Identification of GPD2 and SCL1A5 as Therapeutic Targets in Lung Cancers with Mutations in the Oxidative Stress Pathway

Technology #19211

Applications

This technology is a theranostic and therapeutic technique for non-small cell lung cancer with applications in drug development.

Problem Addressed

Lung cancer is the leading cause of cancer related deaths worldwide. In non-small cell lung cancer (NSCLC), the largest subtype of lung cancer, 30% of patients have mutation of the KEAP1/NRF2 oxidative stress pathway. Patients with mutation of the KEAP1/NRF2 pathway have highly aggressive tumors with poor prognoses. This technology is a novel way to treat patients with dysregulation of the KEAP1/NRF2 pathway.

Technology

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 \textit{in vivo} models. These findings indicate that glutaminase inhibition is an attractive therapeutic target for KEAP1/NRF2 dysregulated NSCLC, and that KEAP1/NRF2 dysregulation could be used as a theranostic marker to direct NSCLC therapy.

Advantages

- Promising \textit{in vivo} pre-clinical data indicating therapeutic value of targeting glutaminase in KEAP1/NRF2 dysregulated NSCLC tumors
- KEAP1/NRF2 dysregulation can be used as a theranostic to identify patients for glutaminase therapy

Categories For This Invention:

- Life Sciences
- Clinical Applications
- Oncology
- Diagnostics
Markers
Therapeutics
Small Molecule

Intellectual Property:
Methods of treating cancers having a deregulated NRF2/KEAP1 pathway
PCT
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Publications:
Keap1 Loss Promotes Kras-Driven Lung Cancer and Results in Dependence on Glutaminolysis
Nature Medicine
November 23, 2017. 23

External Links:
Jacks Lab
https://jacks-lab.mit.edu/