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In Focus

New Models for Therapeutic Innovation from Japan

Peter Karagiannis [a,*], Atsushi Onodera [a], Shinya Yamanaka [a,b,*]

[a] Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan
[b] Gladstone Institute of Cardiovascular Disease, San Francisco, CA, USA

Medical innovation has an extraordinary attrition rate. More than 95% of drug candidates fail to receive final approval for patient care, and to reach market the average drug requires a dozen years of research and development at a cost in the billions of dollars (Giri and Bader, 2015). Medical companies are responding by seeking strategies that lower these costs, including a reluctance to invest in less profitable medications, such as those for rare or complex diseases.

One reason costs remain stubbornly high is the dependence on animal models. For many diseases, animal models are the only option, because human samples are difficult to acquire pre-mortem. Even when human cells are available, they often express phenotypes of the disease at late stage. In the case of Parkinson's disease, for example, it has been estimated that approximately 50% of dopaminergic neurons are already lost when patients begin showing symptoms (Bezard et al., 2001). Most experimental therapies tested on human cells at this stage of the disease are unlikely to recover the lost cells, which is why many Parkinson's patients still await effective treatments.

Induced pluripotent stem cells (iPSCs) may provide an alternative model for cheaper and faster drug discovery. Human iPSCs, which were first reported in 2007, describe somatic cells that have been reprogrammed to the pluripotent state from which they can be differentiated into three germ layers (Takahashi et al., 2007). iPSCs revolutionized our understanding of cell identity and revealed the epigenetic mechanism determining this identity. From a medical perspective, iPSCs also launched research into regenerative medicine that had been hamstrung by legislative limitations on the use of embryonic stem cells (ESCs). To date, there exists only one case study of iPSC-based therapy for human patients. In 2014, researchers in Japan transplanted autologous iPSC-derived retinal cells into the eye of a patient suffering from age-related macular degeneration (AMD). Observation one year later showed the transplanted sheet survived well without immune response or adverse proliferation (Mandai et al., 2017). This study was done conservatively, as the same operation on a second patient was cancelled when some irregularities were found in the iPSC clones. Because there is no international consensus on the criteria of safe iPSCs, the authors chose prudence. Comparatively, another article published the same time reported disastrous results for AMD therapy using autologous adipose stem cells (Kuriyan et al., 2017). In the latter case, the patients saw rapid loss of vision and needed emergency care. In the case of the iPSC-based treatment, the vision ceased to degenerate, and the patient is satisfied with the outcome. Other iPSC-based clinical researches, such as one for Parkinson's disease, are expected to commence before 2020 in Japan.

The creation of patient iPSCs suggests that as a technology, iPSCs could surpass ESCs in medical applications. Patient iPSCs may not always be advantageous for regenerative medicine, because they preserve the genome including all mutations that associate with the disease. For the very same reason, however, they could serve as in vitro human models for the study of disease mechanisms and drug discovery, significantly reducing costs. Like regenerative medicine, there are few examples of drug discovery directly linked to iPSCs. Nevertheless, iPSCs are already the basis for one clinical study of an experimental drug to treat amyotrophic lateral sclerosis that did not rely on mouse models (Mcneish et al., 2015). It should be noted, however, that this example is an exception, and that iPSC models should be assumed as complements and not substitutes for animal models.

Another way in which iPSCs could reduce costs is by stratifying patients into subgroups that are positive and negative responders to a treatment. Kawasaki disease is an inflammatory disease that primarily targets arterial endothelial cells. Treatment with high-dose intravenous immunoglobulin significantly mitigates coronary-related disorders, but a percentage of patients do not respond to this treatment. Recently, researchers used patient iPSCs to find a new biomarker for the identification of non-responders. Endothelial cells induced from Kawasaki patient iPSCs showed that non-responders tended to express more *CXCL12*, a potent chemoattractant for several immune cells (Ikeda et al., 2016). This identification would recognize the necessity of alternative treatments, which would save both cost and precious time.

