Stem cells derived from the patient's own cultured cells could provide new therapies for ALS.

DRUG THERAPY

On the treatment trail for ALS

The disease remains incurable but there are signs of hope on the horizon.

BY ANDREW SCOTT

For decades, the neurodegenerative disease amyotrophic lateral sclerosis (ALS) generally came with a description such as 'grim'. Not only were its effects devastating, but also there was no effective drug for it. ALS is still a grim diagnosis, but rays of hope have begun to shine through.

There is currently no cure for the disease, nor even a way to stop its progression. But drugs with the potential to slow it are arriving, and more-adventurous approaches that might eventually effect a cure are showing promise^{1,2}.

The most immediately promising and widely publicized development comes from Japan, where the drug edaravone was developed and approved for treating ALS in 2015. In May 2017 edaravone became the first new drug in more than 20 years to be approved specifically for ALS by the US Food and Drug Administration

(FDA). Edaravone (also known by the brand names Radicava and Radicut) is a small antioxidant molecule that has been used for many years to treat stroke. In 2015, researchers led by Joseph Palumbo, head of translational research and medical science at Mitsubishi Tanabe Pharma Development America in Jersey City, New Jersey, showed that the drug could also significantly slow the progression of symptoms in the early stages of ALS.

Edaravone is not the only new drug on offer. Masitinib, for example, inhibits enzymes involved in inflammation — an attractive target because nerve inflammation is a significant aspect of ALS. "I think masitinib has more promise" than edaravone, says James Bennett, who for many years studied neurodegenerative disorders at Virginia Commonwealth University in Richmond. Developed by Paris-based AB Science, masitinib has proved effective in slowing ALS progression when given in

combination with riluzole, a drug that blocks specific forms of neurotransmission and that has for many years been the only mainstream option offered to most people with ALS. Out of the mainstream, organizations such as ALS Worldwide are investigating the 'off-label' use of drugs that might improve symptoms (see 'Seeking alternative treatments').

Merit Cudkowicz, director of the ALS programme at Massachusetts General Hospital in Boston, also highlights tirasemtiv, a small-molecule drug that activates muscle tissue. She points out that it is the only drug that has been shown to help patients to ALS to breathe, and breathing difficulties are one of the most distressing and ultimately crucial aspects of the disease.

"I am hoping that we are at a new point with ALS, where things are starting to work," says Cudkowicz. One reason for her optimism is the emerging evidence that the effects of some new drugs may be additive, as with masitinib and riluzole. Cudkowicz feels that, if the combined effects of several drugs add up to more than the sum of their parts, there might even be some hope of combination therapies halting the progression of ALS altogether.

HOPE FROM MOLECULAR GENETICS

One difficulty in attempting to cure, or even treat, ALS is that its causes remain unclear (see page S109). Bennett believes that the development of personalized cancer therapies indicates an approach that will eventually work with ALS. "The causes of ALS are likely to be heterogeneous," he says. "So, rather than a single drug for everyone, we are likely to have more-personalized therapies."

The key to this, he suggests, are fast-paced developments in molecular genetics, which are already contributing to understanding and treating cancer. Scientists worldwide are increasingly making routine use of DNA and RNA sequencing to pinpoint the genes and mutations associated with disease. Techniques to switch genes on or off, or even to edit their nucleotide sequences, are also being developed as disease therapies. Cudkowicz agrees that molecular genetics might hold the key to halting or even curing ALS. She is already "very excited" about the possibilities of one approach, called antisense therapy. Early-phase trials of this approach are now under way at several sites that are part of the Northeast ALS Consortium, of which Cudkowicz is a co-founder.

Antisense therapy uses small sections of DNA, RNA or other oligonucleotides that are designed to bind to specific parts of the messenger RNA copies of genes, thus turning off the ability of the targeted gene to produce protein. The aim is to block the production of proteins that are implicated in causing ALS.

The gene target behind Cudkowicz's excitement encodes a protein called superoxide dismutase (SOD). More than 100 mutations in the gene that encodes SOD have

been implicated in various forms of ALS, but they may cause only a small number of cases — about 2% in the trial that Cudkowicz is involved in. She says, however, that this could be an advantage for the patients affected, because it offers a clear, well-defined target to create the kind of personalized therapies that Bennett is looking for.

Several research groups have also identified a protein in brain cells called C9ORF72 as a promising target for antisense therapy. This protein has been implicated as the cause of around 10% of all ALS cases (see page S106). Ionis Pharmaceuticals in Carlsbad, California, is heavily committed to developing antisense therapy for ALS that targets the C9ORF72 gene, and expects to start clinical trials next year.

