UNIVERSITY OF MARYLAND
UM VENTURES
MPOWERING THE STATE

www.umventures.org

miR-24-3p and miR-27a-3p Mimics as Therapeutic Agents for Modulation of Neuronal Apoptosis after Brain Injury

Summary

Reduced blood flow to the brain due to thrombosis, embolism, cardiac arrest, or injury, can result in focal or global cerebral ischemia. Ischemia leads to alterations in brain metabolism, reduction in metabolic rates, and subsequent neuronal death. Ischemia can have irreversible sequela. Post-injury treatment to curtail cell death due to acute ischemic stroke is limited to a single therapy, Alteplase, that must be administered within 3 hours of the insult. Despite timely intervention in this time frame, ischemia can have irreversible sequela. To address this problem, UMB inventors have characterized two miRNA mimics that can be used therapeutically to modulate neuronal apoptosis following an ischemic injury. Their efficacy has been tested in a mouse model of traumatic brain injury (TBI).

Key Investigator

Boris Sabirzhanov
Bogdan Stoica
Alan Faden

Field

Therapeutics

Technology

miRNA mimics

Advantages

Micro-RNA mimics target a leading cause of permanent disability and patients who have suffered a TBI

Could reduce deleterious side-effects patients experience post-injury due to enhanced protection of ischemic brain tissue

Status

Available for licensing
Available for sponsored research

Patent Status

US 9,434,945 B2
(Issued 9/6/2016)

UMB Docket Reference

AF-2014-011

External References

Sabirzhanov B et al. (2014). *J Neuro.* 34(30): 10055-10071.

Market

TBI is a major cause of death and disability throughout the world. In the US, between 1.1%-1.7% of the population (3.5-5.5 million individuals) live with long-term disabilities due to TBI, highlighting the enormous need for effective therapies. To date, miRNA research has focused on infectious diseases, cardiovascular disease, and oncology, with an miRNA antagonist currently in phase 2 trials for the treatment of hepatitis C infection. miRNA mimics offer the advantage of systemic delivery using technologies used for therapeutic siRNAs, making it easier than gene therapy delivery. miRNA mimics are also expected to be highly specific and well-tolerated in normal tissues, given their endogenous expression patterns.

Technology

miR-24-3p and miR-27a-3p expression levels decrease sharply following apoptotic induction in both a cell model of neuronal death (etoposide treatment) and in the hippocampus of mice with controlled cortical injury (CCI, a TBI model). As a result, there is an upregulation of pro-apoptotic Bcl-2 family proteins (Noxa, PUMA, Bax) that, along with increased p53 activation, result in neuronal cell death. Treatment with miR-23a-3p and miR-27a-3p mimics significantly attenuates the expression of PUMA, Noxa, Bax, and markers of apoptosis in both models. To date, there are no miR-based treatments in clinical use for TBI, or for other neurological disorders. An miR-based method could provide a novel therapeutic approach for TBI management of ischemic events in the brain and CNS.

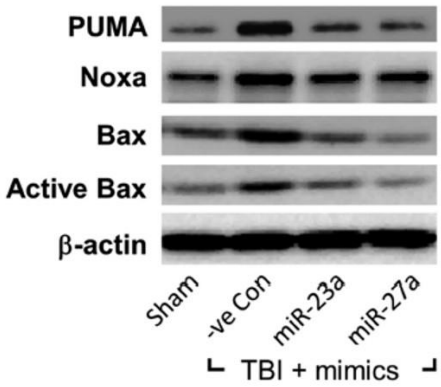

Figure 1. Intracerebroventricular (icv) injection of miR-23a and miR-27a mimics attenuate expression of PUMA, Noxa, and Bax in injured cortex after TBI. Whole-tissue lysates from mouse cortex 24 h after TBI and icv injection of miR-23a-3p or miR-27a-3p or negative control mimics were fractioned immunoblotted with antibodies against PUMA, Noxa, Bax, active Bax, and β-actin. Densitometry analyses show significant differences in the level of PUMA, Noxa, Bax, and active Bax in the groups administered miRNA mimics compared to the negative control group.

Technology Status

This technology has been tested using etoposide treatment as an in *vivo* model of neuronal death and in mice undergoing CCI.

Contact: Nidhi Rumpal, PhD
nrumpal@umaryland.edu
410-706-0645

University of Maryland, Baltimore
620 W. Lexington St., 4th Floor
Baltimore, MD 21201