



## Efficient therapy of Pompe disease by an acid $\alpha$ -glucosidase conjugate



One of the most important issues in the drug delivery field is the strict control of drug destiny to selected organs, tissues, cells and sub-cellular compartments. There have been various attempts to deliver drug formulations to the target site, but with little success. The so-called “targeted” drug delivery, usually to solid tumors in small animal models, constitutes only about 1% of the total administered dose. The observation that it is still more effective than the solution control formulation has morphed into the current notion of “tumor-targeted” delivery. In reality, there is no targeted delivery, as most of the administered dose is distributed throughout the body. The original meaning of “magic bullet” by Paul Ehrlich is a substance that interacts with specific disease-causing agents without harming the body itself. It is far from delivering a drug only to the target. If a drug is only effective at the intended site without any side effect, it appears to be a magic bullet with selective delivery to the target.

In this issue, Basile et al. [1] present an approach that can improve the efficacy of a drug in a particular intracellular compartment, the lysosome. The delivery of recombinant enzymes to lysosomes, known as enzyme replacement therapy (ERT), has been applied to 7 among 53 genetic rare diseases associated with lysosomal dysfunctions. Each ERT is expected to correct the deficiency of a particular lysosomal enzyme and the corresponding lysosomal storage disorder (LSD) [2]. One cause of the variable efficacy of ERT is the ability of the administered enzyme to reach lysosomes of the affected organs. The main player in the delivery of circulating lysosomal enzymes is the cation-independent mannose 6-phosphate receptor (M6PR). This receptor binds M6P-bearing ligands outside the cells, cross all endosomal compartments, and with a fall on pH, finally liberate the enzyme to its final destination [3].

Effective ERT is dependent on the presence of sufficient M6P signals on the recombinant enzymes, as well as on M6PR membrane expression on the tissues. The addition of M6P signals to glycoproteins is a complex enzymatic process only found in eukaryotic cells and difficult to opti-

mize during the recombinant enzyme production [3]. Basile et al. [1] proposed chemical grafting of M6P analogue to acid  $\alpha$ -glucosidase (GAA) for Pompe disease therapy. The grafting of the M6P analogue was found to increase the M6PR affinity of the enzyme without alteration of the catalytic activity. In primary cultures of patient fibroblasts the modified enzyme appeared more internalized and targeted to intracellular acidic compartments than the native enzyme. Furthermore, the glyco-engineered enzyme showed the therapeutic response in a mouse model representative of Pompe disease, as shown by a walking capacity test and biological assays in muscles. Histological and biochemical evidences of therapeutic responses included the decrease of pathological centralized nuclei in myofibers, the enhancement of GAA activity and the reduction of glycogen substrate in various tissues, and the decreased expression of acid phosphatase, which is considered a therapeutic marker. Interestingly, the enzyme engineering did not induce supplementary immune responses in the mouse model. The data by Basile et al. suggest that an improved lysosomal delivery of the enzyme is able to restore some muscle activities even in the late stage of the disease represented by 10-month aged mice. This newly modified enzyme represents a potent drug with a particular interest for the adult-onset form of Pompe disease.

It is noted that the same glyco-engineering reaction using M6P analogue can be applied to other lysosomal enzymes corresponding to orphan LSD. In a broader perspective, further studies are needed to understand whether such M6P analogues might be useful for lysosomal efficacy of other types of drugs or more complex delivery systems, e.g., sustained release systems. The importance of the study by Basile et al. is the development of the M6P analogue having higher M6PR affinity of the enzyme with the catalytic activity, but without side effects. This is an excellent first step toward developing a new ERT drug with the touch of a magic bullet.

## References

- [1] I. Basile, A. Da Silva, K. El Cheikh, A. Godefroy, M. Daurat, A. Harmois, M. Perez, C. Caillaud, H.-V. Charbonné, B. Pau, M. Gary-Bobo, A. Morère, M. Garcia, M. Maynadier, Efficient therapy for refractory Pompe disease by mannose 6-phosphate analogue grafting on acid  $\alpha$ -glucosidase, *J. Control. Release* 269 (2018) 15–23.
- [2] R.H. Lachmann, Enzyme replacement therapy for lysosomal storage diseases, *Curr. Opin. Pediatr.* 23 (2011) 588–593.
- [3] A. Varki, S. Kornfeld, *Essentials of Glycobiology*. A. Varki, R.D. Cummings, J.D. Esko, P. Stanley, G.W. Hart, M. Aebi, A.G. Darvill, T. Kinoshita, N.H. Packer, J.H. Prestegard, R.L. Schnaar, P.H. Seeberger (Eds.), P-Type Lectins, Cold Spring Harbor Laboratory Press, USA, 2017.

## Further Reading

- European Pompe Consortium, 2017 A.T. van der Ploeg, M.E. Kruijshaar, A. Toscano, P. Laforêt, C. Angelini, R.H. Lachmann, S.I. Pascual, M. Roberts, K. Rösler, T. Stulnig, P.A. van Doorn, P.Y.K. Van den Bergh, J. Vissing, B. Schoser European Pompe Consortium, European consensus for starting and stopping enzyme replacement therapy in adult patients with Pompe disease: a 10-year experience, *Eur J Neurol* 24 (2017) 768–e31.

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