International Stem Cell Corporation

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A new approach to Parkinson's disease

Regenerative medicine company International Stem Cell Corporation (ISCO) leads the way in developing new treatments for Parkinson's disease and other clinical conditions using a unique stem cell approach.

California-based ISCO is a clinical-stage biotechnology company developing novel stem cell–based therapies, with revenues of over $7 million in 2014 from its two subsidiary businesses: Lifeline Cell Technology, a leading manufacturer of purified primary human cells and optimized reagents for cell culture, and Lifeline Skin Care, which develops, manufactures and markets dermatological products containing stem cell extracts. The company's therapeutic pipeline includes programs in neurology, ophthalmology and metabolic liver diseases (**Fig. 1**).

ISCO's proprietary stem cell platform is based on parthenogenesis and produces pluripotent stem cells from unfertilized human eggs, a method the company has patented in the United States, Japan and the European Union (EU). Importantly, in the EU, where embryonic stem cells (ESCs) are unpatentable, the company has successfully prosecuted its patents, thereby gaining a significant competitive advantage.

Against the backdrop of a cell-therapy renaissance across multiple clinical areas, ISCO provides unique partnering opportunities from preclinical to later stages of development.

Product	Indication	Preclinical	IND track	Phase 1/2a	Phase 2b/3
Neural stem cells	*Parkinson's disease*	→	→	→	
	Ischemic stroke	→	→		
CytoHep	*Metabolic liver diseases*	→	→		
RPE cells	*Retinal blindness*	→	→		
CytoCor	*Corneal blindness*	→	→		

Figure 1: ISCO's pipeline covers a range of therapeutic conditions. IND, investigational new drug.

Tackling Parkinson's disease

Recently, ISCO began a phase 1/2a clinical study in Parkinson's disease (PD). The trial breaks new ground: despite years of research into cell therapy for PD, this is the first time cells derived from a pluripotent stem cell source have been transplanted into people with the disease.

PD is a progressive neurodegenerative disorder resulting from a gradual loss of the neurons responsible for producing dopamine, and it is characterized by symptoms including tremors at rest, rigidity and impaired movement. According to the Parkinson's Disease Foundation, an estimated 7 to 10 million people worldwide live with PD, with as many as 1 million of those in the United States alone—more than the combined total of people diagnosed with multiple sclerosis, muscular dystrophy and Lou Gehrig's disease.

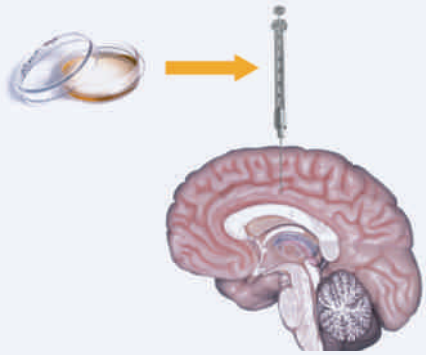

Figure 2: ISCO's PD treatment paradigm is unique in two regards: the neural stem cells are created from human parthenogenetic stem cells, and the cells are transplanted in three locations of the patient's brain—the *substantia nigra*, the putamen and the caudate.

ISCO's PD program builds on earlier clinical work showing that transplanted fetal cells can be effective in treating the symptoms of PD. Indeed, transplanted cells have been shown to persist and provide symptomatic relief for more than 18 years[1], offering the tantalizing possibility that, if the disease is caught early enough, a cell transplant may effectively 'cure' a patient (**Fig. 2**).

One of the major problems with these earlier trials was the availability and supply of fetal cells for transplant. ISCO has solved this problem by using its proprietary stem cell platform to generate stem cell–derived human parthenogenetic neural stem cells (hpNSCs). The company has shown in its preclinical research that neural stem cells—self-renewing, multipotent cells that have the ability to differentiate into dopaminergic neurons and express brain-protecting neurotrophic factors—are a viable alternative to fetal cells and therefore offer a new possibility for the treatment of PD and other neurological disorders.

ISCO has assembled a significant body of preclinical data on hpNSCs and has evaluated the cells' safety and tolerability in different animal species, including non-human primates[2]. Data presented at the annual meeting of the Society for Neuroscience in November 2014 showed that the company's hpNSCs have a clean safety profile, with no evidence of teratoma formation or ectopic tissue up to 12 months after transplant. Proof-of-concept studies, in which hpNSCs were transplanted into animals with induced PD symptoms, validated the postulated mechanism of action. Data showed that the cells migrated to the damaged area of the brain, created dopamine fibers and increased dopamine levels, leading to improved motor function. Evidence was also found to support the hypothesis that the transplanted cells protect the native neuron population by expressing neuroprotective trophic factors.

The phase 1/2a clinical trial is ongoing under the direction of Andrew Evans, director of the Movement Disorders Program at the Royal Melbourne Hospital in Australia. The trial is a single-arm, dose-escalating 12-month study designed to evaluate the safety and efficacy of ISCO's clinical product in 12 subjects with PD. Results are anticipated in 2016.

The platform's edge

ISCO's proprietary stem cell technology uses human parthenogenesis to produce stem cells (hpSCs) that are similar to ESCs: they have the potential to differentiate into all the specialized cells of the human body and, like ESCs, have the capacity to divide an almost unlimited number of times, providing an essentially inexhaustible supply of cells for transplantation. Unlike ESCs, ISCO's hpSCs do not require the destruction of human embryos and, importantly, unlike other allogeneic cell therapies, can be made in a way that may obviate the need for immune suppression in patients receiving stem cell treatments.

ISCO collaborates with researchers at institutions including the Scripps Research Institute, Sanford-Burnham Stem Cell Research Center and the University of California, San Diego.

With its novel stem cell platform having a clear intellectual property advantage in the EU and first results for its phase 1/2a clinical trial in PD expected in 2016, ISCO is now beginning a systematic outreach program to find licensees or co-development partners.

References

1. Kefalopoulou, Z. *et al*. *JAMA Neurol*. **71**, 83–87 (2014).
2. Gonzalez, R. *et al*. *Cell Transplant*. **24**, 681–690 (2015).

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