Old drug offers new hope against Niemann-Pick Type C—rare, deadly childhood disease

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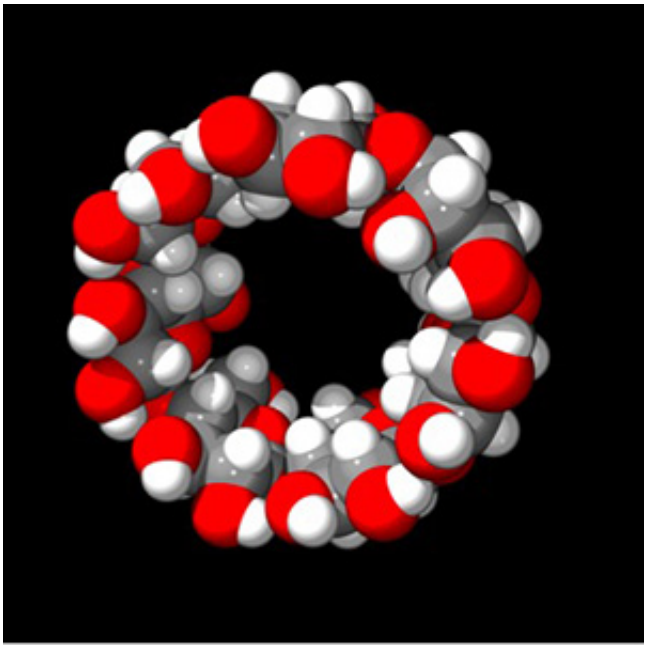

Cyclodextrin molecule. Credit: Daniel S. Ory, MD

(Medical Xpress)—Washington University School of Medicine in St. Louis is playing a leading role in one of the National Institutes of Health's (NIH) first clinical trials to improve treatments for rare and neglected diseases.

In this case, the disease is Niemann-Pick Type C, a disorder that causes excess cholesterol to accumulate in the brain, liver and spleen. It affects about 500 children worldwide, leads to neurodegeneration, and usually

causes death in the first two decades of life. The compound to be tested is called cyclodextrin, a cyclic sugar long used as an ingredient in other drugs.

"You probably ingest cyclodextrins all the time and don't realize it," says Daniel S. Ory, MD, professor of medicine and of cell biology and physiology. "It's used as a carrier in many drug formulations because of its ability to solubilize drugs that don't dissolve well in water."

According to Ory, the trial will test a new application of a compound already approved by the U.S. Food and Drug Administration to help with drug delivery. Cyclodextrin has just never been used in the high doses that successfully treated animal models of Niemann-Pick Type C (NPC).

"We've been studying this disease for many years, and we began looking at this drug in earnest about five years ago," Ory says. "In animal models of NPC, we see significant benefit in both neurological function and survival. It's superior to all other compounds we have tested in the animal models."

The nine patients they are enrolling in this Phase 1 trial are being treated at the NIH Clinical Center in Bethesda, MD. In St. Louis, Ory and his colleagues are tracking their progress with new techniques developed at Washington University. This includes novel methods to monitor whether the drug is having an effect, both in the cerebrospinal fluid and the blood.

"The patients' samples are being shipped to us, and we are using our facilities to monitor the progress of the patients and report the results back to the NIH," Ory says. "Based on our results, the NIH team will make decisions about whether to move forward with escalating the dose."

The disorder causes cholesterol to accumulate inside compartments in cells called lysosomes. The buildup leads to dysfunction and loss of large neurons in the central nervous system. Based on successes in animal studies, Ory says cyclodextrin delivered directly to the brain acts as a key to unlock the trapped cholesterol and allows it to redistribute in the cell where it can be properly metabolized and removed.

In addition to new ways to monitor the effects of cyclodextrin, Ory and his colleagues have developed better ways to diagnose the disease in the first place. He hopes to adapt his group's diagnostic techniques for newborn screening purposes. According to Ory, the disease is under-diagnosed because the earliest symptoms are not specific and are easily overlooked.

"At first, a child might display mild cognitive impairment, perhaps be a little bit clumsy," Ory says. "Eventually, the child will get to a tipping point and begin a slide toward progressive neurological disability."

"But if we can diagnose at birth, and we have treatments like the one we are testing, we could intervene before the onset of neurological symptoms. That would change the natural history of the disease – taking kids who would have died in childhood and helping them live to adulthood."

While this Phase 1 trial will test safety, Ory and his collaborators at the NIH and other institutions are developing plans for a Phase 2/3 trial to be headquartered at Washington University that will test more patients and determine the effectiveness of the treatment.

"This is a great example of a novel partnership between the NIH, academic researchers, industry, patients and family organizations that is having success in addressing a group of patients with unmet needs," Ory says. "We want other researchers to look at this model and think about

applying it to other disorders."

Provided by Washington University School of Medicine in St. Louis