Editorial for focused issue "Pompe disease: from basics to current and emerging therapies"

In this special issue of *Annals of Translational Medicine*, well distinguished clinicians, academic researchers, industry scientists, and patient advocates address recent advances and challenges in current and future therapies for Pompe disease, a prototypical lysosomal storage disorder. As is the case with many maladies, the history of Pompe disease, a severe neuromuscular disorder, is a reflection of the accelerating pace of basic science discoveries and the speed with which scientific knowledge is translated into medical progress.

Pompe disease, also known as glycogen storage disease type II, owes its name to the Dutch pathologist, Johannes Cassianus Pompe, who described a new clinical entity in 1932, a condition we now categorize as classic infantile-onset form of the disease. It took thirty years to establish the underlying cause of the disease—the absence of acid alpha-glucosidase (GAA), which degrades glycogen to glucose in the acidic environment of the lysosome. Later on, a milder late-onset variant was recognized. It took until the early 1990s to map the *GAA* gene and identify the first disease-causing mutations. Since then, however, new discoveries and breakthroughs happened at breakneck speed. The discovery of the gene has led to rapid progress in understanding the molecular basis of the disease, the enzyme biosynthesis, processing, and lysosomal targeting; knockout and transgenic mouse models have been generated; the first specific treatment with recombinant human enzyme, which sharply altered the course of the disease, has been approved; and what only recently seemed an elusive and high-risk idea of gene therapy shifted from theory to practice, offering the possibility to cure this debilitating disorder. What is more, all these major advances paralleled tremendous progress in our understanding of the fundamental role of the lysosome in normal physiology and in disease.

This new environment of rapidly accumulating knowledge and opportunities required a rethink of some of the previously accepted premises about Pompe disease and brought about a set of new challenges. For example, Pompe disease has long been viewed as a muscle disorder, but a great deal of new data has demonstrated the contribution of neurologic damage to muscle wasting and paresis. In addition, the prevailing hypothesis of muscle damage—glycogen storage, enlargement of lysosomes, and malfunction of cell and organ—left a big black box between enlargement of lysosomes and cell/organ malfunction. We now know that the cellular pathology affects all the compartments of the lysosomal degradative system, including defective autophagy, mitochondria abnormalities, and an energy deficit, likely secondary to the failure of lysosomal glycogen degradation in glycolytic muscle.

Another example is the routine implementation of immunomodulation therapy, putting to rest the dispute about the importance of immune response to the recombinant enzyme. Also, it wasn't long ago there were objections to newborn screening for Pompe disease; today the appropriateness of such screening is accepted by the scientific community and is implemented in several countries and a number of states in the US.

Perhaps most significantly, a new phenotype with clinical manifestations of the brain abnormalities has been brought on by the very enzyme replacement treatment that allows so many infants to live much longer. We anticipate that the reader of this collection of papers and reviews will appreciate that many challenges still remain, thus stimulating interest in Pompe disease as well as in other lysosomal storage disorders. As Guest Editors, we would like to express our gratitude to colleagues who have contributed to this focused issue, and to Pompe disease patients who are no longer passive recipients of health care but rather active partners in our common quest for cure.

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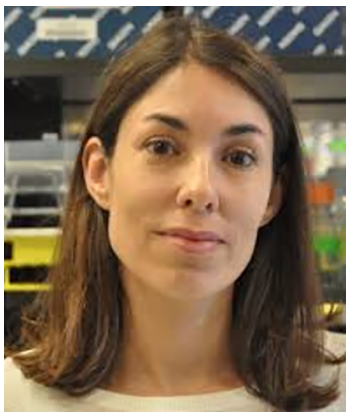

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