67. Identification of DP2 & SCL1A5 as Therapeutic Targets (MIT)

Asset Overview

Product Type	Small Molecule
Disease Area	Oncology
Indication	Non-small Cell Lung Cancer (NSCLC)
Current Stage	Discovery
Target	KRAS-mutant lung adenocarcinoma (LUAD)
MoA	GDP inhibitor regulates NFR2/KEAP1 pathway by inhibiting glutaminase in KRAS-mutant lung adenocarcinoma (LUAD).
Brief Description	• This technology uses glutaminase inhibition as a therapy for KEAP1/NRF2 dysregulated NSCLC. • These inventors identified that mutation of SLC1A5 or GPD2 in combination with KEAP1/NRF2 dysregulation leads to synthetic lethality. This finding led to the observation that KEAP1/NRF2 dysregulation results in dependence on glutamine metabolism and suggested that inhibition of glutamine metabolism may be a therapeutic target for KEAP1/NRF2 dysregulated NSCLC. • In proof-of-concept experiments, the inventors demonstrated that inhibition of glutaminase, a key enzyme in glutamine metabolism, with the small molecule CB-893 led to significantly increased lifespan and decreased tumor burden in both mouse and human patient-derived-xenograft in vivo models. • Glutaminase inhibition is an attractive therapeutic target for KEAP1/NRF2 dysregulated NSCLC, and that KEAP1/NRF2 dysregulation could be used as a theragnostic marker to direct NSCLC therapy.
Intellectual Property	US20210361603A1
Publication	Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. Nature Medicine. (2017)
Inventors	Thales Papagiannakopoulos, Tyler Jacks, Rodrigo ROMERO

Highlights

- Loss of Keap1 hyperactivates NRF2 and promotes KRAS-driven LUAD in mice.
- Keap1- or Nrf2-mutant cancers are dependent on increased glutaminolysis, and this property can be therapeutically exploited through the pharmacological inhibition of glutaminase.
- Provide a rationale for stratification of human patients with lung cancer harboring KRAS/KEAP1- or KRAS/NRF2-mutant lung tumors as likely to respond to glutaminase inhibition.
- Promising in vivo pre-clinical data indicating therapeutic value of targeting glutaminase in KEAP1/NRF2 dysregulated NSCLC tumors.

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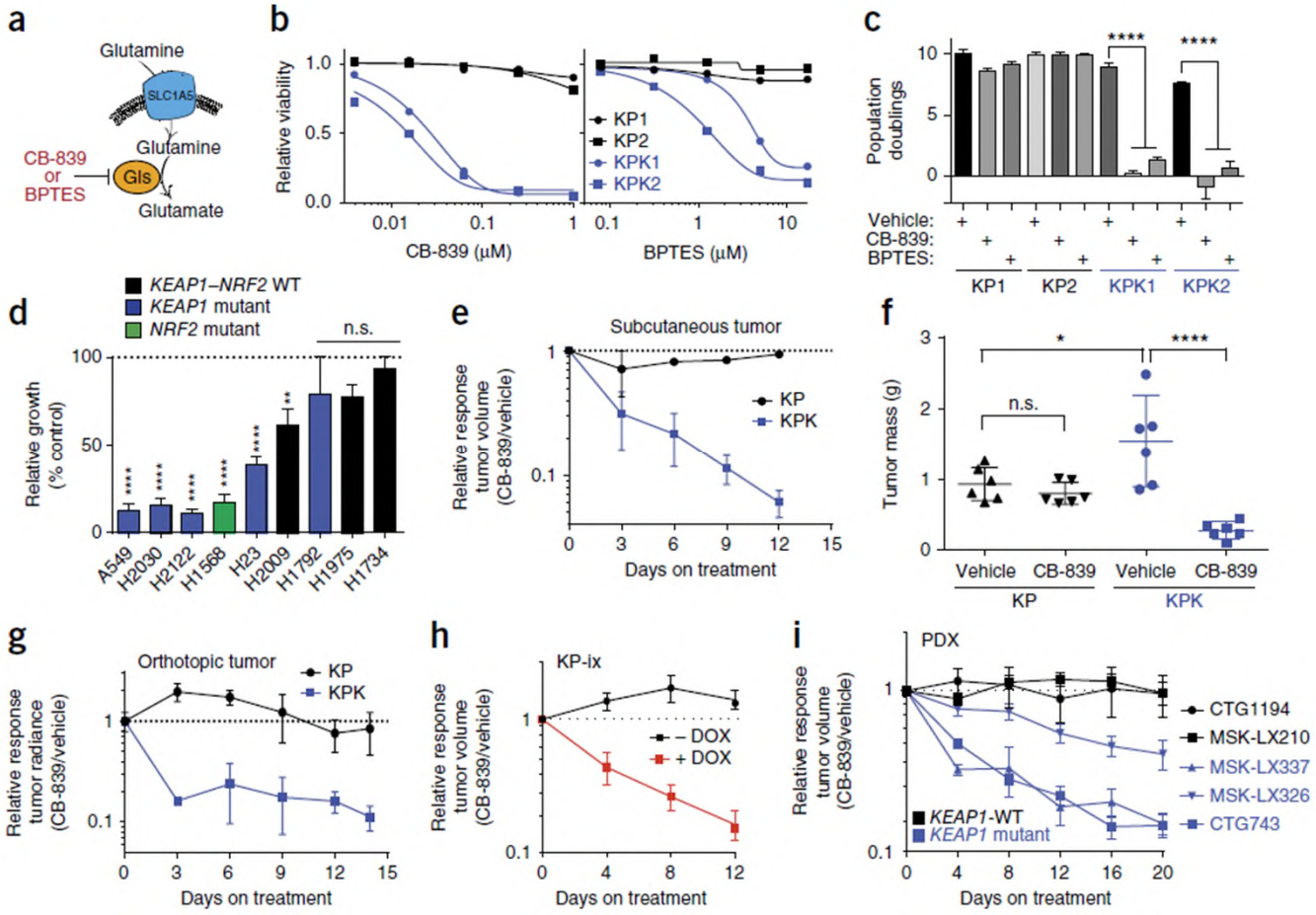
Key Data

