Improvement of the Enzymatic Activity of α-Galactosidase Using Nanovesicles with application to Fabry Disease treatment

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Fabry disease is, among the lysosomal storage disorders, a rare inherited disease caused by loss of function of the enzyme α-Galactosidase A (GLA) [1]. One of the commercially available treatments is based on the intravenous administration of GLA. This enzyme replacement therapy (ERT) demonstrated positive short-term effect reducing the progression of the disease and improving the quality of life in patients. However, ERT exhibits drawbacks such as the degradation of the exogenously administered enzyme, its limited efficacy in patients with an advance stage of the disease and the extremely high cost of the treatment.

In order to improve the delivery efficacy and the systemic circulation of the current treatment, nanovesicles containing GLA were prepared as novel drug delivery systems (DDS). The incorporation of GLA in nanovesicles was obtained following the DELOS-SUSP methodology, based on the use of compressed CO_2 (**Figure 1, left**) [2]. Moreover, a c(RGDfK) peptide ligand was incorporated in the membrane bilayer of the vesicles to enhance the targeting and the uptake efficiency of the GLA-loaded conjugates to the affected cells. The latter constitutes a major challenge in the treatment of lysosomal storage disorders.

Here, the preparation of different nanovesicles and comparative results obtained with the GLA-loaded conjugates and the free GLA enzyme will be presented [3]. Importantly, *in vitro* efficacy studies in GLA deficient cells of Fabry KO mice showed that the GLA-nanoformulations were able to reduce lysosomal Gb3 deposits more efficiently than the free enzyme (**Figure 1, right**), in agreement with a greater specific activity also encountered. This finding indicates that (i) such multifunctional nanovesicles are uptaken by GLA deficient cells, (ii) the GLA-nanovesicles reach the lysosomal compartment, and (iii) the cargo (GLA) is efficiently released so that the GLA activity in the cells is restored. Thus, the remarkable results obtained here prove the great potential of DELOS-SUSP method for the production of new nanomedicine candidates based on enzyme-nanovesicle conjugates. The development of these new GLA-nanoconjugates up to the end of the regulatory preclinical phase will be carried out under the frame of the European Smart-4-Fabry project (H2020-NMBP-2016-2017 GA 720942).

References

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Figures

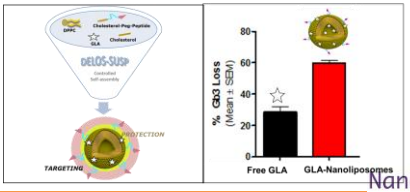

Figure 1: Nano-GLA multifunctional nanoformulation, manufactured by the DELOS-SUSP platform (left). Effect of free GLA and GLA-Nanoliposomes in the reduction of Gb3 deposits in aortic endothelial cells of Fabry KO mice (right). Represented values correspond to mean ± SEM value.