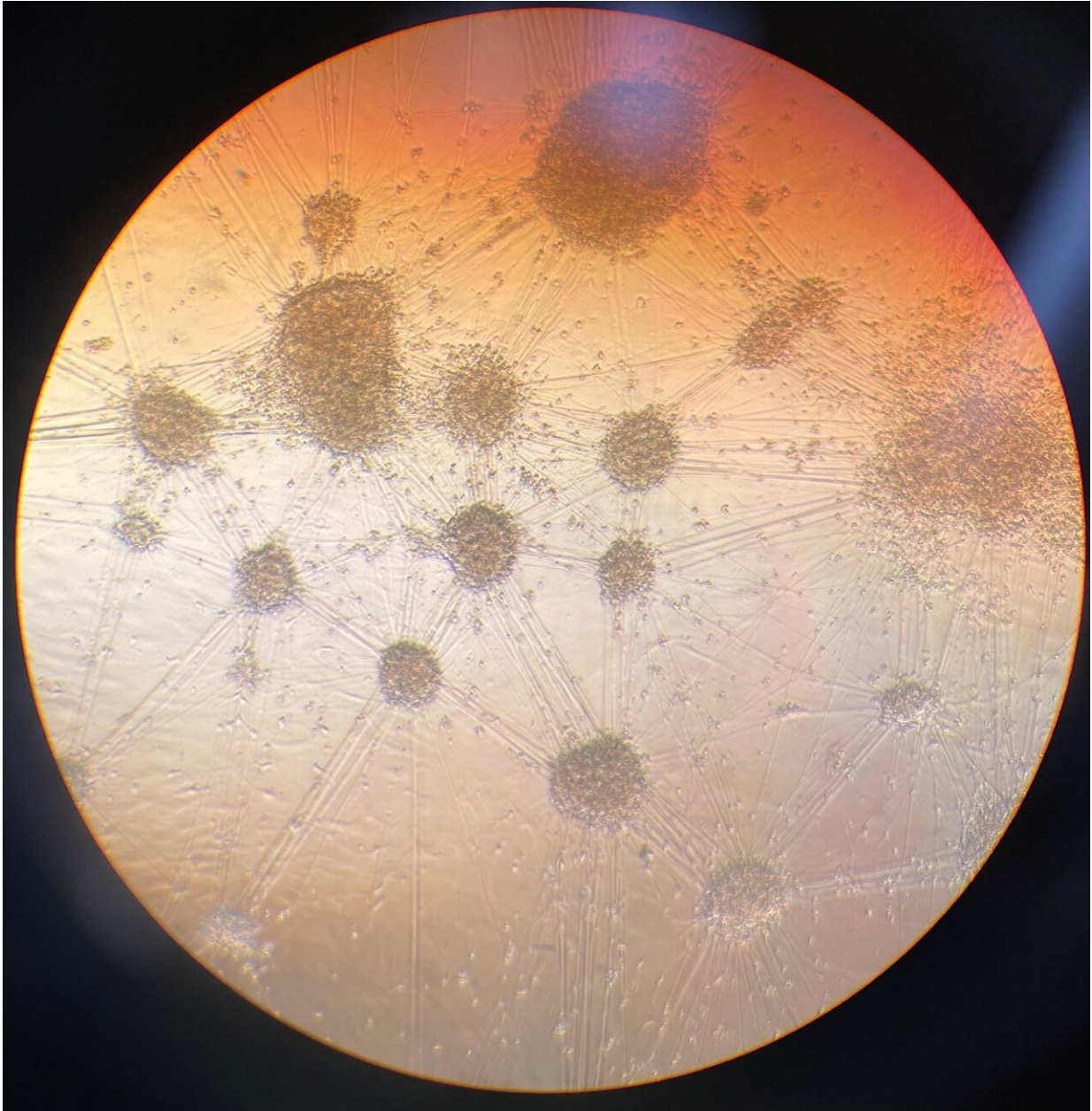


ALS and dementia attacked by an RNA-hunting compound that recruits cell's own virus fighter

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To study the effectiveness of their compounds, the scientists directed cells from patients with ALS to become stem cells and then specialize into nerve cells.
Credit: Jessica Bush, Disney Lab at Scripps Research, Florida

One of the most commonly inherited forms of ALS and frontotemporal

dementia is referred to as C9 ALS/FTD, so named for the repeated section of DNA on chromosome 9 that causes it. A collaboration led by scientists at Scripps Research in Florida has successfully treated the genetic disease in mice, with a potential drug molecule engineered in the lab of chemist Matthew Disney, Ph.D. The compound works in a new way, by directing the cell's own immune machinery to degrade and eliminate the disease-causing RNA.

