Extended Abstract | Acute and Chronic Disease Reports | 2019 | Vol.3 No.2

# Rare Diseases Congress 2019: Red blood cell-encapsulated enzymes: An innovative therapeutic approach to overcome challenges of enzyme replacement therapies for rare diseases - Emmanuelle Cecile Dufour-Erytech Pharma

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Many inborn errors of metabolism (IEM) disorders are due to defects in single genes encoding key metabolic enzymes. In most cases, clinical manifestations of these disorders are driven by the over-abundance of a metabolite or the scarcity of an essential metabolite. Though rare, IEM disorders can have devastating consequences for patients and their families. While some Enzyme Replacement Therapies are commercially available for a few IEM disorders, the clinical benefits of these approaches are often outweighed by the emergence of hypersensitivity and the rapid clearance of enzymes. Therefore, there is a high need for better tolerated and longer-acting replacement enzymatic activity to alleviate the burden of IEM disorders. RBCs are the most abundant cell type in the human body and their biology is characterized by a long lifespan and access to all tissues and organs. Thanks to their biocompatibility and shielding properties, they can serve as a circulating bioreactor when loaded with enzymes. ERYTECH is a leader in RBC therapeutics. Its ERYCAPS platform enables the encapsulation, at industrial scale, of active drug substances inside RBCs using hypotonic loading, which has been shown to maintain all the RBC functionalities. ERYTECH has demonstrated that RBC-encapsulated enzymes exhibit substantially improved in vivo performance vs. non-encapsulated enzymes, several limitations such as the high-cost of the treatment and various inadvertent side effects including the occurrence of an immunological response against the infused enzyme and development bone, cartilage, cornea, and heart still remain unresolved. Different methods have been developed to overcome the limited access of enzymes into the difficult pathological sites. Based on the receptor-mediated lysosome enzyme delivery system, it has been shown that increasing the presence of M6P residues on the recombinant enzyme or enhancing the expression all these shortcomings necessitate can also be used in crossing the biological barriers such as BBB and blood-ocular-barrier (BOB). Thus, they are being considered as innovative and effective approaches for the treatment of brain disorder the development of more effective diagnosis and treatment modalities against LSDs. Taken all, maximizing the therapeutic response with minimal undesired side effects might be attainable by the development of targeted enzyme delivery systems of resistance to enzymes persist. Currently used ERT modalities are not completely effective for all types of LSDs. We envision that the ultimate therapy of LSDs in the future would be based on the gene and/or cell therapy. For example, in the case of Krabbe disease, AAVrh10 gene therapy has been shown to ameliorate the central and peripheral nervous system's pathologies in murine and canine models of this disease these issues may limit the desired therapeutic outcomes of a majority of the lysosome storage diseases including extended enzymatic activity.

Results from two early programs using enzyme-loaded RBCs in in vivo models for Arginase-1 Deficiency and Classical Homocystinuria will be presented. These promising results combined with ERYTECH??? extensive clinical experience with RBC therapeutics, support the possibility that RBC-loaded enzymes may provide superior safety and efficacy as compared with traditional ERT approaches for the treatment of IEM disorders. Replacing the defective enzymes with a recombinant human enzyme in lysosome storage diseases (LSDs) and restoring the enzymatic activity was first proposed by Christian de Duve in 1964.1 Despite the therapeutic features of systemically-administered ERTs against LSDs, the bio distribution of the enzymes into the difficult sites of pathology The LSDs, as a heterogeneous group of disorders, are involved in various genetic defects. Patients during their early childhood suffer from multifaceted clinical symptoms that can affect their musculoskeletal system, lung, heart, liver, spleen, and eyes. In addition, most LSDs patients have mild to severe central nervous system. The intravenous (IV) administrations of approved enzymes in the LSDs generally represent significant clinical benefits, including improved walking ability, ameliorated respiration, and improved life-quality.7 The LSDs require continuous treatment for optimal clinical outcomes, Cross-reactive immunologic materials therefore the cost-effectiveness and accessibility to ERT should be considered as an essential point in the treatment of these diseases. They can interact with the active site of the enzyme and/or ligands involved in the binding to a receptor on the target cells mannose-6-phosphate receptors for most LSDs, mannose and lysosome integral membrane protein 2 receptors for Gaucher disease that lead to blocking the cellular uptake and lysosome targeting of the enzyme Despite the financial and regulatory advantages for the "orphan drug" in the U. S., pharmaceutical industries have priced the LSDs therapy products among the most expensive treatment modalities in the market. Besides, the major impediment to the development of enzymes as drugs for

This work is partly presented at 9th World Congress on Rare Diseases and Orphan Drugs June on 17-18, 2019 held at Berlin, Germany

the LSDs is the limited clinical trials due to patient's paucity in the population. Furthermore, while performing pre-clinical studies in animal models has been strongly recommended, in most cases

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3. Thomas X and Le Jeune C (2016) Erythrocyte encapsulated l-asparaginase (GRASPA) in acute leukemia. Int J Hematol Oncol. 5(1):11-25.

4. Yew N, et al., (2013) Erythrocytes encapsulated with phenylalanine hydroxylase exhibit improved pharmacokinetics and lowered plasma phenylalanine levels in normal mice. Mol Genet Metabol. 109(4):339- 344.

5. Bourgeaux V, et al., (2012) Efficacy of homologous inositol hexaphosphate-loaded red blood cells in sickle transgenic mice. Br J Haematology. 157(3):357-369.