Editorial

Regenerative Medicine

iPSC in the past decade: the Japanese dominance

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In August 2006, Kazutoshi Takahashi and Shinya Yamanaka published a report describing the reprogramming of somatic cells into pluripotent, embryonic-like cells (induced pluripotent stem cells [iPSC]) and all of us in the stem cell field understood that this heralded the beginning of a new era. The scientific community quickly embraced the technology and a surge of papers from laboratories around the world followed. Stem cell and non-stem-cell scientists were jumping on a bandwagon. However, it was not only the scientific community that saw the potential of the discovery; shortly after the Nobel Prize Committee announced that Yamanaka shared the 2012 Nobel Prize in Medicine or Physiology, the Japanese Government committed more than US$300 million to his research. The interest of the Japanese Government in stem cell technology did not end there. Recently, they changed legislation and eased rules, which sped the approval process for clinical trials; this has made Japan, with its economic power, the world's most desirable place for bringing regenerative medical products to the market.

The availability of iPSC represented a paradigm shift in disease modeling, drug discovery and regenerative medicine and it was no wonder that biotech entrepreneurs also jumped on this bandwagon. In the USA, new companies, backed up with powerful star-studded advisory boards, mushroomed: Fate Therapeutics, Stemgent, iZumi/iPierian, Cellular Dynamics International… But now, this American dominance of the iPSC market is gone. Today, large Japanese corporations, such as Takara, FUJIFILM, Astellas (Mitsubishi), control worldwide commercialization aspects of the iPSC technology.

In the early days, the stem cell community and their entrepreneurs were watching every move of Big Pharma, expecting that the giants would understand and accept the power of iPSC technology and start showering money to cash-starved start-ups. However, conservatism, reluctance and lack of support from Big Pharma left the field open for business (ad)venture. Seeing the opportunity, Japanese corporations took over, injecting the much-needed capital to develop businesses and in a short period, a range and number of the iPSC-related products offered commercially expanded greatly.

The first one to venture to biotechnology was Takara. This company, known for its fermentation technology and the production of beverages (mostly sake), acquired Cellectis AB and now virtually dominates the iPSC market in the Europe.

Although in the last decade a demand for traditional photo-film plummeted and

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leading brand American giant Eastman Kodak, went bankrupt, FUJIFILM has shown unprecedented flexibility for a large corporation, shifting focus to stem cell research and regenerative medicine. Acquisition of Wisconsin-based Cellular Dynamics International made FUJIFILM a powerhouse in the new science market. Recent co-development and commercialization agreements with Australian company, Cynata, which include Cynata's lead iPSC-derived therapeutic mesenchymal stem cell product, CYP-001, is likely to take FUJIFILM even further. Cynata has received approval from the UK Medicines and Healthcare products Regulatory Agency to proceed with its Phase I clinical trial of CYP-001 in patients with steroid-resistant graft-versus-host disease.

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Tokyo Electron Limited, a leading supplier of innovative semiconductor and flat panel display production equipment, has opened a Stem Cell Technology Centre in the UK and is developing a fully automated smart cell factory that can economically and safely produce standardized clinical grade iPSC and iPSC-derived cell products. They are not the only one. Kawasaki Heavy Industries, known as a manufacturer of motorcycles, heavy equipment, aerospace and defense products, developed an automated culture system, AutoCulture® that can automate every step of manual cell culture under current good manufacturing practice grade [1].

The newly introduced policies of the Japanese Government supported clinical application of iPSC-based regenerative therapies [2]. It was not then a surprise that the world's first iPSC-based clinical trial started in Japan. Only a few years ago, California company, Geron, has filed 21,000-page application with US FDA for human embryonic stem cell (hESC)-based clinical trial in spinal cord injury and it took 4 years till the trial was approved [3,4]. The costs for the company were enormous and no wonder that it had to end the trial or face bankruptcy. Since then, the FDA eased the procedure and approvals for subsequent hESC trials. How easy it will be to obtain the approval for the first iPSC-based clinical trial remains to be seen, though with the ongoing clinical trial in Japan and a green light for another one in the UK, the procedure may not take as long as it took for the initial hESC-based trial.

In the early days, iPSC technology captured the public interest with a notion of personalized medicine – every patient in need of the regenerative power of iPSCs, would have his or her own iPSC lines derived, which could then be used to bioengineer any tissue required. However, the first-in-man study with autologous iPSC-derived retinal pigment epithelial cells for therapy of macular degeneration of the retina, led by a Japanese researcher, Masayo Takahashi, from RIKEN Centre for Developmental Biology in Kobe, was halted after unexpected mutations were found in the second patient. So although very appealing and full of promise, the strategy was not sustainable for a number of reasons, including prohibitive costs, timing difficulties and risks linked to mutations accumulated over lifespans. The formation in Kyoto of the first HLA-homozygous iPSC bank for clinical purposes changed the game. The bank is depositing clinical grade iPSC lines homozygous for HLA-A, -B, and -DR haplotypes; these are found in the Japanese population at a high frequency [5]. To avoid mutations acquired and accumulated over lifespans, cord blood and samples from cord blood banks were targeted as a main source of the cells for reprogramming. The macular degeneration trial is restarting, using allogeneic retinal pigment epithelial cells derived from iPSC lines procured from the HLA-homozygous iPSC bank. The first person in the original trial might end up being the only one who will ever receive autologous iPSC-based cellular therapy.

Sooner or later, following the Japanese example, other countries are likely to set up similar iPSC banks, even without the population homogeneity of Japan. However, standards for procurement, banking and release of products from national clinical grade iPSC banks are likely to differ. If regulatory bodies do not show flexibility and act in time, nonharmonized regulations may hinder acceptance of iPSC lines from foreign haplobanks [2].

Advantages and utilization of the iPSC technology in drug discovery and regenerative medicine are quite obvious and have been discussed and described on numerous occasions by many scientists and ethicists. I would like to single out the work of Katsuhiko Hayashi at Fukuoka University. He demonstrated that in a mouse system it is possible to reconstitute the full female germline cycle in a dish using adult fibroblasts as starting material [6]. Fibroblasts were reprogrammed into iPSC lines, which were used to generate *in vitro* fully potent mature oocytes capable of producing offspring. It is only a matter of time till the first mouse will be created from *in vitro* generated gametes. Developing similar culture systems in other species should only be a technicality and we might be able to rewind the process of mammalian extinction. Although only three living northern white rhinoceros (*Ceratotherium*

simum cottoni) are left on earth [7], generation of their iPSC lines has been already reported [8]. One day we may see a herd of iPSC-derived white rhinos roaming the savanna.

Can we, by the same token, recreate a human being? Technically, it should be possible. However, the result would be disappointing [9]. Although the DNA sequence would be a carbon copy of the original cell donor, we humans are not only the product of our genes, but also of environment (including our microbiome), community, society, time and people. Everything around, within and without us, makes us who we are.

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