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Repurposed drugs may offer improved treatments for fatal genetic disorders

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University of Rochester Medical Center researchers believe they have identified a potential new means of treating some of the most severe genetic diseases of childhood, according to a study in *PLOS Biology*. The diseases, called lysosomal storage disorders (LSDs), are caused by disruptions in the functioning of the stomach of the cell, known as the lysosome. LSDs include Krabbe disease, Gaucher disease , metachromatic leukodystrophy and about 40 related conditions. In their most aggressive forms, they cause death of affected children within a few years after birth.

The URMC team, led by the article's corresponding author Mark Noble, Ph.D., discovered for the first time how specific toxic waste products that accumulate in LSDs cause multiple dysfunctions in affected cells. They also found that several drugs already approved for other uses have the unexpected ability of overcoming the cellular toxic build-up, providing new opportunities for treatment.

Two postdoctoral fellows in the URMC Department of Biomedical Genetics, Christopher Folts, Ph.D., and Nicole Scott-Hewett, Ph.D., conducted the experiments to better understand the biology of lysosomal disorders. They demonstrated:

- Just like the stomach, lysosomes are usually more acidic than other parts of the cell and toxic substances that accumulate in several LSDs disrupt maintenance of the acidic environment.
- Restoring the normal acidity of the lysosome with drug treatment

> was sufficient to prevent multiple disruptions of normal lysosome function and to maintain critical cell functions, such as division and survival.

In a mouse model of Krabbe disease (one of the most severe LSDs), Noble's team found that their lead study drug, colforsin, increased survival as effectively as seen in studies where disease-causing mutations were corrected by gene therapy. Colforsin is approved in Japan to treat cardiac disease, which provides information to investigators about its use in humans.

Increased survival in mice occurred even though treatment was started later than is necessary for gene therapy. The research treatment also decreased damage to the brain and improved the quality of life in the diseased mice. All of these outcomes are critical goals in the treatment of children with Krabbe disease or related illnesses, said Noble, who is the Martha M. Freeman, M.D., Professor in Biomedical Genetics at URMC.

"One of the great challenges in these diseases is that they are both rare and come in many different varieties, and advances have tended to focus on single diseases," Noble said. "In contrast, our findings suggest our treatments will be relevant to multiple disorders. Also, we saw benefits of our treatment even without needing to correct the underlying genetic defects. That gives us great hope that we could combine our treatments with other candidate approaches to gain additional benefits."

If the results can be translated into humans, Noble said, the repurposed drugs might improve the quality of life for afflicted children while more difficult experimental genetic treatments are pursued.

Lysosome dysfunction is recognized as important in other diseases, such as diabetes and macular degeneration. The latest discoveries, Noble

added, may extend beyond the treatment of lysosomal storage disorders.

Provided by University of Rochester Medical Center