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Parkinson's disease drug ropinirole safely slows the progression of amyotrophic lateral sclerosis, finds clinical trial

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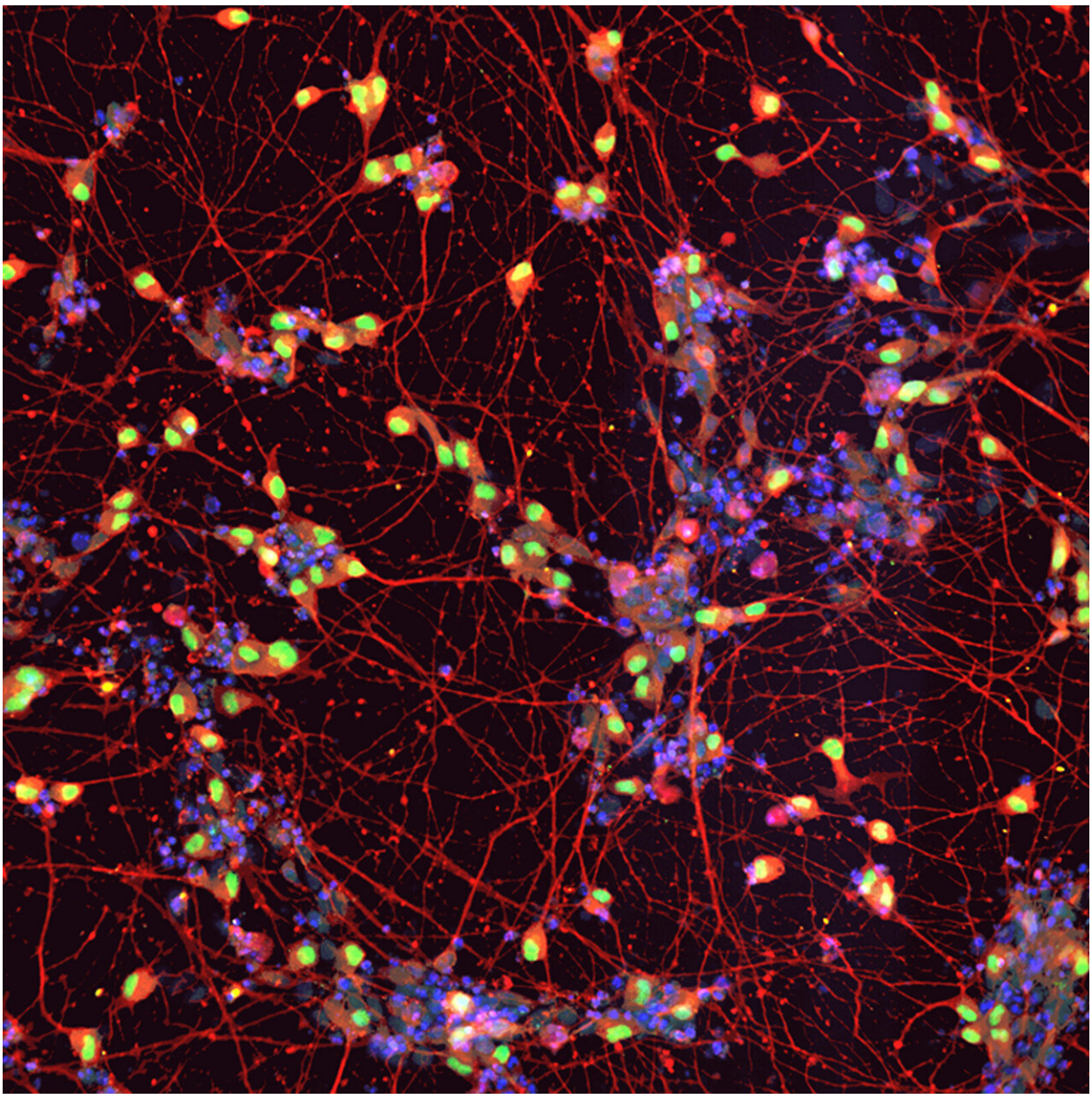


Photo of iPSCs-derived Motor neurons derived from an ALS patient. Credit: Morimoto et al/*Cell Stem Cell*

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a fatal motor neuron disease that causes people to gradually lose control of their muscles. There is no cure, and current treatments focus on reducing symptoms and providing supportive care. Reporting June 1 in the journal *Cell Stem Cell*, researchers from Japan show in an early clinical trial that the Parkinson's disease drug ropinirole is safe to use in ALS patients and delayed disease progression by 27.9 weeks on average.

