Partners

Lead partner
IRET Foundation

Partners
- CIRI-SdV – University of Bologna
- CIDSTEM of the University of Modena and Reggio Emilia

Companies
- *Chiesi Farmaceutici S.p.A.*
- *TransMed Research Impresa Sociale S.r.l.*

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N2ERT

N2ERT: Platform for the prototyping of Nanomedicines for therapeutic proteins: enzyme replacement therapy for rare neurometabolic diseases

Introduction to the project

There are more than 7000 known rare diseases today, with an overall prevalence of 3.5-5.9%, which equates to 263-446 million people affected globally. The prevalence of neurological symptoms is estimated at 70%.
In this area, **enzyme replacement therapies** (ERTs) are emerging as promising therapies and to date, 17 ERTs have been approved for lysosomal storage disorders.
However, the development of these biologic drugs is hampered by biological limitations and formulation difficulties related to their properties. Moreover, one of the major challenges is to achieve their targeted and controlled release in the central nervous system (CNS), overcoming the blood-brain barrier (BBB).

N2ERT develops a technology platform for the **prototyping of therapeutic protein delivery solutions** by means of nanoparticles, designed to protect biological activity and reach the CNS. These will be tested for the restoration of biological function in cellular and animal models of disease, using ERTs approved for rare neurometabolic diseases by lysosomal accumulation as platform pivots.
The alpha-mannosidase and sphingomyelinase enzymes supplied by Chiesi Farmaceutici will be used, producing the new NMeds with FDA/EMA approved materials for human use. These will be tested on cell systems based on primary cultures derived from transgenic mice and patient-derived cells **to study efficacy and safety in the GLP** (Good Laboratory Practice, TransMed Research company) **environment**.

Objectives

N2ERT aims to eliminate some bottlenecks in the development of enzyme replacement proteins by optimising the flow of technological activities (NMed production) and safety and efficacy testing.

It addresses the need to deliver ERT into the CNS, for the neurological complications of alpha-mannosidosis deficiency disease (aMAN) and acid sphingomyelinase. For both diseases there are approved enzyme therapies (Lamzede and Xenpozyme), but limited to peripheral complications of the diseases, as the enzyme is unable to cross the BBB.
After the design and production of the NMed (CIDSTEM, NanoTech lab), they **will be tested for safety and efficacy** on cellular platforms based on *in vitro* models of the target diseases coupled to high content screening systems (IRET Foundation, CIRI-SdV) and, finally, *in vivo* (IRET Foundation), also following the GLP regulatory framework in both cases.

Activities

N2ERT aims to bridge the gap between the production of therapeutic systems and their biological validation, with an integrated platform for prototype production, evaluation and validation of advanced nanomedicines for therapeutic protein replacement. It will employ recombinant human therapeutic enzymes (aMAN alpha-mannosidase and AM acid sphingomyelinase) used for the treatment of rare neurometabolic lysosomal storage diseases.
N2ERT has the following technological objectives:

1. **Development of 2 NMed** to protect the biological activity of the enzyme (nERT-aMAN and nERT-ASM);
2. **Development of at least 1 NMed** designed for delivery across the blood-brain barrier (BBBnERT);
3. **Ability to deliver an effective dose** (up to 10% of the injected dose) of enzymes into the CNS;
4. **Consolidation of** rapid, accurate, efficient and robust **'high-throughput'** *in vitro* safety tests for rare lysosomal storage diseases;
5. **Identification and validation of efficacy readout assays** by rescuing the enzymatic activities of nERT-aMAN and nERT-ASM i*n vitro* and i*n vivo*.