Keap1-mutant cells display a robust sensitivity to glutaminase inhibition



(a) Schematic of glutamine uptake by SLC1A5 and hydrolysis of glutamine to glutamate by glutaminase (Gls). Inhibitors of glutaminase are shown in red. **(b)** Relative viability assayed by CellTiter-Glo (relative luminescence units) of KP and KPK cells after treatment with CB-839 (left) or BPTES (right) for 72 h. All data points are relative to vehicle-treated controls (n = 4 technical replicates per data point). **(c)** Cumulative population doublings of KP and KPK cells in the presence of vehicle, CB-839, or BPTES (n = 4 technical replicates per data point) after 6 d in culture. **(d)** Trypan blue exclusion viability counts of indicated human lung cancer cell lines. Each cell line was cultured in the presence of vehicle or 500 nM CB-839 (n = 4 technical replicates per cell line). Displayed results are normalized against vehicle-treated cell lines after 72 h of treatment. A549 and H1975 cells harbor WT *TP53*; all other cell lines harbor mutant *TP53*. **(e,f)** Subcutaneous tumor volumes of KP and KPK cells treated with vehicle or CB-839 starting from day 13 and measured over time for 25 d (n = 6 tumors per genotype per treatment) **(e)** and final masses of those tumors, also shown in **Supplementary Figure 11b (f)**. **(g)** Orthotopic growth measurements of KP and KPK cells treated with vehicle or CB-839 starting from day 13 (n = 4 mice per genotype per treatment). Quantification of luminescence (photon flux) was performed in mice orthotopically transplanted with KP or KPK cells transduced with a vector expressing luciferase. The relative photon flux was calculated by normalizing all time points per mouse to initial measurements at 10 d following transplantation. Individual groups harboring inducible *Nrf2*-GOF cDNA are depicted in **Supplementary Figure 11c**. **(h)** Subcutaneous tumor volumes of KP-ix cells (harboring inducible *Nrf2*-GOF) treated with vehicle or CB-839 in the presence or absence of doxycycline (DOX; n = 6 mice per doxycycline treatment group). Individual groups and the full experiment are depicted in **Supplementary Figure 11d**. **(i)** Five PDX models treated with vehicle or CB-839 for the indicated number of days. Individual groups and full experiments are depicted in **Supplementary Figure 11g,h**. Data are presented as means, with error bars depicting s.e.m. Statistical analyses were performed using one-way ANOVA with Tukey's *post hoc* test in c and f, a Student's t-test in d, and two-way ANOVA in e and g–i. n.s., not significant. *P < 0.05, **P < 0.005, ****P < 0.0001.