Building Better Laboratory Models to Test Gene Therapies for a Rare Childhood Muscle Disease

The problem:

X-linked myotubular myopathy (XLMTM) is a severe muscle disease that affects babies from birth, causing severe muscle weakness and breathing difficulties. It is caused by changes in a gene called *MTM1*. The *MTM1* gene contains the information to make the myotubularin protein, which helps maintain healthy muscles. When the MTM1 gene is incorrect, the myotubularin protein doesn't work properly, or is missing altogether, which causes XLMTM. Currently, there is no cure.

Scientists have been working on gene therapies to treat XLMTM. These are treatments that deliver a functional copy of the *MTM1 gene*. In lab and animal studies, these therapies appeared safe. But when tested in a clinical trial, they caused serious side effects for some people treated with the gene therapy. This is why it's so important to find better ways to test these treatments before they are given to people living with XLMTM.

What the researchers did:

Our team grew human muscle cells in the laboratory using cells from people living with and without XLMTM. We used different types of models: simple ones where the cells grow in a single layer at the bottom of a dish, and more advanced 3D "mini-muscles" that look and behave more like real muscle.

These lab-grown mini muscles shared some similarities with muscles from people living with XLMTM. For example, the cells contained less functioning myotubularin protein. We also observed changes in the size of the muscle cells, which are known to be smaller in people living with XLMTM.

We then tested gene therapy approaches on these mini muscles. To do this we used modified versions of viruses, as a packaging system for the working copy of the *MTM1* gene. We confirmed the therapy could successfully enter the muscle cells and increase production of myotubularin protein.

Why this matters:

This work could help scientists test new gene therapies more safely in a system that resembles human muscle. Because these new models more closely mimic XLMTM, they could also help us learn more about the condition and predict how people might respond to different treatments.