Editorial

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Regenerative Medicine

Hope for regenerative treatments: toward safe transplantation of human pluripotent stem-cell-based therapies

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Keywords: cell-based therapies • clinical trials • embryonic stem cells • induced pluripotent stem cells • regenerative medicine

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Safety first

Ever since their discovery and isolation in 1998, human embryonic stem cells (hESCs) have been touted as the future of regenerative medicine, with a heavy burden of promise and expectation placed upon them to deliver an unprecedented number of cell-based therapies. In theory, their ability to undergo unlimited self-renewal and to generate any cell type in the body makes pluripotent stem cells (PSCs) such as human embryonic stem cells and induced pluripotent stem cells (iPSCs) an ideal starting material for treating a wide variety of diseases with cell-based therapies. Yet, in reality, potentially serious risks including the propensity to form tumors or trigger an immune response, technical hurdles in directing their in vitro differentiation and ethical concerns over the destruction of embryos have thwarted efforts to bring PSC-based therapies to the clinic. After decades of work, strict regulations surrounding the use of PSC-based therapies have finally culminated in their careful and deliberate application in a handful of new clinical trials, which are helping allay fears over their safe use. Below, we discuss the status of PSC-based therapies in regenerative medicine, including safety considerations, currently approved clinical trials and a look at what is on the horizon.

Given the scarcity of data on the effects of PSC based therapies in humans, safety is paramount during the development of any such new product. Preclinical animal studies should examine not only efficacy but also biodistribution, toxicity and tumorigenicity, preferably using the route of administration and dosing equivalent to those intended in humans. In the USA, PSC-derived cellular therapies are controlled under the US FDA's Code of Federal Regulations Title 21, part 1271 (21 CFR 1271) which is in place 'to prevent the introduction, transmission and spread of communicable diseases by [human cells, tissues and cellular and tissue-based products] HCT/Ps'. Several related guidance documents regarding cell source, preclinical animal studies and manufacturing recommendations have been issued by the FDA [1,2] yet, there are no absolute set of requirements to dictate what is necessary to gain approval for a PSC-based investigational new drug (IND). Each new application is considered by the FDA on a case by case basis to determine if it is reasonably safe for testing in humans. For the immediate future, PSC-based products that can be locally contained, removed or otherwise have a low risk of immunogenicity are less risky and thus will likely have an easier time gaining approval than those involving systemic injection.

'Eye' will be the first to benefit

There are now 11 approved trials involving PSC-based therapies on the clinical trials website, [3], nine for ocular indications (eight from hESCs, one from iPSCs), one for diabetes, one for severe heart failure. This is not surprising since, compared with other organs and tissues, the eye is particularly well suited for first-in-man cellular therapies. It is a relatively immunoprivileged site, allowing non-HLA matched cells to be injected into

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patients with reduced risk of immune rejection and providing an isolated environment for containment of injected cells, thus limiting the potential area in which cells may travel or form tumors. Ocata Therapeutics (formerly Advanced Cell Technology, Marlborough, MA, USA) and collaborators began the first PSC eye-based trials in 2011, to test safety and tolerability of hESC-derived retinal pigmented epithelium (RPE) for dry age-related macular degeneration (AMD) and the related juvenile Stargardt's disease. Preliminary short-term data for the first two patients treated in the US RPE trial suggested that subretinal injections of hESC-RPE cells are well-tolerated and safe [4]. Medium to long-term safety data for 18 patients, nine with Stargardt's and nine with dry AMD (with an average follow-up period of 22 months) confirmed that the implanted hESC-RPE persist as a graft and do not pose any serious adverse ocular or systemic effects [5]. Despite being only a Phase I/II trial with end points of safety and tolerability, data suggested that the hESC-based therapy may be helping restore visual acuity and improve vision-associated quality-of-life indices.

> "...the human embryonic stem-cell-based therapy may be helping restore visual acuity and improve vision-associated quality-of-life indices."

Similar hESC-RPE clinical trials are also being carried out in Europe (UK) for Stargardt's disease, and in Asia (South Korea) through an Ocata licensing partnership with CHA Bio & Diostech for both dry AMD and Stargardt's. hESC-RPE therapy has also recently been cleared for a new US-based clinical trial for myopic macular degeneration. Not to be outdone by a small biotechnology company such as Ocata, London-based pharmaceutical giant, Pfizer has carved out a niche for itself in the emerging regenerative medicine eye disease market by developing a membrane-immobilized hESC-RPE monolayer as a therapeutic treatment for the wet or exudative form of AMD. Their trial will be conducted in the United Kingdom although it is not yet open for enrollment. Lastly, Cell Cure Neurosciences (Jerusalem) was also granted approval in late 2014 to begin a hESC-RPE clinical trial; they will test their cell suspension product, Opregen for dry AMD.

