KDDF
Korea Drug Development Fund

Asset #35
University of Toronto

NUAK Inhibitors as Therapeutics for Cancer and Fibrosis

Therapeutic Area	Oncology	**Indications**	Cancer and Fibrosis
Modality	Small Molecule	**Development Stage**	Hit to Lead/Lead Optimization

Overview

Background

- The Hippo signaling pathway regulates cell proliferation and death, impacting diseases like cancer and fibrosis. YAP and TAZ, transcriptional regulators, are controlled by the Hippo kinase cassette through phosphorylation.
- Phosphorylated YAP/TAZ are cytoplasmic and inactive, while unphosphorylated forms drive gene transcription for pro-oncogenic and pro-fibrotic effects. Enhancing YAP/TAZ phosphorylation holds therapeutic potential against cancer and fibrosis.

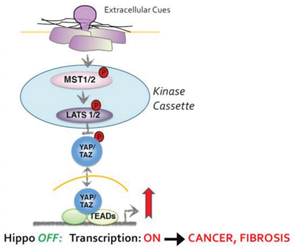
Technology Advantages

- Two classes of novel inhibitor compounds for NUAKs: IC50 in the nM range
- NUAK1 and NUAK2 are elevated in broad disease indications based on Cancer and Fibrosis
- Drug screening capabilities: Identification of NUAK2 as a negative regulator of Hippo provides a new opportunity to develop kinase inhibitors that would counteract the oncogenic functions of YAP/TAZ

Key Data

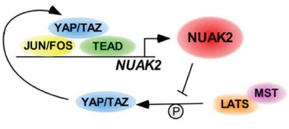
YAP/TAZ and NUAK2 act in a positive feed forward loop in MDA-MB231 cells

A



Extracellular cues turn on the Hippo pathway which results in phosphorylation and cytoplasmic retention of YAP/TAZ; unphosphorylated TAP/TAZ localize to the nucleus where they exert pro-oncogenic, pro-fibrotic functions.

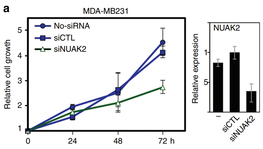
B



Negative regulation of the Hippo pathway by NUAK2 promotes oncogenesis and fibrosis.

YAP/TAZ and NUAK2 act in a positive feed forward loop in MDA-MB231 cells

C



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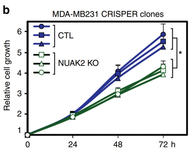

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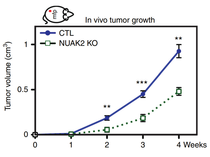

Loss of NUAK2 expression using siRNA or in NUAK2 knockout clones inhibits cell growth as measured by the SRB assay. Data are plotted as the mean ± SD of a representative experiment (C) or mean ± SEM (*p value <0.05, unpaired two-tailed t test) of three to five independent experiments per clone (B). NUAK2 knockdown efficiency in the siRNA experiment (D) is plotted as the mean ± range of a representative experiment.

Loss of NUAK2 reduces tumor growth in vivo. (E) Data are plotted as the mean ± SD (**p <0.005, ***p <0.001, unpaired two-tailed t test)

IP Status & Publication(s)

Intellectual Property

Patent Number	Patent Family
PCT-CA2022-050016 (2022.01.07)	AU, CA, CN, EU, JP, US
PCT-CA2022-050014 (2022.01.07)	AU, CA, CN, EU, JP, US

Publication(s)

- Gill, M et al. (2018) A feed forward loop enforces YAP/TAZ signaling during tumorigenesis. *Nature Communications*.
- Zhang, T et al. (2022) NUAK1 promotes organ fibrosis via YAP and TGF-β/SMAD signaling. *Science Translational Medicine*.