Docket #: S20-426

An orally, bioavailable, and non-toxic salt to induce DNA demethylation and overcome retinoic acid-resistance in neuroblastoma

Dysregulated DNA methylation is associated with poor prognosis in cancer patients, promoting tumorigenesis and therapeutic resistance. DNA methyltransferase inhibitors (DNMTi) reduce DNA methylation and promote cancer cell differentiation in in vitro and in vivo models, with two DNMTi approved for cancer treatment. However, DNMTi have several major clinical limitations: they only prevent formation of new methylation marks rather than remove existing methylation; they promote demethylation through 'dilution' of methylation through cell division; they also target normal cells, causing toxicity; and they are weak mutagens incorporating into DNA. The Ye lab at Stanford has developed an effective metabolic intervention to achieve global DNA demethylation by leveraging niclosamide ethanolamine (NEN). NEN is a cell-permeable, orally bioavailable, and non-toxic salt that acts as a reversible and mild uncoupler of mitochondria. The inventors demonstrated NEN treatment increases ?-ketoglutarate (?KG), a substrate of TET DNA demethylase, reduces global DNA methylation and induces tumor suppressor gene and differentiation marker gene expression in neuroblastoma cells. Importantly, NEN not only increases ?KG under normoxic conditions, but also reduces 2-hydroxyglutarate (2HG), an inhibitor of TET DNA demethylase under hypoxic conditions, suggesting that NEN may be an effective strategy to promote differentiation and inhibit tumor growth in hypoxic tumors. Neuroblastoma (NB) is a cancer of the sympathetic nervous system, which accounts for 7% of all childhood cancers and 15% of childhood cancer-related deaths. In high-risk patients, disease relapse occurs frequently after surgery or chemotherapy and eventually becomes fatal. For over 15 years, the main treatment for NB utilizes retinoic acids (RA), chemicals derived from vitamin A, to induce differentiation in neuroblastoma cells. However, about 50% of neuroblastoma

patients who initially respond to RA therapy develop RA-resistance. One of the major causes of RA-resistance is due to the epigenetic silencing of the retinoic acid receptor (RAR) signaling through DNA methylation. The inventors demonstrated that NEN treatment restored RAR signaling, overcoming RA-resistance. In addition to neuroblastoma, the inventors demonstrated that NEN also shows anticancer effects in cell lines from multiple cancer types including ovarian, lung, and other cancers. As the first successful application of NEN for RA-resistance, the invention has the potential to be used as a prescribed medicine for cancer treatment and overcoming resistance in neuroblastoma.

Stage of Development:

- proof of concept – in vitro

Applications

- DNA-based therapeutics
- Oncological treatment
- Research tool for metabolic disorders

Advantages

- Nontoxic and biocompatible agent
- Can be used in vivo or in vitro
- Induces differentiation through epigenetic reprogramming
- Efficient reduction of global DNA methylation within an hour

Publications

- Haowen Jiang, Rachel L. Greathouse, Sarah Jane. Tiche, Man Zhao, Bo He, Yang Li, Albert M. Li, Balint Forgo, Michaela Yip, Allison Li, Moriah Shih, Selene Banuelos, Meng-Ning Zhou, Joshua J. Gruber, Erinn B. Rankin, Zhen Hu, Hiroyuki Shimada, Bill Chiu, Jiangbin Ye. Mitochondrial uncoupling induces epigenome remodeling and promotes differentiation in neuroblastoma. Cancer Res 2022
- Haowen Jiang, Rachel L Greathouse, Bo He, Yang Li, Albert M. Li, Balint Forgo, Michaela Yip, Allison Li, Moriah Shih, Selene Banuelos, Meng-Ning Zhou, Joshua

J. Gruber, Hiroyuki Shimada, Bill Chiu, Jiangbin Ye. Reprogramming the neuroblastoma epigenome with a mitochondrial uncoupler bioRxiv 2021.09.05.459035

Patents

- Published Application: 20220175704
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