The team's study is published Wednesday in the journal *Science Translational Medicine*. Collaborators include Leonard Petrucelli, Ph.D., of the Mayo Clinic in Jacksonville, and Jeffrey Rothstein, MD, Ph.D., of Johns Hopkins University in Baltimore.

Also known as Lou Gehrig's [disease](#), ALS causes progressive loss of motor neurons, the elongated nerve cells that connect muscles to the central nervous system. As motor neurons die, paralysis, muscle loss, swallowing and eventually, breathing difficulties develop, leading ultimately to death. Scientists are learning that ALS has multiple causes, some of them sporadic, and some inherited or familial.

Frontotemporal dementia similarly has both familial and sporadic causes. It involves progressive damage to neurons in the brain's frontal and temporal lobes. Symptoms may include difficulty walking or odd behavioral and emotional states. Like ALS, [frontotemporal dementia](#) has no cure.

One disease, many symptoms

While people with FTD appear outwardly to have a completely different illness than people with ALS, those whose condition is caused by the C9 genetic repeat have the same disease. Manifestations differ according to cell types affected. The more times the sequence repeats, the earlier and more severe the disease symptoms.

The disease-causing mutations involve repeats of the nucleotides guanine and cytosine, specifically repeats of GGGGCC segments on chromosome 9, open reading frame 72. The number of disease-causing repeats can range from around 60 into the thousands. People who inherit the diseased gene can develop ALS, FTD or both. Studies have estimated that around 1 in 5 people diagnosed with familial ALS, and around 1 in 10 people with familial FTD carry the C9 mutations. The average age of symptom onset is 58.

"This is a disease that runs in families. Based on the number of repeats, doctors can assess whether a patient would be affected with the disease. So, you know before a patient has symptoms that they have a high likelihood of developing it, and yet there is no treatment," Disney says. "That makes it even more imperative to develop strategies to that could create a medicine."

A team effort

To assess the effectiveness of their [compounds](#), the team needed both diagnostic biomarkers and patient-derived neurons displaying the C9 mutations. The Petrucelli group at Mayo Clinic has extensively studied C9 ALS/FTD and developed the diagnostic biomarkers. The Rothstein group at Johns Hopkins treats and researches ALS and provided stem cells, which the Disney Lab then brought forward into neurons that displayed the diseased array of GGGGCC repeats.

In their research, Disney's team designed a compound that targeted the RNA involved in transcribing the gene causing the disease. The compound causes an interaction between the RNA and pathways that a cell uses to eliminate RNAs. The compound eliminated 70 percent of the toxic protein fragments from mice bred to have the disease, and removed most hallmarks of the disease from the patient-derived nerve cells.

A single injection in the mice showed benefit through the entire length of the study period, which was six weeks, says Jessica Bush, a graduate student at Scripps Research's Skaggs Institute for Chemical Biology, who was the paper's first author.

"I think that it's so exciting that we can look at a disease like ALS, and by taking a different approach or new perspective, we can open the door to a whole new world of possibilities, and start down the road toward therapies," Bush says.

Basic science behind the discovery

Disney designed the compound by applying nearly 15 years of his group's research on finding druggable structures on RNA, a notoriously changeable and transient molecule, and building a library of compounds able to bind those druggable structures.

The successful compound works by binding tightly to the disease-causing RNA in multiple places, while also attracting an enzyme that eliminates RNAs. Nature apparently created the degrading enzyme to defend cells from viral infection and provide quality control for protein production.

"We co-opt a natural process to eliminate disease-causing RNA," Disney says. "A full analysis of the RNAs in the cells treated with the compound showed it was very specific and selective."

Moving the technology forward to where it can be tested in humans requires a large amount of additional tests and refinements, a process that may take several years, Disney adds.

"These studies, we hope, will advance new ways of targeting the RNA that causes ALS as well as other diseases," he says. "There is a possibility

here to eventually treat these patients before they develop symptoms, but it will be a long road before reaching the clinic."

More information: Jessica A. Bush et al, Ribonuclease recruitment using a small molecule reduced c9ALS/FTD r(G 4 C 2) repeat expansion in vitro and in vivo ALS models, *Science Translational Medicine* (2021). [DOI: 10.1126/scitranslmed.abd5991](https://doi.org/10.1126/scitranslmed.abd5991)

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