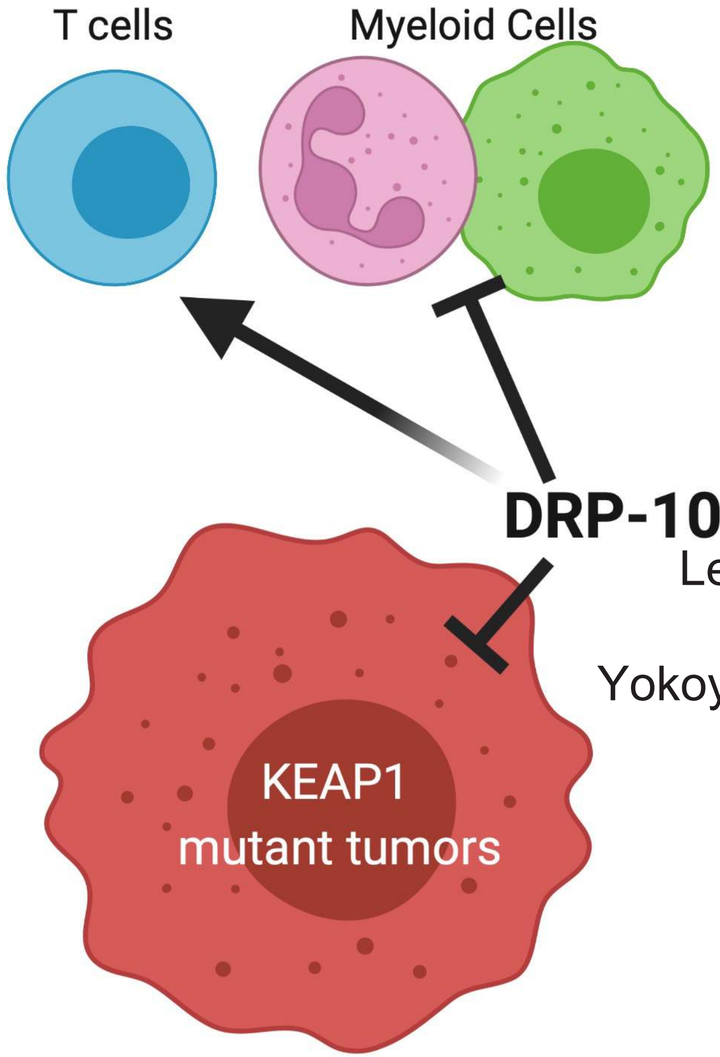
Biomarkers for enrollment to phase 2 trial:

- Genetic (e.g. *KEAP1 mutation)*
- Tumor tissue staining (e.g. *NQO1 stain)*
- Transcriptome (Nanostring-based NRF2 target set)

DRP-104 may overcome checkpoint inhibitor resistance in *KEAP1* mutant patients



Arbour et al; *Clinical Cancer Research 2018*



Leone et al., Science, 2019
Oh et al., JCI, 2020
Yokoyama et al., Cancer Res 2021

Zavitsanou et al., BioRxiv, 2021

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