



*“There are no rare disease experts in my institute, and so the Harrington rare disease expertise has been invaluable.”*

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Neuroscience Lecturer,  
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70 RARE DISEASES.

# ONE POTENTIAL BREAKTHROUGH

**FOCUS:** Treating lysosomal storage disorders, causes of widespread organ damage.

Lysosomes are organelles containing enzymes that break down many kinds of biomolecules. Lysosomal storage disorders (LSDs) are a group of more than 70 rare genetic diseases caused by defects in lysosomal proteins. Although LSDs have a collective frequency of less than one in 5,000 live births, they are the most common cause of childhood neurodegeneration.

Disease-modifying therapies are available for just 16 LSDs, but even these are not suitable for all patients. LSD therapies in development are mostly gene and enzyme replacement therapies, each targeting just a single one of these disorders.

Dr. Waller-Evans’ work takes a different approach, focusing on toxic lysosphingolipids, common to nearly all LSDs. Lysosphingolipids are formed via degradation of accumulated sphingolipids—lipids that play important roles in cell recognition and transduction (when cells convert one signal or stimulus into another).

“Sphingolipids are basically fat with sugars on top,” Dr. Waller-Evans says. “Normally these fats get taken into a part of cells called lysosomes, where enzymes chop up these fats, which the cells reuse to build different fats. In LSDs, there may be a defect that negatively affects that chopping process or makes the lysosome less efficient, and so these fats accumulate and are then converted to more toxic lysosphingolipids by the enzyme acid ceramidase (AC).”

It has recently been shown that in one LSD, Krabbe disease, inhibiting AC activity prevented production of lysosphingolipids, which in turn normalized LSD cells. Dr. Waller-Evans and her team have uncovered good reasons to believe that this approach would be effective in at least four other LSDs—and of course, the hope is for efficacy in 66 more.

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