TRANSLATING BASIC RESEARCH INTO MEDICAL ADVANCES

Advances in induced pluripotent stem cell (iPSC) technology could drive the development of **NEW OPTIONS FOR TREATING INTRACTABLE NEUROLOGICAL DISEASES.**

Prior to 2006, the scientific consensus was that cell differentiation was a one-way street: once mature, cells could not be returned to their initial embryonic-like state, having lost the potential to develop into any kind of cell.

That all changed when Shinya Yamanaka of Kyoto University, in Japan, identified just four transcription factors that could reprogram mature cells back into a pluripotent state, a ground-breaking discovery that won him the 2012 Nobel Prize in Physiology or Medicine. Since then, scientists the world over have been seeking to use induced pluripotent stem cells (iPSC) in applications ranging from disease modelling to drug development and regenerative medicine.

For disease modelling, researchers can reprogram cells into a pluripotent state and then differentiate them to generate 'disease-in-a-dish' models. Such models are not only useful for understanding the underlying causes of disease and identifying new drug targets, but also for drug screening.

SCREEN DRUG CANDIDATES

Patient-derived iPSC models are being used to screen drug candidates for efficacy and toxicity at the earliest stages of drug development, potentially eliminating the need for animal models and increasing the likelihood of success in clinical trials. Furthermore, iPSC-derived cells can be transplanted to replace damaged or malfunctioning tissue, holding great promise for the treatment of injuries and degenerative diseases.

To translate some of the cutting-edge research on iPSCs carried out at Keio University, Tokyo, Japan, into treatments for neural diseases, Komei Fukushima, Hideyuki Okano, and Masaya Nakamura, founded spinoff company K Pharma Inc. in 2016.

"I have known Professor Okano for more than 20 years," says Fukushima, K Pharma's CEO who has more than 25 years' experience in the pharmaceutical industry. "Our shared ambition to deliver the benefits of iPSC research to society drives our efforts to develop treatments aimed at restoring neuronal function."

Together with researchers at Keio University, the team at K Pharma was a world-leader in terms of initiating clinical trials for subacute spinal cord injury[1] using iPSCs and to demonstrate the clinical efficacy of a drug identified in an iPSC-based drug screening programme for amyotrophic lateral sclerosis (ALS)[2]. The company has 12 product candidates in its pipeline for a range of neurological and neurodegenerative diseases, including cerebral hemorrhage, frontotemporal dementia, and Huntington's disease.

DRUG DISCOVERY FOR ALS

Amyotrophic lateral sclerosis is a devastating neurodegenerative disease that causes progressive muscle paralysis and death within three to five years of onset. Approved drugs for ALS only modestly slow disease progression in a limited population of patients.

ALS research has largely focused on inherited or familial ALS, which only accounts for around 10% of cases. In most cases, the exact molecular pathway causing motor neuron degeneration is unknown. As with other neurodegenerative diseases, various genetic and environmental factors have been implicated in triggering pathogenesis.

K Pharma, also based in Tokyo, has developed a proprietary method to produce iPSCs from blood cells from healthy individuals and patients, and differentiate them into motor neurons. "Our ALS patient-derived motor neurons faithfully mimic features of the disease that are associated with both familial and sporadic ALS, such as excitatory cell death and axonal degeneration," says Okano, Chief Science Officer at K Pharma and Vice President of the International Society for Stem Cell Research.

"OUR ALS PATIENT-DERIVED MOTOR NEURONS FAITHFULLY MIMIC FEATURES OF THE DISEASE."

The company is using these cells to screen for candidate drug compounds in existing drug libraries. Drug repurposing is an attractive approach for pharmaceutical companies as it greatly reduces drug development time and costs.

In 2018, through *in vitro* cellular models, Okano and colleagues found that a dopamine D2 receptor agonist approved for the treatment of Parkinson's disease and restless leg syndrome had protective effects in most familial and sporadic ALS models , suggesting that it could be effective in a wide range of ALS cases[2].

"Our drug candidate suppresses the effects of disease in cells through dopamine-receptor dependent mechanisms, involving potassium channel activation and autophagy, as well as D2-independent mechanisms, which reduce reactive oxygen species," Okano adds.

K Pharma has conducted a Phase 1/2a trial of the drug in 20 ALS patients[3] and now, in partnership with Alfresa Pharma Corporation, will be proceeding with a Phase 3 trial in which the effectiveness of different drug doses will be examined in more patients.

The company's drug screening programme using iPSC-derived cells has also identified candidate compounds for frontotemporal dementia and Huntington's disease. "We are talking with Japan's regulatory agency, the Pharmaceuticals and Medical Devices Agency, about starting clinical trials with these agents soon," Okano says.

