Molecular Surgeons for Huntington's Disease Catch a RIDE with CRISPR Advancements

A new CRISPR-based technology, called RIDE, is a leap forward for this trail-blazing technology. With the precision of a scalpel sharp enough to rewrite the very code of life, researchers have used it with the hope of treating Huntington's disease.

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Imagine a tiny, microscopic surgeon moving through the body, making precise genetic repairs exactly where they're needed. That's the vision behind a groundbreaking new gene-editing delivery system called RIDE—**Ri**bonucleoprotein **De**livery—recently featured in *Nature Nanotechnology*. This system offers a novel way to deliver CRISPR, a powerful gene-editing tool, to specific cells in the body. Researchers have tested RIDE in mice and monkeys, with promising results for diseases like Huntington's disease (HD). Let's dive into how this innovative system could shape the future of HD treatments.

CRISPR Challenges

CRISPR has revolutionized the way scientists approach genetic diseases, acting as a molecular "find and replace" tool for DNA. For HD, where an expanded CAG repeat in the huntingtin (HTT) gene leads to breakdown of brain cells, CRISPR could potentially correct or silence the faulty gene. However, several key challenges have stood in the way:

RIDE is like giving CRISPR a navigation system, allowing it to precisely deliver gene editing technology to specific cells, like brain cells in Huntington's disease.

Image credit: William Hadley

- **Off-Target Effects** – CRISPR must be highly precise to avoid accidental edits in unintended parts of the genetic code.
- **Immune System Response** – The body may recognize the CRISPR components as foreign invaders and attack them.
- **Targeted Delivery** – The therapy must reach the right cells in the brain, specifically nerve cells in the very center of the brain that's most affected in HD, without affecting other tissues.

RIDE aims to overcome these hurdles by packaging CRISPR into engineered particles that have been given brain-specific navigation systems that lets them go to specific cell types.

How RIDE Works

RIDE delivers CRISPR in the form of ribonucleoproteins , which are pre-formed complexes of the editing enzyme and guide RNA—think of this like the genetic navigation system that directs RIDE exactly where to go. The complex is packaged inside a virus-like particle, which acts as a protective car. These particles can be engineered with molecular tags, similar to putting a precise street address in your car's navigation system, so that they target specific cells, ensuring precise delivery.

> **"RIDE has the potential to be a safe, effective, and highly targeted method for delivering CRISPR-based drugs. And the researchers are already exploring ways to expand RIDE's capabilities, including the potential to use systemic delivery. "**

The key innovation of RIDE lies in its ability to be customized for different cell types. By modifying the outer shell of these nanoparticles with specific molecular tags, scientists can direct them toward desired cells, ensuring that the CRISPR machinery reaches the correct targets. This is a big leap forward for CRISPR-based gene editing.

To visualize the process, imagine a package being delivered. Current CRISPR approaches can make deliveries to the right neighborhood, but RIDE is a door-to-door service that drops the package at the exact address. RIDE's customization allows the CRISPR machinery to be sent exactly where it's needed, reducing off-target effects and improving efficiency.

Testing RIDE for HD

Researchers tested RIDE in mice that model HD, focusing on neurons in the striatum—the central brain region most affected by HD. The goal was to silence or edit the mutated HTT gene that causes HD to slow or stop disease progression.

The results were striking: treated mice showed a reduction in HTT protein levels and improved behavior compared to untreated HD mice, such as their movement control on obstacle courses. Importantly, the editing efficiency was much higher than what has been

achieved with other delivery methods that don't have a cellular navigation system, and there were fewer signs of unwanted genetic changes or immune responses.

Another promising aspect of RIDE is its potential to provide long-lasting effects. All the results in these mice were achieved with just a single injection of RIDE; they didn't need to continuously administer the treatment. They monitored the mice for over 110 days (which is quite a long time in a mouse's lifespan!), and the improvements persisted.

A major advancement of RIDE is that the CRISPR machinery is destroyed by the cell after the gene is edited, hopefully reducing the chances of off-target effects and any unintended consequences of having the molecules stick around.

An important safety component of the RIDE system is that the gene-editing tools are delivered as an assembled complex rather than as genetic material. This means that it's only around for a short time, long enough to do its job, before being quickly degraded by the cell's natural processes—another big leap forward for this CRISPR-based gene editing approach. This reduces the risk of persistent off-target effects that could arise from prolonged CRISPR activity.

Beyond Mice

To really assess the potential of RIDE for treating HD in humans, the researchers needed to move beyond mice. That's where the monkey studies come in. These studies help get a better understanding of how RIDE might behave in a system that's more closely related to humans.

Safety was the top priority considering this treatment involves injecting something directly into the brain. They used MRI scans to look for any signs of brain damage after a RIDE injection, and they didn't find any. They analyzed brain tissue samples and found that RIDE was in fact able to reduce levels of the non-expanded HD protein in the targeted areas. So they're seeing consistent results in both mice and monkeys, which is a good sign.

The researchers also went a step further to confirm that RIDE could work in human cells. To do this, they used stem cells that they turned into neurons. These studies checked many of the boxes that suggested this technology is working: they were able to target and edit the

HD gene and there were surprisingly minimal off-target effects. So they got the green light for RIDE in a human-based model as well.

What This Means for HD Families

> **“By combining the precision of CRISPR with an advanced delivery system that targets specific cell types and shuts off after editing, scientists are getting closer to making genetic therapies for HD a reality. ”**

While these results are promising, RIDE is still in early stages of development. Further studies in larger animals, and eventually human trials, will be necessary before this approach can be considered for clinical use.

However, this study is a major step forward in the field of gene therapy. It demonstrates that RIDE has the potential to be a safe, effective, and highly targeted method for delivering CRISPR-based drugs. And the researchers are already exploring ways to expand RIDE’s capabilities, including the potential to use systemic delivery.

Systemic delivery could mean scientists would be able to inject RIDE into the bloodstream and have it reach cells within the brain. This would be incredible, and a game-changer for HD and many other genetic diseases. Research breakthroughs around CRISPR are moving quickly—this technology has the potential to change the landscape of medicine as we know it.

Looking Ahead

RIDE represents an exciting step forward in the search for effective HD treatments. By combining the precision of CRISPR with an advanced delivery system that targets specific cell types and shuts off after editing, scientists are getting closer to making genetic therapies for HD a reality. And this team isn’t the only one working on this type of approach.

While we’re still in the early stages of this research, this breakthrough brings new hope to the HD community. This study offers a glimpse into a future where we might be able to treat genetic diseases, like HD, with unprecedented precision and effectiveness. Stay tuned for more updates on how gene-editing technologies like RIDE continue to evolve and push the boundaries of what’s possible in HD research.

The authors have no conflicts of interest to declare.For more information about our disclosure policy see our FAQ...

GLOSSARY

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

stem cells Cells that can divide into cells of different types

neuron Brain cells that store and transmit information

CRISPR A system for editing DNA in precise ways

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
