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# Mood-stabilizing drug could treat inherited liver disease

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Opening up a can of worms is a good way to start hunting for new drugs, recommend researchers from Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh School of Medicine. In a study published today in the *Public Library of Science One*, they used a primitive worm model to show that a drug typically used to treat agitation in schizophrenia and dementia has potential as a treatment for α-1 antitrypsin (AT) deficiency, an inherited disease that causes severe liver scarring.

In the classic form of AT deficiency, which affects 1 in 3,000 live births, a gene mutation leads to production of an abnormal protein, dubbed ATZ, that unlike its normal counterpart is prone to clumping, explained David H. Perlmutter, M.D., physician-in-chief and scientific director, Children's Hospital, and Distinguished Professor and Vira I. Heinz Endowed Chair, Department of Pediatrics, Pitt School of Medicine.

"These protein aggregates accumulate in liver cells and eventually lead to scarring of the organ or to tumor formation," Dr. Perlmutter said. "If we could find a drug that slows or stops this process, we might be able to prevent the need for liver transplantation in these patients."

To find that drug, Dr. Perlmutter's team worked with Pitt's Stephen Pak, Ph.D., assistant professor of pediatrics, and Gary Silverman, M.D., Ph.D., Twenty-five Club Professor of Pediatrics, Cell Biology and Physiology, who developed a model of AT deficiency in Caenorhabditis

elegans, or C. elegans, a harmless microscopic worm or nematode typically found in soil. Previous experiments conducted by Drs. Pak and Silverman, in which more than 2,000 compounds were screened, showed that fluphenazine, a drug approved for human use as a mood stabilizer, could reduce ATZ accumulation in the worm, so the team studied it further.

Worms that produce ATZ die sooner than normal ones, which typically have a life span of fewer than 20 days. Those that were exposed to fluphenazine, however, had lower burdens of ATZ and lived more than a day longer that untreated animals. The lifespan of normal worms was unchanged by fluphenazine exposure. The researchers also labeled with fluorescent markers intracellular structures called autophagosomes, which help clear abnormal proteins out of the cell in a process called autophagy. Fluphenazine exposure was associated with a greater presence of autophagosomes, suggesting that increased autophagy led to reduced ATZ accumulation.

Follow-up experiments showed that fluphenazine reduced ATZ accumulation in several mammalian-cell line models of AT deficiency, D. Silverman said.

"We found when we gave this drug for three weeks to mice with the disease, autophagy is activated, the abnormal protein load is diminished, and liver scarring is reversed. It's truly amazing," he said. "And because fluphenazine is already being safely prescribed for other conditions, it should be easier to bring it to clinical trials for AT deficiency."

The project also reveals the power of the worm model to rapidly screen drug candidates, Dr. Perlmutter noted.

"This is the first extensive investigation of a drug that was discovered through the C. elegans screening method," he said. "It's remarkable that

you can take a completely unbiased, high-content screen using a primitive organism and end up identifying a drug that reduces the accumulation of an abnormal protein in mammalian cell lines and a living mouse. It's proof-of-principle of this research pipeline. Furthermore, this drug is very similar pharmacologically to carbamazepine, another mood stabilizer that we found to enhance autophagy and reverse liver fibrosis in the mouse model of α1-antitrypsin deficiency."

Provided by University of Pittsburgh Schools of the Health Sciences

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