Study shows innovative ERT-based solution has the potential to address unmet clinical needs across a range of lysosomal storage diseases

Manchester, UK – 19th November, 2012 – Oxyrane, today announced the publication in Nature Biotechnology, results of its landmark study in novel enzyme replacement therapy (ERT) for lysosomal storage diseases (LSDs). Oxyrane, in collaboration with VIB researchers from Ghent University and Vrije Universiteit Brussels, have developed a new technology that enables a more efficient approach to ERT production for LSD treatments, as well as the potential to significantly improve future treatments for debilitating and often life-threatening LSDs such as Pompe disease, Fabry disease and Hunter's syndrome.

This innovative ERT-based solution has the potential to address numerous unmet clinical needs across a range of lysosomal storage disorders. Using a proprietary, glycoengineered yeast platform (based on the yeast *Yarrowia lipolytica*), Oxyrane has manufactured human lysosomal enzymes with significantly higher levels of mannose 6-phosphate, the sugar-based targeting mechanism that enables clinically effective enzyme uptake and localisation, as well as facilitating efficacy at low product doses.[1]

"Lysosomal storage diseases can be treated with modified enzymes provided they end up in the patient's lysosomes, but this hasn't been easy to do. Until now, these modified enzymes could only be produced in mammalian cells. This study indicates that we can successfully develop a significantly more efficient method using yeast cells as an alternative", said Professor Nico Callewaert from VIB-UGent.

Oxyrane intend to progress their lead candidate further. Currently at pre-clinical stage with its first potential ERT treatment targeting Pompe disease, Oxyrane are preparing to advance their research into the clinical trial stage.

"Data suggest that this platform has the potential to enable production of more efficacious ERTs in the years to come. The results are very encouraging – the enzyme for the treatment of Pompe disease is absorbed 17 times as efficiently by patient cells in vitro than current treatments", said Dr Wouter Vervecken, Chief Technology Officer, Oxyrane.

Oxyrane's Chief Executive Officer, Michael Campbell added, *"we are now in a position where we can rapidly explore a number of product concepts in order to find the best possible engineered solution using our now proven technology. The priority now is to start developing our clinical programme in Pompe disease".*

About Pompe Disease

Pompe disease, (also known as glycogen storage disease type II or acid maltase deficiency) is a rare and serious lysosomal storage disease where the progressive accumulation of glycogen results in muscle weakness – particularly heart and skeletal muscle.[2] Pompe disease is caused by a deficiency

of an enzyme called lysosomal acid alpha glucosidase (GAA) which is responsible for breaking down glycogen – a complex sugar to release energy. When there is a deficiency of GAA, glycogen gradually accumulates in cells disrupting cell functions and impacting muscle function. The severity of the disease varies to some extent based on the level of residual GAA activity. The infantile-onset form of the disease is typically diagnosed between 3–8 months and generally involves an enlarged heart which may result in heart failure if left untreated. If untreated, the infantile form of Pompe disease is fatal – often before age one – due to cardiorespiratory failure.

The late-onset form manifests later and the disease severity varies more although the risk of respiratory failure remains a serious concern. The infantile-onset form has an incidence of one in 138,000 births and the late onset form has an incidence of one in 57,000 births.

About Lysosomal Storage Disease

LSDs are a class of inherited disorders which result from a deficiency in one of the enzymes responsible for intracellular recycling. These enzymes are naturally produced within cells and guided to the lysosome – a sub-cellular compartment where recycling occurs – by a specific targeting structure called mannose 6-phosphate (M6P). ERTs use this recognition system to direct intravenously administered recombinant therapeutic proteins to the lysosomes in order to re-establish the impaired recycling process.

One in 5,000 newborns has a lysosomal storage disease, but it can also appear later in life.[3] Lysosomes are found in all cells of our body, and are responsible for breaking down cell components to be reused by the cell. In LSDs, one or more of the enzymes that accomplish this process are lacking or insufficient. The result is that the non-processed substances accumulate in the lysosomes and eventually poison the cell, leading to organ damage that keeps on worsening if left untreated.

About Oxyrane

Oxyrane is a privately-owned biotechnology company with a head office in Manchester, (England), research operations in Gent, (Belgium) and medical/regulatory activities in Boston (US); dedicated to developing enzyme replacement therapies (ERTs) for lysosomal storage diseases (LSDs).

Oxyrane is developing an ERT for Pompe disease using its proprietary yeast host that is engineered to produce high levels of the targeting motif M6P with the goal of obtaining highly potent therapeutic product. In addition, Oxyrane's process enables cost-effective batch production at very large industrial scale using relatively low-cost, standard production equipment/facilities.

About VIB, UGent and Vrije Universiteit Brussels

VIB

VIB is a non-profit research institute in life sciences. About 1,250 scientists conduct strategic basic research on the molecular mechanisms that are responsible for the functioning of the human body, plants, and microorganisms. Through a close partnership with four Flemish universities – UGent, K.U.Leuven, University of Antwerp, and Vrije Universiteit Brussel – and a solid funding program, VIB unites the forces of 72 research groups in a single institute. The goal of the research is to extend the boundaries of our knowledge of life. Through its technology transfer activities, VIB translates

research results into products for the benefit of consumers and patients and contributes to new economic activity. VIB develops and disseminates a wide range of scientifically substantiated information about all aspects of biotechnology. More information: www.vib.be

UGent

After more than twenty years of uninterrupted growth, Ghent University is now one of the most important institutions of higher education and research in the Low Countries. Ghent University yearly attracts over 30,000 students, with a foreign student population of over 2,200 EU and non-EU citizens. Ghent University offers a broad range of study programmes in all academic and scientific branches. With a view to cooperation in research and community service, numerous research groups, centres and institutes have been founded over the years. More info: www.UGent.be

Vrije Universiteit Brussel

The Vrije Universiteit Brussel (VUB) is a thriving university in the heart of Belgium and Europe, which in 1969-1970 split off from the Université Libre de Bruxelles (ULB), founded in 1834. VUB combines excellence in teaching with excellence in research. Several of its 150 research groups are topranked worldwide. The principle of independent research is central at VUB, but the quality of its undergraduate and graduate programs is no less important, as the university provides an environment where students are treated as individuals and supported in their personal development. Currently, VUB has some 10,000 students and 2,700 staff, divided over eight faculties and two Brussels campuses (in Etterbeek/Elsene and Jette). The VUB University Hospital is adjacent to the Medical Sciences campus in Jette and employs 3,000 people. More info: www.vub.ac.be/.

For further information, please contact:

Natalie Henson
AXON
Tel: +44 (0) 208 439 9492
Email: nhenson@axon-com.com

Professor Nico Callewaert
VIB
Tel: +32 9 3313630
Email: nico.callewaert@dmbr.vib-ugent.be

REFERENCES

[1] Tiels P, Baranova E, Piens K, et al. A bacterial glycosidase enables mannose-6-phosphate modification and improved cellular uptake of yeast-produced recombinant human lysosomal enzymes. In Press: *Nature Biotechnology*

[2] Kishnani PS, Howell RR. Pompe disease in infants and children. J Pediatr. 2004;144(5):35-43

[3] Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of Lysosomal Storage Disorders. JAMA. 1999;281(3):249-254. doi:10.1001/jama.281.3.249