Some patients were more responsive to ropinirole treatment than others, and the researchers were able to predict clinical responsiveness in vitro using motor neurons derived from patient stem cells.

"ALS is totally incurable, and it's a very difficult disease to treat," says senior author and physiologist Hideyuki Okano of the Keio University School of Medicine in Tokyo. "We previously identified ropinirole as a potential anti-ALS drug in vitro by iPSC drug discovery, and with this trial, we have shown that it is safe to use in ALS patients and that it potentially has some therapeutic effect, but to confirm its effectiveness we need more studies, and we are now planning a phase 3 trial for the near future."

To test ropinirole's safety and effectiveness in patients with sporadic (i.e., non-familial) ALS, the team recruited 20 patients receiving care at Keio University Hospital in Japan. None of the patients carried genes predisposing to the disease, and, on average, they had been living with

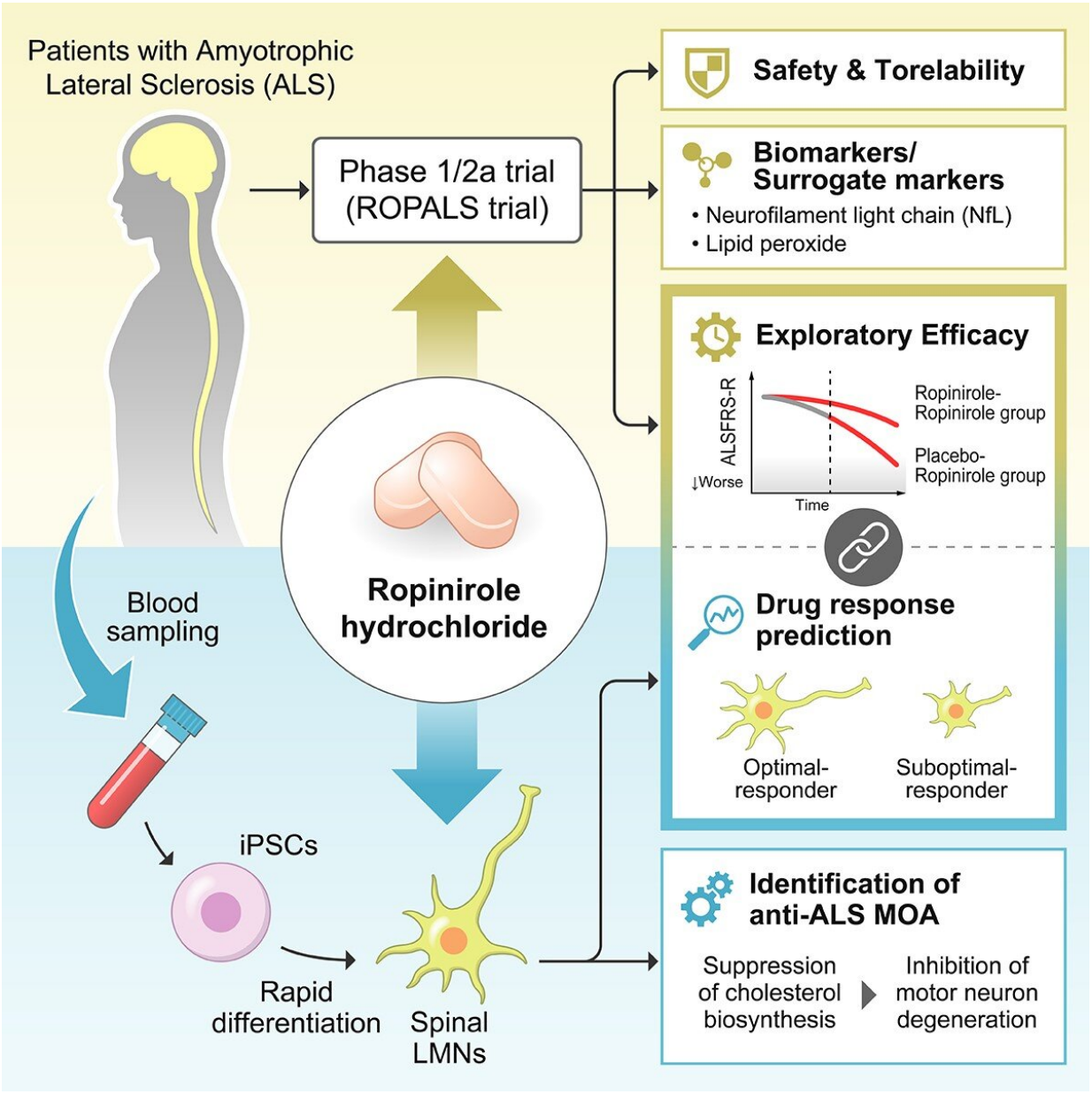
ALS for 20 months.

