Two approaches to treat Lysosomal Storage Diseases

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Enzyme therapy proves effective in treating LSDs, whilst gene therapy is an upcoming contender.

Lysosomes are membrane-bound organelles found in most animal cells. They are responsible for treating cellular waste. Genetic mutations in lysosomal enzymes lead to lysosome malfunction and waste accumulation. And this leads to a whole range of complex metabolic

disorders, collectively called Lysosomal Storage Diseases (LSD). There are two kinds of LDSs: those that affect the brain (neuropathic) and those that do not (non-neuropathic). The EU-funded EUCLYD project, completed in 2011, studied four non-neuropathic LSDs out of the 50 currently known. These were Gaucher disease, Pompe disease, the mucopolysaccharidosis (MPS) VI and the multiple sulfatase deficiency.

Enzyme replacement therapy was one of the approaches successfully implemented by the project. "As the name suggests, it consists of artificially synthesising the malfunctioning enzyme and administering it to patients through an injection every seven to fifteen days," says project coordinator Generoso Andria, director of the Paediatrics Department of the University of Naples, Italy. The newly synthesised enzyme is then able to reach the lysosome directly and perform its functions. The project also studied a gene therapeutic approach. "We can operate 'upstream' with respect to the enzyme therapy," Andria tells youris.com. "We prepared a viral vector that could insert the normal gene directly in the affected chromosome," he explains, adding: "In December 2012 we started testing this gene therapy to make sure it is not toxic. And we plan to recruit patients soon."

Importantly, the project also changed how the lysosome is viewed. "We used to think that the lysosome functioned as the 'incinerator' of the cell," explains Andria. "It is quite an appropriate metaphor, at least here in Naples, with all the waste problem we have had," he adds jokingly. Yet the reality is a bit more complicated than that, as Andria tells youris.com. "Just as with the waste in a city, we realised that rather than 'incinerating', for the lysosome, it is more efficient to 'recycle' different molecules, like sugars, after degrading them."

One expert believes that enzyme therapy is a simple solution. "Most of the LSDs are due to mutations that inactivate a single protein that encodes an enzyme in a metabolic pathway in the lysosme," explains

Peter Lobel, an independent expert who is professor at theDepartment of Biochemistry and Molecular Biology of the Robert Wood Johnson Medical School, New Jersey, USA. "Therefore, in principle it is very simple to correct this. When you are missing a particular enzyme, if you replace it, you restore the function. The biggest problem is for the enzyme to be taken up by the cells that need it. But other than that, this is an effective way to fix the disease," he tells youris.com.

Another expert agrees that this is the best approach for now. "Provided you can reach the right target organs, the therapy works really well," explains Thomas Kirkegaard Jensen, chief scientific officer at Orphazyme, a biotech company based in Copenhagen, Denmark, that also focuses on these diseases. "The problem is that organs like kidney, heart, and cartilage are much harder to get to than the liver or the spleen. Not to mention the brain, of course, protected by the impenetrable blood brain barrier," he tells youris.com.

Diseases affecting the brain were explicitly excluded from the project because of the hurdles posed by the blood brain barrier. "Today it is nearly impossible to reach the brain, unless you inject it directly with a viral vector," says Kirkegaard. "It is a very big organ, 2,000 times bigger than a mouse brain where we have performed the tests. You need multiple infusions and, most importantly, we need to control and balance the production levels of the missing enzyme. Even too much of it might be harmful," he says. He adds: "I am confident, though, that this is the way to go,"

On the other hand, gene therapy has received a number of setbacks in the past due to the death of some patients treated with this method. The sector is, however, improving. "In the last ten years, though, science has improved significantly in this sector," Kirkegaard notes. "We are currently lacking the economic incentive for industries to invest in this field. It is very expensive to guarantee safety and efficacy. But once we

secure a viable payment model, this is the future," he tells youris.com.

Both Kirkegaard and Lobel mention a paper in Science in 2013 that showed very promising results treating a neurodegenerative lysosomal storage disease, called MLD, with gene therapy. However, "while it is an advance over enzyme replacement therapy, current gene therapy is not perfect," warns Lobel. "In the enzyme replacement therapy, the 'good' gene is expressed by a limited number of cells, practically turning them into factories." But with gene therapy, "if the new DNA in the cell persists, you do not have to cure patients once a week with a recombinant enzyme," he tells youris.com. "There might be unanticipated effects with the viral vectors we use. But today we can control them better and avoid vectors that cause the cells to proliferate and produce cancer. We won't know for sure if gene therapy will show long term efficacy or adverse effects, but for the medium term, it looks very promising," says Lobel.

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