Nations have taken notice and responded with several new policies intended to stimulate collaboration between academia and industry for iPSC clinical translation. The United States implemented the 21st Century Cures Act in 2016 with the intent of expediting the development and review of regenerative medicine. One year earlier, Japan established the Japan Agency for Medical Research and Development (AMED). AMED consolidates the budgets of several ministries in which medical research was only one portfolio of many (Azuma and Yamanaka, 2016). One of

* Corresponding authors.
E-mail addresses: peter@cira.kyoto-u.ac.jp (P. Karagiannis), yamanaka@cira.kyoto-u.ac.jp (S. Yamanaka).

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the major initiatives at AMED is the creation of iPS cell stocks. The Center for iPS Cell Research and Application (CiRA) at Kyoto University is currently contributing to two stocks. The first involves the creation of clinical-grade iPS cells. These cells are distributed to partnering medical centers that differentiate them into specific cell types for therapies and are intended primarily for the innovation of regenerative medicines. Complementing this work is a patient iPS cell stock that provides cells for disease modeling, drug discovery and toxicity assays.

Besides drug discovery, iPSCs could be an ideal model for drug repurposing. It has been estimated that drug repurposing can take only one third the time and cost of drug discovery (Nosengo, 2016). In 2014, the first proof-of-concept using iPSCs for drug repurposing was reported (Yamashita et al., 2014). Here, scientists prepared iPSC-differentiated chondrocytes from skeletal dysplasia patients and found that statin could rescue cell development and promote bone growth.

Building on these discoveries, a new partnership between CiRA and Takeda Pharmaceuticals known as T-CiRA was commenced at the end of 2015 and brings together the pharmaceutical expertise at Takeda with the expertise of academic researchers like those at CiRA to translate iPSCs to clinical application. The partnership is distinct from other biomedical collaborations between academia and industry, both in its financial scale and structure. The project is completely funded by Takeda, which is investing 20 billion yen (approximately $180 million USD) for research along with another 12 billion yen for infrastructure. This amount is intended to remove the need for venture capital, with the goal of reducing cost of the translation and sensitivity to investor capriciousness. The amount is also one reason why T-CiRA is secure for at least ten years, whereas most academic-industry collaborations in Japan rarely exceed three-year commitments. Accordingly, there are fundamental differences between the organization at T-CiRA and other academy-industry partnerships that are hoped to become a model for future translation of academic innovations. First is that all labs are located on Takeda property. Normally, industry representatives will work at the academic lab during the collaboration, but at T-CiRA, all members will be based at Takeda, which allows more company employees to engage the project. Further, although Takeda completely funds T-CiRA, the leader of each lab holds primary appointment at an academic institution. The T-CiRA staff permanently ensconced at Takeda constitutes a mix of Takeda employees and members of the partnering academic institutes. Because CiRA was the original partner, CiRA faculty members were appointed as the principal investigators (PI) of the first seven T-CiRA laboratories. An eighth lab has since been added and is affiliated with a separate academic institute. It is expected that more institutes will be represented at T-CiRA as the project grows. Second is the division of intellectual property. In principle, all patents are to be shared between the academic institute and Takeda regardless of the inventors' primary affiliation. Third, in response to the creation of AMED and the expertise of its academic partners, T-CiRA aims to expand Takeda's interests to new regenerative medicine and cell therapies, while academic partners will have easy access to many of Takeda's resources such as compound libraries for drug discovery.

At the same time, there is an awareness that the grand size of T-CiRA risks discouraging other potential industry partners from collaborating with T-CiRA's academic partners. For this reason, PIs are maintaining a clear separation between their academic research and T-CiRA research. For example, research done previously by one T-CiRA lab leader that has led to a new mechanism and drug targets for the rare disease fibrodysplasia officans progressiva will be in the exclusive domain of CiRA, since that is where the research was done (Hino et al., 2015). CiRA itself is a critical node in the Japan iPSC network and is already distributing cells from its stocks. T-CiRA is the biggest, but just one of many industry collaborations that CiRA deems necessary for the translation of iPSCs.

Having only begun its second year, T-CiRA is still adapting and is a long way from realizing products for patients. Nevertheless, there is expectation in Japan that this organization will become a model for lowering the cost and time of translating academic innovation to patient care.

Conflict of Interest

Shinya Yamanaka is a scientific advisor of iPS Academia Japan without salary.

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