The trial was double blinded for the first 24 weeks, meaning that the patients and doctors did not know which patients were receiving ropinirole and which were receiving a placebo. Then, for the following 24 weeks, all patients who wished to continue were knowingly administered ropinirole. Many patients dropped out along the way—partially due to the COVID-19 pandemic—so only seven of 13 ropinirole-treated and one of seven placebo-followed-by-ropinirole-treated patients were monitored for the full year. However, no patients dropped out due to safety reasons.

To determine whether the drug was effective at slowing the progression of ALS, the team monitored a variety of different measures throughout the trial and for four weeks after treatment concluded. These included changes in the patients' self-reported physical activity and ability to eat and drink independently, activity data from wearable devices, and physician-measured changes in mobility, muscle strength, and lung function.

"We found that ropinirole is safe and tolerable for ALS patients and shows therapeutic promise at helping them sustain daily activity and muscle strength," says first author Satoru Morimoto, a neurologist at the Keio University School of Medicine in Tokyo.

Patients who received ropinirole during both phases of the trial were more physically active than patients in the placebo group. They also showed slower rates of decline in mobility, muscle strength, and lung function, and they were more likely to survive.



Researchers tested the safety and efficacy of ropinirole in ALS patients in an early-phase clinical trial paired with stem cell research to explore ropinirole's mechanism of action. Credit: Morimoto et al/Cell Stem Cell

The benefits of ropinirole relative to the placebo became increasingly pronounced as the trial progressed. However, placebo group patients who

began taking ropinirole halfway through the trial did not experience these improvements, which suggests that ropinirole treatment may only be useful if treatment is started earlier and administered over a longer duration.

Next, the researchers investigated the mechanisms behind ropinirole's effects and looked for molecular markers of the disease. To do this, they generated induced pluripotent stem cells from the patients' blood and grew these cells into motor neurons in the lab. Compared to healthy motor neurons, they found that motor neurons from ALS patients showed distinct differences in structure, gene expression, and metabolite concentrations, but ropinirole treatment reduced these differences.

Specifically, motor neurons grown from ALS patients had shorter neurites compared to healthy motor neurons, but these axons grew to a more normal length when the cells were treated with ropinirole. The team also identified 29 genes related to cholesterol synthesis that tended to be upregulated in motor neurons from ALS patients, but ropinirole treatment suppressed their gene expressions over time. They also identified lipid peroxide as a good surrogate marker for estimating the effect of ropinirole both in vitro and clinically.

"We found a very striking correlation between a patient's clinical response and the response of their motor neurons in vitro," says Morimoto. "Patients whose motor neurons responded robustly to ropinirole in vitro had a much slower clinical disease progression with ropinirole treatment, while suboptimal responders showed much more rapid disease progression despite taking ropinirole."

The researchers say that this suggests that this method—of growing and testing motor neurons from patient-derived induced pluripotent stem cells—could be used clinically to predict how effective the drug would be for a given patient. It's unclear why some patients are more

responsive to ropinirole than others, but the researchers think that it's probably due to genetic differences that they hope to pinpoint in future studies.

More information: Hideyuki Okano, Ropinirole hydrochloride for amyotrophic lateral sclerosis: a single-center, randomized, double-blind, placebo-controlled phase 1/2a feasibility trial, *Cell Stem Cell* (2023). DOI: 10.1016/j.stem.2023.04.017. www.cell.com/cell-stem-cell/fu … 1934-5909(23)00135-2

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