Novel RNA therapeutic targeting sodium channelopathies

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Genetic epilepsies caused by mutations to voltage-gated sodium channels do not currently have adequate treatment options. These diseases begin in the early years of life, with infants suffering severe seizures as well as developmental deficits such as ASD. RCSI researchers are developing a new and innovative treatment which selectively restores the function of specific voltage-gated sodium channel genes.

BACKGROUND

Certain types of epilepsy are caused by mutations to specific genes which are involved in brain excitability. These genetic epilepsies typically begin very early in life and are associated with severe developmental deficits and drug-resistant seizures. Clinically available anti-seizure drugs cause wide ranging adverse effects in these patients due to global dampening of brain activity. This creates an urgent need for innovative treatments which better control seizures, assist with developmental deficits, and have fewer or no adverse effects.

We have identified microRNA-335 as a naturally occurring molecule in the brain which acts to dampen the expression of several key genes associated with brain excitability. Mutations in a number of these genes (eg. SCN1A, SCN2A) can cause genetic epilepsies and are also strongly associated with autism spectrum disorders. Modulation of microRNA-335 alters expression of these genes and therapeutically modulates neuronal excitability.

VALUE PROPOSITION

MicroRNA-335 is a hugely promising new therapeutic target for epilepsy in general, and this represents a precision approach to restore the function of specific genes in certain genetic epilepsy syndromes. Manipulation of miR-335 is a potential new treatment option for diseases caused by mutations to Scn1a (Dravet syndrome) or Scn2a (epilepsy or autism) without the adverse effect profile of current drugs.

TECHNOLOGY

The inventors have shown that ant-335, an miR-335 antagomir, upregulates the expression of sodium channels in the mouse chain with upregulation of SCN1A, SCN2A and SCN3A.

Ant-335 increases the excitability of hippocampal pyramidal neurons in line with an increase in expression of functional voltage-gated sodium channels. AAV9-miR-335 has been demonstrated to upregulate the expression of miR-335 in mouse brain. Levels of miR-335 are upregulated two weeks after the injection of AAV9-miR-335. Target Site Blockers are in development to enable precise modulation of the individual gene targets of miR-335.

The interaction between miR-335-5p and SCN2A is preserved in human brain. iCLIP data from human epilepsy patients identified that the SCN2A gene which is located in chromosome 2, has a target site for miR-335 which confirms the translational potential of this therapeutic approach.

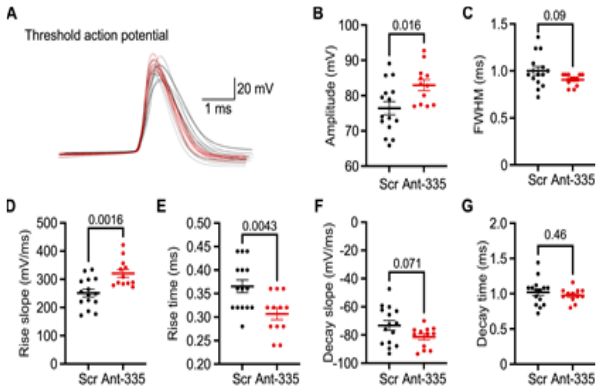

Fig 1. Effect of Ant-MiR-335 on neuronal action potentials

FEATURES	BENEFITS
Unique MoA acting on sodium channel expression	Precision medicine for loss-of-function epilepsies
RNA Therapeutic	Reduction in off-target activity potentially leading to reduced side-effect profile

TECHNOLOGY READINESS LEVEL

Patent filed
In vivo POC for antagomir delivery

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