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System may help treat rare genetic disorder, reduce severe side effects

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Researchers at Oregon State University and other institutions have discovered a type of drug delivery system that may offer new hope for patients with a rare, ultimately fatal genetic disorder - and make what might become a terrible choice a little easier.

No treatment currently exists for this disease, known as Niemann Pick Type C1 disease, or NPC1, that affects about one in every 120,000 children globally, and results in abnormal cholesterol accumulation, progressive neurodegeneration and eventual death.

However, a compound that shows promise is now undergoing clinical trials, but it has major drawbacks - the high doses necessary also cause significant hearing loss and lung damage, as well as requiring direct brain injection.

New findings, published today in *Scientific Reports*, outline the potential for a nanotech-based delivery system to carry the new drug into cells far more effectively, improve its efficacy by about five times, and allow use of much lower doses that may still help treat this condition without causing such severe hearing loss.

The same system, they say, may ultimately show similar benefits for 50 or more other genetic disorders, especially those that require "brain targeting" of treatments.

"Right now there's nothing that can be done for patients with this

disease, and the median survival time is 20 years," said Gaurav Sahay, an assistant professor in the Oregon State University/Oregon Health & Science University College of Pharmacy, and corresponding author on the new study.

"The new cholesterol-scavenging drug proposed to treat this disorder, called cyclodextrin or HPβCD, may for the first time offer a real treatment. But it can cause significant hearing loss and requires multiple injections directly into the brain, which can be very traumatic. I'm very excited about the potential of our new drug delivery system to address these problems."

In this approach, the HPβCD drug is attached to an extraordinarily small, nanotech-sized lipid particle that can carry it into cells, where it helps to flush out cholesterol. Researchers were surprised to discover, however, that the carrier itself also helped address the problem, while working in synergy with the drug it carries to greatly increase its effectiveness.

This should allow use of much lower dosages, Sahay said, and possibly an easier delivery through intravenous injection, instead of brain injection. In the form currently used, only 0.2 percent of the drug is able to cross the blood brain barrier.

In previous research with the HPβCD drug in animal models, the treatment did slow the progression of this disease, but did not reverse it. The disease focuses its damage on liver and brain cells.

In their report, researchers noted that this type of drug delivery system has several advantages, including prolonged circulation times, the ability to incorporate multiple drugs with different mechanisms of action, and a variety of "targeting ligands" that can help cross the blood brain barrier.

The researchers have also partnered with Dr. Edward Neuwelt at the

OHSU Blood Brain Barrier Program, who has pioneered temporary opening of the blood brain barrier in humans to access drugs to the brain.

"Taken together, nanocarriers can serve as a platform that can effectively deliver small molecules, genes and perhaps imaging agents for treatment and diagnosis of a wide variety of other rare lysosomal storage disorders," the researchers wrote in their conclusion.

More information: *Scientific Reports*, DOI: 10.1038/srep31750

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