Advancing clinical trial readiness to expedite the development of therapies for CTNNB1 syndrome

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CTNNB1 Foundation

Poster

Introduction

CTNNB1 syndrome :
- Severe neurodevelopmental disorder
- 2.6 to 3.2 / 100,000 births
- Around 500 patients are known worldwide
- Caused by mutations in the *CTNNB1* gene
- β-catenin - a crucial component in Wnt signaling

CTNNB1 Foundation
- Research-driven patients-led organization,
- *Committed to pave the way to a first clinical trial for the CTNNB1 syndrome*

Challenges
- Funding for trials sponsored by a foundation in such rare condition.
- Poorly described natural history and phenotypic spectrum

Preclinical research

Therapies in development:
- ASO
- miRNA
- Small molecules
- Prime edit
- **AAV9 vector gene replacement therapy**:

These studies demonstrate effective β-catenin replacement and phenotype improvement, with favorable biodistribution and safety profile.

Visit the ESGCT lecture:

A Perez-Iturralde et al.:

Towards the translation of an AAV-mediated gene therapy for an incurable disease.

Clinical Research

1.Genotype-phenotype correlation study (NCT04812119) in 127 CTNNB1 patients

a. **Phenotype** :
- Consistent dysmorphic features
- Central hypotonia
- Peripheral hypertonia
- Dystonia,
- Spasticity
- Global delay (mild to severe)
- Regression in speech or walking in 25% of patients

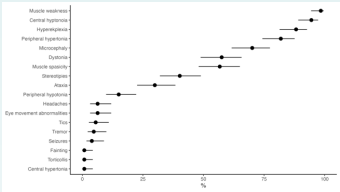

Figure 2. Neurological status of CTNNB1 patients as reported by parents with 95% confidence intervals. (Žakelj et al. In preparation)

b. **Genotype**:
- Most mutations are loss-of-function
- Rare cases dominant-negative
- Rare gain-of-function effects

2. Prospective longitudinal, observational **natural history study** in 83 children living with CTNNB1 mutation and their parents

Duration : 5 years

Outcome:
- Clinical examinations and medical history
- Validated questionnaires and Carer diaries
- Genetic and serum analysis,
- EEG if available,
- Brain MRI if available
- Holter of Movement (ActiMyo/Syde®)

Candidate Therapy

- **GMP production** by Viralgen with similar properties than the the research-grade product for tox study and clinical trial
- **Tox studies using GLP-product** in mice planned Q4 2024
- Tox study in **non-human primates**
- In January 2025, we aim to initiate GMP manufacturing for the **First-in-Human (FIH) trials**

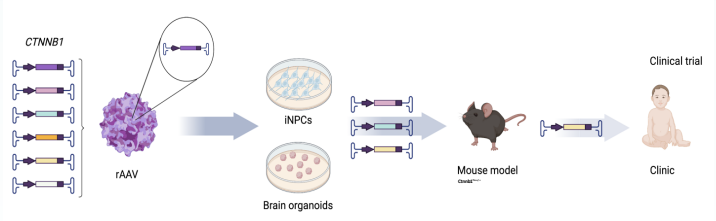

Figure 1. Schematic representation of development of the gene replacement therapy for the CTNNB1 neurodevelopmental syndrome.

Regulatory Engagement

With EMA and Slovenian Regulators for clinical trial development

First-in-human trial

- **Intracerebro-ventricular (ICV) injection** of the medicine, an experienced clinical team is required
- Plan Q4 2025 at the University Medical Centre Ljubljana, Slovenia
- We are also looking into **expanding collaboration** to other medical centers who could perform treatment at remote sites, i.e. Australia

Conclusion

Development of novel disease modifying treatments in a research environment outside a pharmaceutical company is possible - but lack of sustainable funding constitutes a major obstacle. The process is complex, elaborate, expensive and there is no guarantee of success.

Collaboration of preclinical and clinical scientists as well as regulatory experts is essential for potential success.

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