# Nanotechnology for Genome Editing in Multiple Muscles Simultaneously

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The Akitsu Hotta Project at T-CiRA reports an immunologically safe, synthetic nanoparticle to correct Duchenne muscular dystrophy mutations in multiple muscle tissues.

Many intractable diseases are the result of a genetic mutation. Genome editing technology promises to correct the mutation and thus new treatments for patients. However, getting the technology to the cells that need the correction remains a major challenge. A new study led by CiRA Junior Associate Professor Akitsu Hotta and in collaboration with Takeda Pharmaceutical Company Limited as part of the T-CiRA Joint Research Program reports how lipid nanoparticles provide an effective means for the delivery to treat Duchenne muscular dystrophy (DMD) in mice.

Last year's Nobel Prize for Chemistry to the discoverers of CRISPR-Cas9 cemented the impact of genome editing technology. While CRISPR-Cas9 can be applied to agriculture and livestock for more nutritious food and robust crops, most media attention is on its medical potential. DMD is just one of the many diseases that researchers foresee a treatment using CRISPR-Cas9.

"Oligonucleotide drugs are now available for DMD, but their effects are transient, so the patient has to undergo weekly treatments. On the other hand, CRISPR-Cas9 effects are long lasting," said Hotta.

DMD results in progressive muscle atrophy throughout the body. Patients normally begin to show symptoms, such as falling easily and an inability to run before school age, and are often on respirators before adulthood.

For a disease like DMD, it is necessary to target a broad range of skeletal muscles, which means multiple injections are important. Currently investigated delivery systems utilize nonpathogenic viruses to deliver CRISPR-Cas9, but these viruses induce immune reactions and the production of antibodies, which prohibit multiple injections.

Lipid nanoparticles can prevent these reactions. As their name suggests, lipid nanoparticles are tiny particles less than 0.1 μm in diameter and made up of lipids that change their properties in response to acidity. This feature allows them to stay intact outside the cell, but once inside they rupture to release their content, such as CRISPR-Cas9, which is then free to correct the gene mutation. Lipid nanoparticles are being used for COVID-19 vaccines, but their utility for genome editing therapy is still under investigation. As one part of the T-CiRA Joint Research Program, Hotta has been developing lipid nanoparticles that can deliver genome editing technology to the cell.

After experimenting with several formulations, the study reports a novel lipid nanoparticle that encapsulates CRISPR-Cas9 inside and target muscle cells in mice.

Unlike oligonucleotide drugs, whose effects in mice constantly diminished after treatment and disappeared after a few months, the study shows that delivering CRISPR-Cas9 with the new lipid nanoparticle sustained a constant effect in muscle that lasted beyond one year.

Furthermore, the effects were evident even when delivering the particles with multiple intramuscular injections, whereas the virus-based delivery failed to have an effect after the second injection. In addition, intravenously perfused lipid nanoparticles into the limbs had therapeutic benefit on multiple muscle tissues.

Adding to the safety, Hotta noted, "CRISPR-Cas9 disappeared from the body within a few days. That means the risk of off-target genome editing is minimal, but the therapeutics effects last a long time."

Read the original article on Kyoto University.