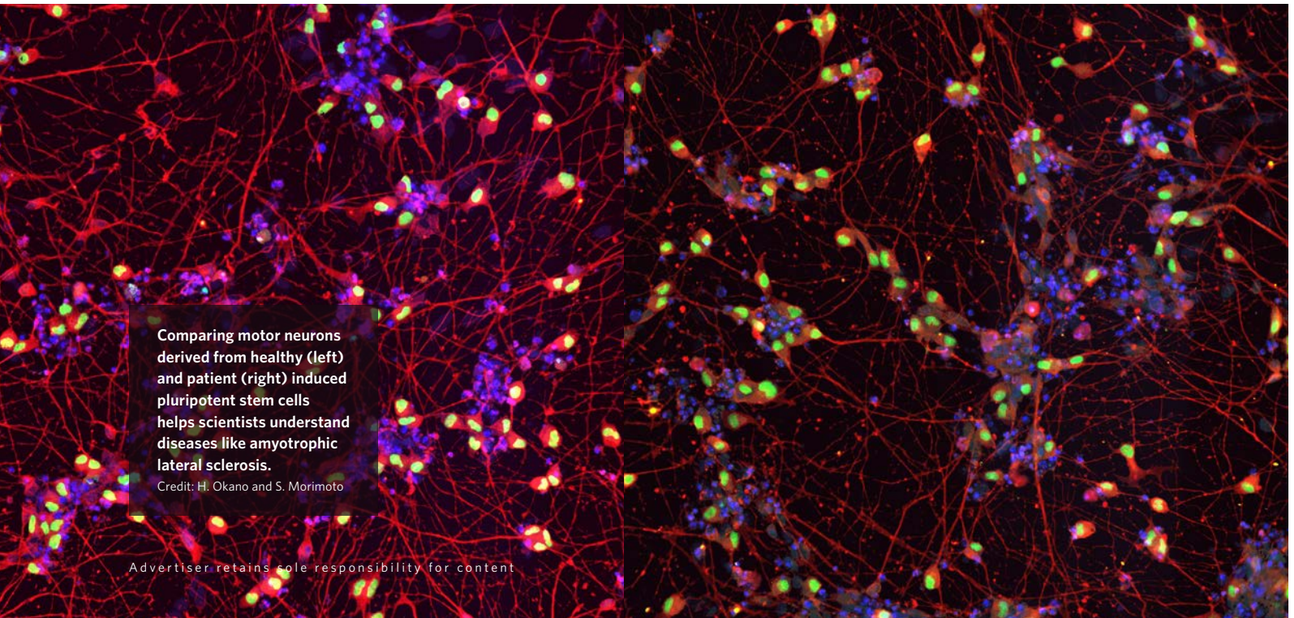
SPINAL CORD INJURIES

In addition to drug screening, iPSCs may be used to produce cells that can be transplanted into sites of injury or degeneration. K Pharma is focusing on spinal cord injury, a life-changing neurological condition that is estimated to affect more than 20 million people globally[4]. Because of the reduced capacity of mature neurons in the spinal cord to grow, patients with severe spinal cord injury suffer perpetual loss in sensation and mobility. To date, no therapeutic approach has been established for regenerating injured spinal cord neurons.

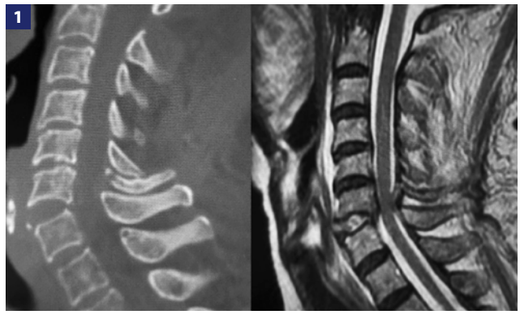
Okano and colleagues have shown in animal models of spinal cord injury that transplanted human iPSC-derived neural stem cells (NSC) can steadily grow in the injured area and promote functional recovery, without causing tumours[5]. In December 2021, Keio University started its first-in-human clinical study with human iPSC-derived NSC harvested from healthy donors and established by the iPSC Stock Project at Kyoto University's Center for iPS Cell Research and Application (CiRA). The trial results are expected to be announced in 2024.

As Fukushima explains, the clinical grade human iPSC-derived NSC have been extensively characterized and are injected into subjects two to four weeks after injury, in what is called the subacute phase. "In animal models, we have seen that the maximum therapeutic effect is achieved at the subacute injury stage when inflammation has started to die down, and there is less risk of immune rejection," he says.

K Pharma is also exploring the possibility of using human iPSC-derived NSC for the treatment of traumatic brain injury, chronic spinal cord injury and common disorders of ageing, such as stroke and Alzheimer's disease. "We are interested in partnering with companies outside Japan to deliver novel medicine and regenerative medical products to patients with currently uncurable neurological conditions all around the world," Fukushima concludes. ■



Comparing motor neurons derived from healthy (left) and patient (right) induced pluripotent stem cells helps scientists understand diseases like amyotrophic lateral sclerosis.
Credit: H. Okano and S. Morimoto



▲ **1. Scientists hope that induced pluripotent stem cells could one day be used to treat spinal cord injury as seen in this CT (left) and MRI (right) scan.** Credit: N. Nagoshi and M. Ozaki
2. Masaya Nakamura, Komei Fukushima, and Hideyuki Okano (left to right) ringing the bell at the Japanese Stock Exchange to celebrate the listing of K Pharma on 17 October 2023.

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