An 'i' for an 'eye'

The advent and optimization of iPSC technology has provided an ethically sound alternative to hESCs as a starting cell source. Adding a new twist to PSC-based RPE therapies, researchers at the RIKEN institute in Japan became the first to test an iPSC-based therapy in humans when they initiated wet AMD clinical trials involving iPSC-derived RPE sheets in September 2014 [6]. iPSC technology, initially developed in Japan by Yamanaka *et al.*, has come a long way since its 2006 inception [7]. Improvements in the safety and efficiency of reprogramming methods used to generate iPSCs have transformed them into a strong competitor of hESCs. However unlike hESCs, an abundance of starting material is available for their derivation, they are ethically noncontroversial and can easily be used to generate banks of HLA-matched or even personalized cellular therapeutics, thus reducing concerns over potential immunogenicity. These factors make them desirable as a source of PSCs for regenerative medicine endeavors. For now, however, the world will continue to watch the progress of both the hESC- and iPSC-RPE clinical trials very closely to see the long-term safety and efficacy of these therapies.

Making progress in big indications: diabetes & more

Potentially powerful (and lucrative) uses for hESCs and iPSCs, including the treatment of widespread indications such as diabetes and heart disease, have been in development for many years. Excitingly, the first clinical trial for each of these uses has recently begun and is actively recruiting. In both instances, the PSC-based product is being tethered to or embedded in a solid support, which assists with the cell-based product's function but is also an important safety feature for these first-in-man trials. Viacyte, Inc. (San Diego, CA, USA) [8]) is testing a subcutaneously implanted device called VC-01 for Type 1 diabetes. It consists of their hESC-derived pancreatic endoderm cells (termed PEC-01) encapsulated in a biologically-compatible medical device. Encapsulation prevents direct exposure of the PEC-01 cells to cells of the immune system, thus preventing the provocation of an immune response. Moreover, the fact that the device is implanted under the skin means that it can easily be removed if serious adverse events are noted. Previous work shows that PEC-01 cells can differentiate into, among other cell types, glucose-sensing, insulin-producing cells similar to pancreatic β cells [9] and can regulate blood glucose levels after transplantation into mice [10,11]. In addition to this trial, a new study by Doug Melton's group at Harvard Medical School shows that functional insulin-producing cells, with all the characteristics of adult human pancreatic β cells, can now be produced from hESCs in a manner amenable to large scale manufacturing [12]. Similar to Viacyte's device, Melton *et al.* are now trying to develop a way to encapsulate their cells so that they can persist in a diabetic patient without immune rejection [13].

Targeting the biggest killer of all

Heart disease is the leading cause of death around the world [14] and people afflicted with it may soon start benefiting from PSC-based therapies. Philippe Menasche's group at the University of Paris is testing their CD15$^+$ Isl-1$^+$ hESC-derived cardiac progenitors in a clinical trial for patients with severe heart failure. The hESC-derived progenitors are embedded in a fibrin gel patch which is then engrafted onto infarcted epicardium in attempts to improve cardiac function [3]. These progenitors have been extensively studied in both rodent and nonhuman primate models of myocardial infarction where they improved left ventricular end systolic volume [15,16]. Interestingly, while cardiac function improved, the engrafted cells disappeared by 4 months post surgery, suggesting that the mechanism for their therapeutic effect is induction of endogenous repair mechanisms or growth and differentiation of endogenous progenitors [16]. Other scientists are taking an alternative approach and testing mature cardiomyocytes differentiated from hESCs for therapeutic effects in myocardial infarction. A recent study in a nonhuman primate model showed that engraftment of 1 billion hESC-derived cardiomyocytes resulted in large areas of healthy cardiac muscle that could conduct electromechanical signals within the infarcted area [17]. The study also noted the appearance of nonfatal arrhythmias though, suggesting more work needs to be done to improve the safety of the therapy before it can be tested in human clinical trials.

PSC-based therapies for neurological diseases: Parkinson's leads the way

Other substantial indications being targeted by PSC-based therapies include neurological conditions such as Parkinson's disease (PD), where degeneration of midbrain dopaminergic (DA) neurons are one of the causative agents leading to progressive motor impairment. A recent article by Malin Parmar's group shows that hESC-derived DA neurons transplanted into a rat model of PD can survive long-term and innervate appropriate regions of the mid to forebrain. The data suggests their functional engraftment rivals that of fetal tissue-derived neurons, which have been safely used in humans, albeit with variable success [18]. Another 2014 study led by Jun Takahashi, demonstrated that *in vitro*-purified iPSC-DA progenitors differentiated into mature DA neurons and rescued motor function upon injection into a rat model of PD [19]. Takahashi's group has performed safety studies in nonhuman primates, using autologous iPSC-derived therapies, and has asserted they plan to test an autologous iPSC-based PD therapy in human clinical trials within the next 1–2 years [20]. The precedent for clinical use of iPSC-derived products has been established in Japan and investment in technology may also help bring an iPSC-based therapy for spinal cord injuries to clinical trials within the next few years as Shinya Yamanaka is working with Keio University's Hideo Okano toward this goal [21].

With various clinical trials underway and new trials on the horizon, pluripotent stem cell based therapies are beginning to flourish – even under the strict regulations imposed to ensure their safe application – and may just live up to the tremendous expectations placed upon them decades ago.

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Financial & competing interests disclosure

EA Kimbrel and R Lanza are both employees of Ocata Therapeutics, formerly known as Advanced Cell Technology, a biotechnology company focused on stem-cell-based therapeutics and regenerative ophthalmology. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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