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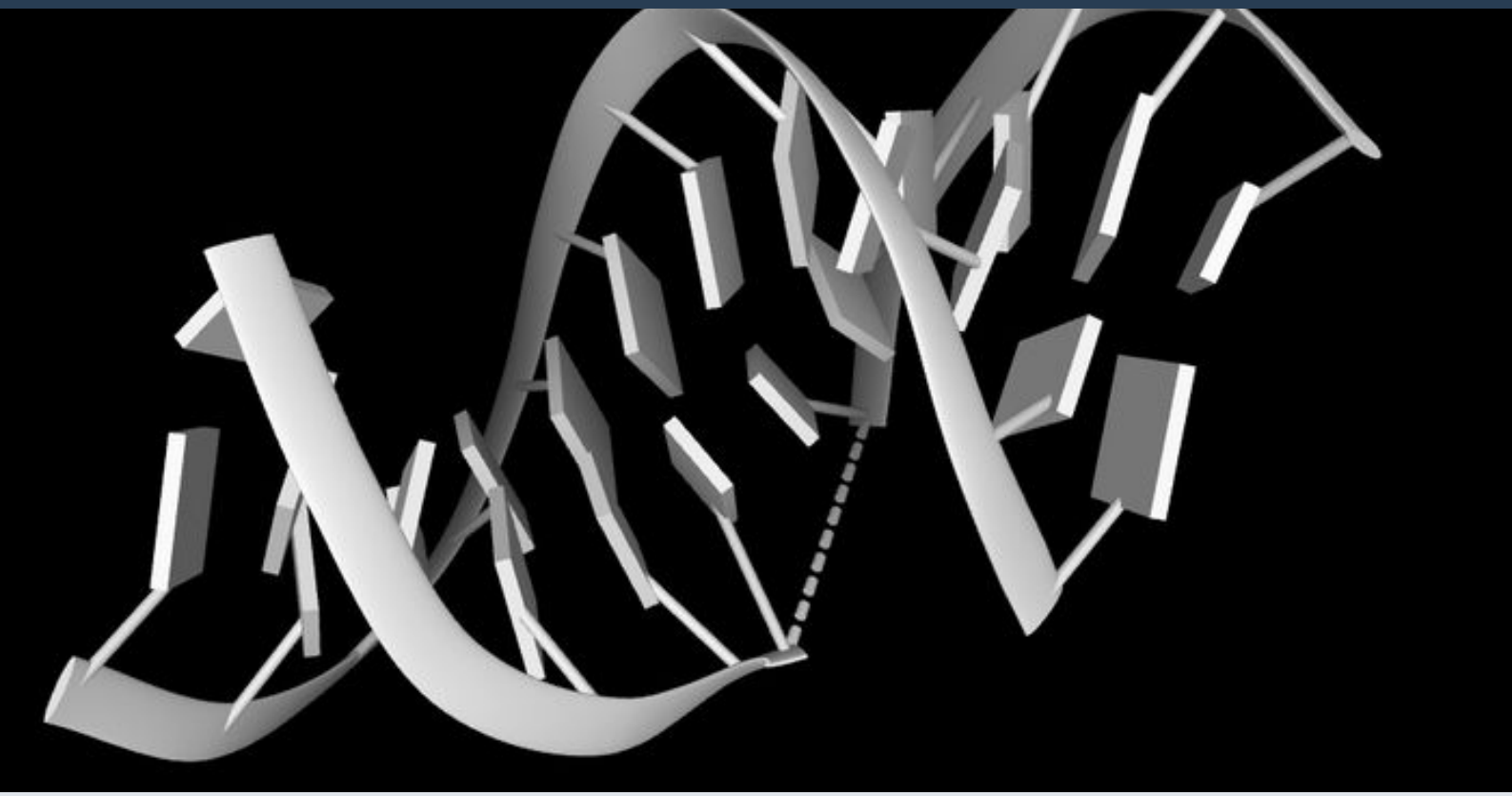
TreatSplice - Systematic Personalized Correction of Splice Defects in Mitochondrial Disorders

Characterization of pathology-driving processes to identify novel keys for therapeutic intervention in Mendelian disorders



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Seeking

Development partner

About **LMU Munich**

Ludwig-Maximilians-Universität München is the University in the heart of Munich. LMU is recognized as one of Europe's premier academic and research institutions. The LMU Munich community is engaged in generating new knowledge for the benefit of society at large.

Background

Aberrant splicing is one of the major causes of Mendelian diseases, whereby even single nucleotide variants can activate non-functional splice isoforms, lead to gene loss of function and severe phenotypes. Recently, the researchers established RNA sequencing (RNA-Seq) and quantitative proteomics as diagnostic tools and further improved the diagnostic rate. Altogether, about 15% of Mendelian disease patients carry pathogenic variants affecting splicing.

Antisense oligonucleotides (ASOs) are short reverse complementary RNA stretches that can potently interfere with aberrant splice sites and revert at least in part to canonical splice isoform distributions. For its apparent simplicity and generic applicability, ASO therapy is today one of the most promising personalized medicine avenues to treat a broad spectrum of rare diseases. However, ASOs have so far only been developed for a few splice defects. Hence, there are no guidelines established for their design and application.

Tech Overview

LMU Munich researchers propose to perform a cascade screen to characterize 1,000 ASOs and small molecular splice modulators (SMSM) targeting 50 different pathogenic splice defects at the phenotype, transcriptome and proteome level in patient cell lines. From this unique resource, an algorithm for ASO design will be trained. Furthermore, combining RNA-Seq and machine learning, TUM researchers will derive sequence signatures predictive of splice-site specific efficiency for tens of SMSM. Finally, the researchers will systematically study tissue-specific ASO delivery procedures in mouse models.

As a consortium from TUM and LMU, the team combines expertise in diagnostics of Mendelian disorders by genome and transcriptome profiling, and machine learning for regulatory genomics. They leverage on a global patient registry for mitochondrial disorders including the largest collection of fibroblast cell lines with clinically relevant biochemical defects and genome, transcriptome and proteome datasets attached.

The expected outcome will be a number of novel treatments, a valuable database for study of ASO design, open source software for diagnostics of aberrant splicing and for personalized therapy design through ASO in potential combination with splicing modulators.

Further Details

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Stage of Development

- Algorithms for a genome-wide screen of splice aberrations developed
- Protocol to quantify close to 8.000 proteins in a patient cell line established
- Already identified 50 fibroblast cell lines with defects in 35 different genes
- RNA-Seq profiles (covering 120,000 splice sites), including private mutations and frequent variants diagnosed in more than 30 patients

Benefits

- Characterization of pathology-driving processes to identification of novel keys for therapeutic intervention and to develop personalized treatment options for up to 15% of patients with Mendelian disorders

Applications

- Development of novel treatments for Mendelian disorders
- Design of ASOs that are efficient and specific to target splice sites and tissues

Opportunity

Seeking a partner to support the team in design and synthesis of ASO and to provides SMSM.

For further information, please contact us.

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