Docket #: S21-376

Treatment of Timothy syndrome using an antisense oligonucleotide

Scientists in Sergiu Pasca's group at Stanford University have used patient-derived organoids, assembloids and in vivo transplantation to discover and validate an antisense oligonucleotide drug for the treatment of Timothy syndrome.

Timothy Syndrome is a severe developmental disorder that causes long QT syndrome, autism spectrum disorder, epilepsy, syndactyly and immune dysfunction. While scientists have discovered the genetic basis for the disorder in many patients (mutations in exon 8A of the calcium channel CACNA1C), there are no available treatments that act on this root cause.

Researchers therefore developed a treatment strategy to modulate the splicing of CACNA1C. Using human cortical spheroids derived from patient cells, they screened a series of antisense oligonucleotides (ASOs) to identify one that biases pre-mRNA splicing to include the healthy exon 8 instead of the mutated exon 8A. Scientists showed that this candidate could restore calcium defects in patient-derived cortical neurons, influence interneuron migration, and restore activity-dependent dendritic retraction in transplanted cortical organoids. This ASO therefore has significant promise for the treatment of Timothy syndrome.

Stage of Development
In vitro: selectively causes mutagenic exon 8A exclusion in patient-derived cortical organoids, restores calcium defects in patient-derived cortical neurons, influences interneuron migration, restores activity-dependent dendritic retraction in transplanted cortical organoids.

Applications

- Treatment of Timothy syndrome type 1

- ASO development for other CNS disorders using a multi-level patient-derived organoids and assembloids

Advantages

- No available treatment that acts on the genetic basis of Timothy syndrome
- ASO is highly selective for exon 8A exclusion
- ASO has been extensively validated in human cellular models

Publications

- Xiaoyu Chen, Fikri Birey, et al. (2024). Antisense oligonucleotide therapeutic approach for Timothy syndrome . Nature, (featured on cover) 628, 818–825.
- Goldman, Bruce and Digitale, Erin. "Brain organoids and assembloids are new models for elucidating, treating neurodevelopmental disorders," *Stanford Medicince News Center* April 2024.
- The Future of Everything Podcast featuring Russ Altman with guest Sergiu Pasca May 2024.

Patents

- Published Application: 20240150759

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