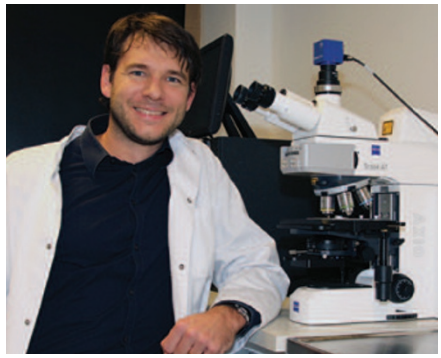
EDITORS' pick

Orphazyme

This Danish startup intends to use a chaperone protein to treat lysosomal storage disorders.



Dr. Thomas Kirkegaard, Chief Scientific Officer at Orphazyme.

Last March, The European Patent Office in Munich issued a patent to Copenhagen-based startup Orphazyme for the use of heat shock protein 70 (Hsp70) for treating lysosomal storage disorders. The patent was unusual because the claims encompassed multiple disorders, which currently can only be treated individually, if at all. And, individually, these disorders are extremely rare. But because orphan drug development has proven so lucrative for biotech (enzyme replacement therapies for treating Gaucher disease and Fabry disease cost up to $550,000 and $250,000 a year, respectively, per patient), a drug that works in multiple lysosomal storage disorders would not only be medically important but also provide a financial windfall to its maker.

Most lysosomal storage disorders are triggered by defects in a lysosomal enzyme, which causes substrates to accumulate in lysosomes, intracellular organelles that digest and degrade used and defective macromolecules as well as entire organelles like mitochondria. This abnormal buildup leads to cellular damage and death, including (in most lysosomal disorders) neuronal death. Enzyme replacement therapy, in some of these diseases, has worked to a degree. Hsp70, however, is a chaperone protein, which Orphazyme claims boosts lysosomal enzyme activity and stabilizes lysosomes, preventing cell death.

Orphazyme takes an unconventional view of Hsp70. Its standard chaperone function, the promotion of protein folding, is only part of the hypothesized therapeutic mechanism, the company's scientific founders suggest. Marja Jaattela, a professor in cancer biology at the University of Copenhagen, reported in 2004 that Hsp70 could protect cancer cells by stabilizing lysosomes and preventing lysosomal membrane permeabilization, which leads to cell death. Her laboratory is now pursuing ways to inhibit Hsp70 function to induce cancer cell death (work that Orphazyme is not involved in).

Orphazyme's intellectual foundation was mostly laid by Thomas Kirkegaard, a graduate student in Jaattela's laboratory beginning in 2005. Kirkegaard set out to understand how Hsp70 stabilized lysosomes and prevented cell death. After many false leads, a finding by Finnish biophysicist Paavo Kinnunen led Kirkegaard to the solution. Kinnunen reported that Hsp70 interacted strongly with a lipid closely related to bis(monoacylglycerol)phosphate (BMP), a phospholipid that stimulates the lysosomal degradation of sphingolipids, key components of cell membranes. Kirkegaard showed that Hsp70 bound to BMP and that this interaction was necessary for Hsp70's lysosome-stabilizing effect.

Kirkegaard, Kinnunen and Jaattela reported these findings in *Nature* (**463**, 549–553, 2010). The medical implications were obvious because BMP was known to bind to acid sphingomyelinase (ASM), an enzyme that is depleted in two lysosomal storage diseases, Niemann-Pick disease types A and B, leading to the buildup of sphingomyelin and eventually cell death. Kirkegaard's work showing that Hsp70 could, through BMP, boost ASM activity and stabilize lysosomes in cells from Niemann-Pick patients immediately suggested a novel therapy. Six months before the *Nature* paper, Kirkegaard and three others founded Orphazyme to develop it. The company has now raised more than €17 ($22.7) million in venture capital funding.

Orphazyme is also developing small-molecule 'heat shock protein amplifiers' for lysosomal storage disorders. It obtained these molecules in 2011 from CytRx in Los Angeles.

Worldwide, there are only about 1,200 cases of Niemann-Pick disease types A and B. But Orphazyme CEO Anders Hinsby believes the company's recombinant Hsp70 can be used to treat many other lysosomal storage diseases, especially the sphingolipidoses, a category that includes Niemann-Pick, Tay-Sachs, Gaucher and Fabry diseases, among others. There are two reasons for this versatility, says Kirkegaard, now Orphazyme's CSO. One is that lysosomal destabilization seems to be a common feature of the sphingolipidoses. The second is that BMP is a cofactor to other enzymes besides ASM that are dysfunctional across these diseases and Hsp70 binding to BMP should similarly restore enzyme function in all these cases. So far, says Kirkegaard, experiments in patient cells have confirmed this broad effect.

Such a general therapy for lysosomal storage diseases is very desirable, says Steven Walkley, a neuroscientist at the Albert Einstein College of Medicine in New York. But, he says, Orphazyme's approach raises some questions. First, it's not clear how the mutant enzyme reaches the lysosome to be activated by Hsp70 because misfolded proteins generally are destroyed in the endoplasmic reticulum, the organelle where protein folding takes place. Second, says Walkley, lysosomal membrane permeabilization is a newcomer to the list of pathogenic mechanisms in lysosomal storage disorders. More is known about other effects, such as a deficit in protein salvage. A major role for lysosomal instability and membrane permeabilization in these diseases, Walkley says, remains to be shown.

Kirkegaard cites work by geneticist Edward Schuchman at the Mount Sinai School of Medicine in New York showing that Niemann-Pick A and B patients have a normal amount of mutant enzyme in lysosomes (*Mol. Genet. Metab.* **95**, 152–162, 2008). And Kirkegaard says that lysosomal membrane permeabilization is a well-reported initiator of cell death, which could lead directly to inflammation and neurodegeneration through the release of proteases and lipases into the cytoplasm.

Pediatrician Andrea Ballabio, director of the Telethon Institute of Genetics and Medicine in Naples, Italy, considers dysregulation of autophagy—a process that delivers cellular cargo to the lysosome for degradation—a critical source of damage to cells in lysosomal storage disorders. (If lysosomes cannot degrade cargo, autophagy backs up.) He asks whether recombinant Hsp70 is able to boost autophagy.

Kirkegaard only has preliminary data on autophagy, but he contends that normalizing lysosome function will remove the autophagy bottleneck. He reports clear neurological improvements, both biochemical and behavioral, in animal models, and no drug-related toxicity even at chronic exposures of up to six months. Although Orphazyme has yet to disclose its initial disease indication, Hinsby expects clinical trials to begin by the end of 2013.

Ken Garber, *Ann Arbor, Michigan*

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Corrigendum: Editor's Pick: Orphazyme

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In the version of this article initially published, Steven Walkley's name was misspelled as Steven Walkely. The error has been corrected in the HTML and PDF versions of the article.