FIXING GENES AND CELLS

A more adventurous, and possibly more permanent, way to attack the genetic causes of ALS is gene therapy — inserting new copies of genes to replace the faulty ones in affected cells. Adding new genes and getting them to work properly is fraught with challenges — not least that of knowing which genes to add — but ALS is increasingly being viewed as a disease target to aim for. “I am convinced that it is time to make a serious effort to treat ALS using gene therapy,” said James Wilson, director of the Orphan Disease Center at the University of Pennsylvania in Philadelphia, when launching a programme in January to pursue that goal.

Wilson hopes to build on some success in clinical trials that used modified viruses to transfer normal genes to replace the mutated gene in patients with spinal muscular atrophy (SMA). The genes implicated in SMA are different from those involved in ALS, but they affect the same motor neuron cells.

Cells other than the motor neurons directly affected in ALS are also being considered as targets for gene therapy. Modifying genes in the glial cells that surround and support motor neurons might also help to restore motor neuron function. This idea comes from evidence suggesting that, although it is the motor neurons that die in ALS, problems in glial cells may be at least partly to blame.

A second possible long-term fix, which may even develop into a cure, is stem-cell therapy. Several research groups around the world are investigating the possibilities of administering stem cells that could multiply and develop into a variety of cells needed to keep motor neurons alive and functioning. A phase II clinical trial at the Hadassah Medical Center in Jerusalem demonstrated significant inhibition of disease progression in 87% of patients with ALS. Stem cells collected from the patients’ own bone marrow were cultured and stimulated into producing nerve-cell growth factors, then transplanted back into the patients.

At the Mayo Clinic in Rochester, Minnesota, a team led by neurologists Anthony Windebank and Nathan Staff is exploring the stem-cell

OFF-LABEL DRUGS

Seeking alternative treatments

Stephen Byer consulting with a patient.

Drug development is a long, slow process. In the meantime, many patients and their relatives and care-givers are keen to explore any avenues for help — even if the drugs concerned may not be approved for ALS in their own countries. As is the case in many incurable diseases, this desperation opens the door to many offerings of dubious merit. But one organization, ALS Worldwide, is providing help on the alternative fringe of formal clinical practice, while working with qualified medical collaborators.

The organization was established in 2008 by the parents of a young American man who died of ALS. In addition to providing guidance and support, they help to provide drugs, including medicines that are ‘off-label’ in at least some countries but for which they claim there is some evidence of benefit in ALS. These include methylcobalamin, glutathione, atropine sulfate, and a combination of dextromethorphan and quinidine marketed as Nuedexta.

“We do feel the freedom to suggest off-label use of existing medicines to try to bring symptomatic relief,” says Stephen Byer, founder and co-executive director of ALS Worldwide. He adds that some medications that the organization initially recommended when they were outside mainstream consideration are now widely prescribed or endorsed by the medical community for ALS.

Neurologist and ALS researcher Vincenzo Silani at the University of Milan Medical School in Italy is supportive of ALS Worldwide, but adds a note of caution: “They perform a useful function that can be very helpful for most of the patients,” he says, “but the medical community would not endorse every drug they recommend if not adequately tested.”

Despite the national variations in drug use that ALS Worldwide tries to bridge, there are no credible claims of drug ‘cures’ yet, merely varying reports of benefits ranging from symptomatic relief to a slowing of disease progression. **A.S.**

route using cells called mesenchymal stromal cells, which they have isolated from adipose tissue. These cells secrete small proteins that support the survival of motor neurons. They also support the immune system, which may be relevant, given a role for the immune system and its associated inflammation in the complex web of ALS causation. The Mayo Clinic researchers have completed a phase I clinical trial to confirm safety and acceptably low side effects. The results are sufficiently promising to allow phase II trials to begin.

Gene therapy and stem-cell therapy can be combined by adding selected genes to the stem cells before their administration. Cedars-Sinai Medical Center in Los Angeles,

California, received FDA approval to begin a phase I trial in late 2016.

The incurable status of ALS is unquestionably being attacked vigorously on many fronts. Cudkowicz thinks that the chances of at least one or two of the new approaches making it into clinical practice are high. Those living with the disease will be sharing her hopes and watching progress intently. ■

Andrew Scott is a science writer in Perth, UK.

1. ALS Association Research News Archive. Available at www.alsa.org/research/research-news
2. ENCALs (European Network to Cure ALS) 2017. Abstracts available at https://www.encals.eu/wp-content/uploads/2016/12/ENCALS_2017_Book_of_abstracts_2.pdf