KDDF
Korea Drug Development Fund

Asset #48
Duke-NUS Medical School

Treatment of Seizures Associated with Angelman Syndrome (AS)

Therapeutic Area	Neurology	**Indications**	Angelman Syndrome (AS), Related Neurological Disorders
Modality	Small Molecule	**Development Stage**	Target Identification/Validation

Overview

Background

- Angelman syndrome (AS) is a neurodevelopmental disorder characterized by delayed development, intellectual disability, and seizures. The absence of a cure and challenges in treating seizures persist. The loss of UBE3A function in the majority of AS cases contributes to disease through substrate buildup.
- Despite insights into impaired synaptic connectivity, network imbalance, and delayed neurodevelopment, the precise mechanism underlying AS-related epilepsy remains unclear. Furthermore, AS patient-derived stem cells have yet to fully reveal the pathological mechanism or UBE3A's biological role.

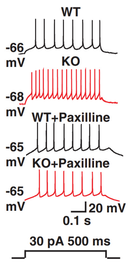
Technology Advantages

- Human neurons and brain organoids were utilized to discover how UBE3A degrades BK channels, regulating neuronal hyperexcitability.
- This discovery sheds light on the pathophysiology of AS and provides new insights into network dysfunction and hyperactivity.
- The team's expertise in human cortical brain organoids and UBE3Am-/p+ mice enhances their ability to study potential BK antagonists as therapies.

Key Data

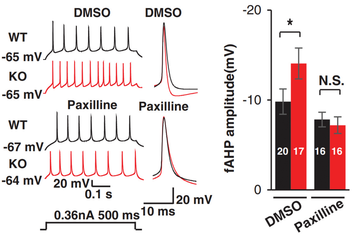
UBE3A deletions increase BK channel function in human neurons

A



Representative traces and quantification of BK currents isolated from WT and KO neurons treated with paxilline (5 mM), showing the impact of UBE3A deletions on BK channel function

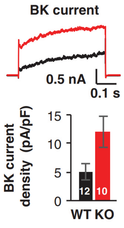
B



Representative traces and quantification of fAHP with and without paxilline (5 mM), demonstrating the pharmacological rescue by the BK antagonist paxilline

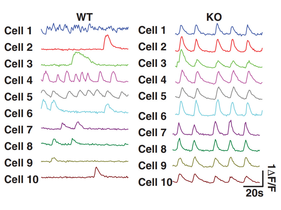
Altered functional properties of neurons and enhanced network activity in UBE3A-deficient organoids

C



Altered electrophysiological properties in neurons from KO organoids, illustrated with representative traces showing the impact of UBE3A deficiency on electrophysiological behavior

D



Calcium transient traces extracted from individual neurons of WT and KO organoids, demonstrating the altered calcium dynamics in UBE3A-deficient organoids using two-photon live calcium imaging

IP Status & Publication(s)

Intellectual Property

Patent Number
PCT-SG2020-050762 (2020.12.18)

Patent Family
PCT, US, EP

Publication(s)

- Sun at al. (2019). Potassium channel dysfunction in human neuronal models of Angelman syndrome. Science