2021 LEAD Capstone Poster Session

Establishing a Treatment Pathway for Rare Genetic Forms of Autism

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Abstract

- For rare neurodevelopmental disorders including the different genetic subtypes of autism that affect up to 15% of children in the United States, the journey from gene identification to drug discovery is a very long one, and sometimes this journey doesn't happen at all

- At UTSW we see an annual average of 5,000 patients with rare neurodevelopmental disorders, including autism, that have no treatment. Recently, the FDA issued guidance for a mechanism called n-of-1 therapies to address rare diseases

- This project's objective is to establish an efficient pipeline for developing n-of-1 therapies to translate genetic mutations to treatment, and to position UTSW as one of the leading centers for personalized neurodevelopmental disease treatments

Objectives

- Establish an efficient pipeline for developing n-of-1 therapies to translate genetic mutations to treatment for rare genetic subtypes of autism

- Position UTSW as one of the leading centers for personalized treatments of rare neurodevelopmental disorders

Background Information

- For rare neurodevelopmental disorders including the different genetic subtypes of autism that affect up to 15% of children in the United States, the journey from gene identification to drug discovery is a very long one, and sometimes this journey doesn’t happen at all, because there’s very little interest from big pharma or biotech to invest in ultra-rare treatments due to the lack of commercial incentive

- At UTSW we see an annual average of 5,000 patients with neurodevelopmental disorders, including autism. They are managed through our clinical programs and some are enrolled in my lab’s genetic studies that are aimed at identifying causative genes for these disorders. However, the number of patients impacted by mutations in the same gene is typically too low to trigger a threshold for starting proof of concept studies that could eventually lead to clinical trials

- Recently the FDA issued guidance for a mechanism called n-of-1 therapies. These are therapies created to address ultra-rare diseases similar to the cases we encounter. I am proposing to establish a pathway and a process to build an n-of-1 pipeline for rare genetic forms of autism, so that when these patients come to clinical attention here at UTSW, we can take them all the way from disease gene identification to treatment

Specific Aims

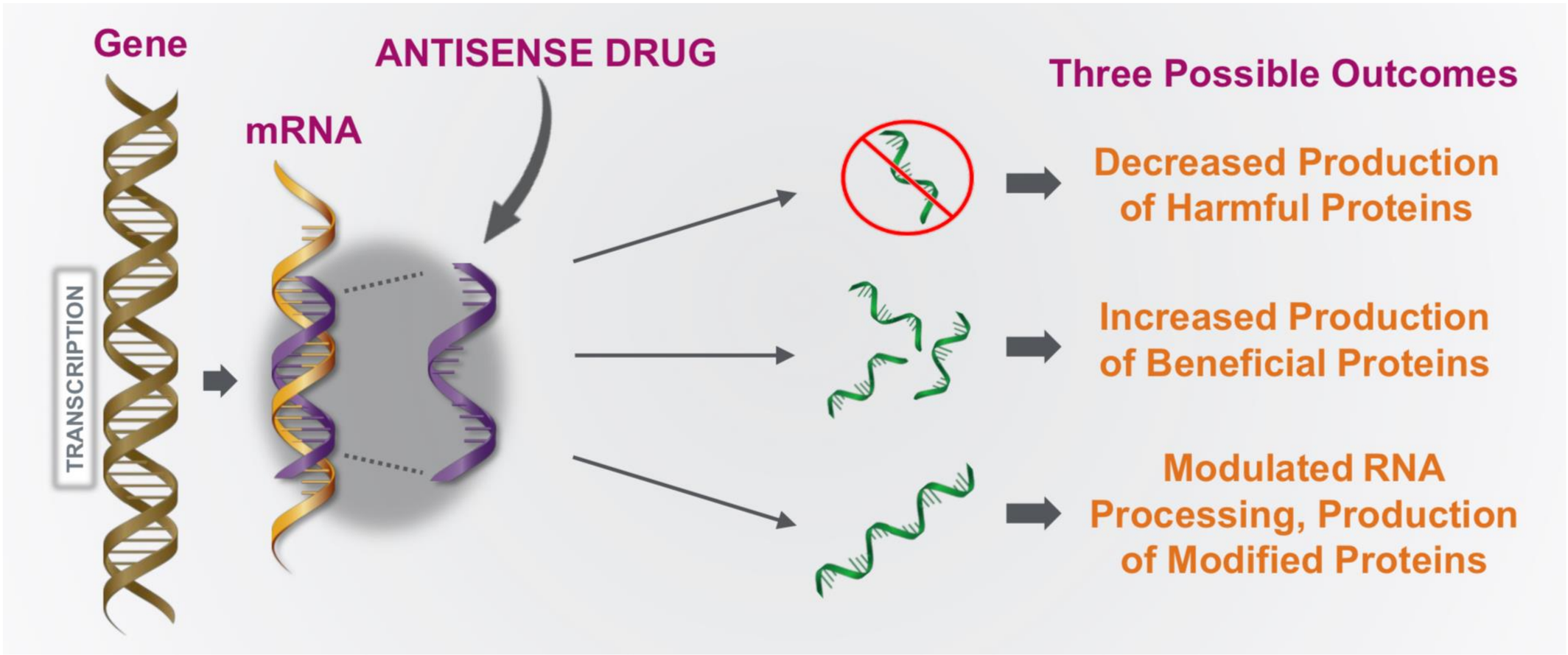
1. *In silico* testing for antisense oligonucleotide (ASO) drugs and generation of an animal model carrying the specific targeted mutation

2. Establish collaborations and funding mechanisms to conduct the safety, pharmacology, and toxicity studies

3. Submit IND-enabling studies to the FDA and initiate clinical trials at UTSW with the help of our clinical colleagues

Why ASO?

Antisense technology provides versatility to modulate all RNA



Modified from Ionis Pharmaceuticals

Project Plan

Animal model generation

In silico testing for ASO

Safety, pharmacology, and toxicity studies

IND package & FDA review

Clinical Trial (Design, IRB, Initiation)

- A typical high level plan for progressing an ASO therapy
- We already have 2 animal models generated and we will initiate *in silico* testing for one ASO
- Establishing an efficient pipeline will depend on our ability to reduce the typical process timeline through collaborative efforts at UTSW

Application of What You Learned at LEAD

- Leadership skills:
  - Articulating a vision
  - Synthesizing ideas into actionable plans
  - Identifying personal and team strengths

- Institutional knowledge:
  - Understanding UTSW strategic priorities
  - Defining the objectives of the project to align with UTSW priorities and resource allocations

Proposed Budget

Budget range to bring a typical ASO therapy to FDA submission is $1.7M - $3.2M

Animal model generation

- $20k - $30k (includes generation and maintenance of model)

***In silico* testing for ASO**

- $100k - $350k (depends on experiments and end points)

Safety, pharmacology, and toxicity studies

- $200k - $350k (or outsource to a CRO)

IND package & FDA review

- $350k - $500k (external consulting fees)

Clinical Trial (Design, IRB, Initiation)

- $1M - $2M based on trial design

Innovation and Significance

- Developing n-of-1 therapies to translate genetic mutations in autism patients to treatments will enable us to dramatically speed up the gene to drug pathway and give a fraction of these children an opportunity for a treatment

- The potential for personalized treatments for multiple neurodevelopmental disorders holds unique promise for patients and starting this program will position UTSW as a leader in making brain therapies a reality

References

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