The uptake and diffusion of innovations: a case of stem cell technology

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Abstract: Recent stem cell-related technologies, human somatic and pluripotent stem cells in particular, have been markedly progressing and being focused for an origin of medical and pharmaceutical innovations. However, many issues still remain to realize accomplishments of basic research and even strategy for technology development has yet to be sufficiently developed. In this report we attempted to extract current issues regarding formation and application of intellectual properties by looking at the state of patent landscape and also tested a successful business development approach through cases studies on two representative Japan-based bio start-up companies. We found limitation of the pro-patent approaches for the embryonic and induced pluripotent stem cell business and confirmed a shift to pro-innovation strategy by acquiring variable means including know-how, tangible asset and external network to protect rights. As per standardization strategy a stepwise model based on internal integrality ahead of external modularity was proposed.

Keywords: Somatic stem cell; embryonic stem cell; induced pluripotent stem cell; regenerative medicine; pharmaceutical; technology management; intellectual property; standardization; biotech company; business modelling.

1 Introduction

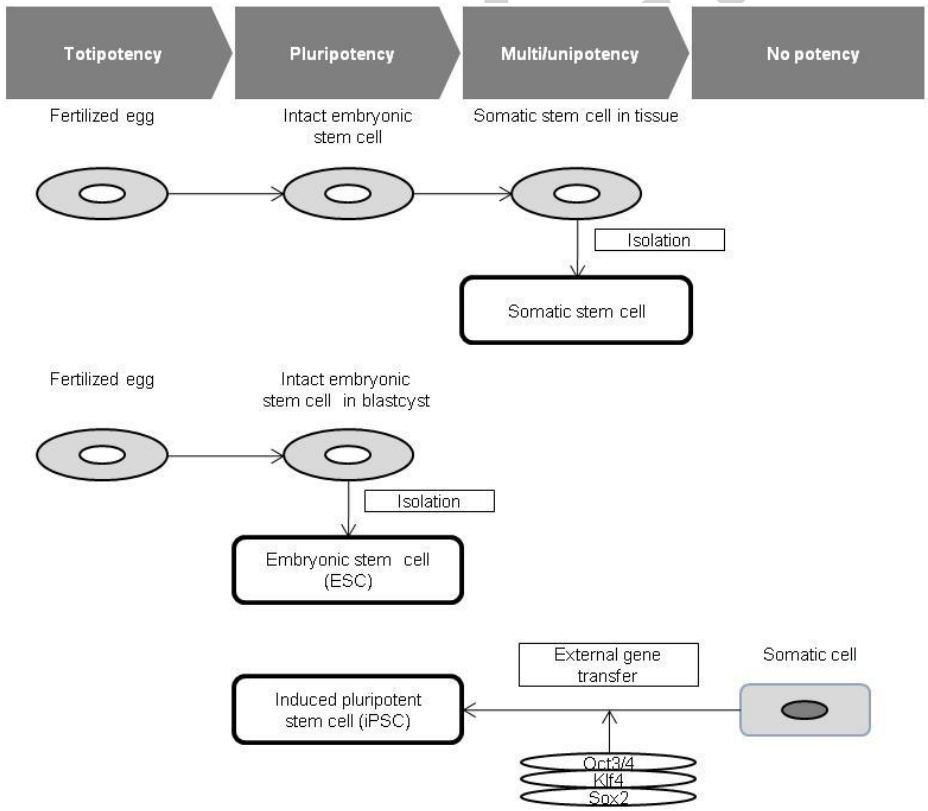
Stem cells have the remarkable potential to develop into many different cell types. By applying its intrinsic function as a part of self repair system they are already useful tools

for modelling of diseases and drug development, and strongly expected to contribute to transplantation medicine. To date various somatic stem cells, the embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSC) were established and have been gathering attention as technology that takes on next-generation medicine [1-8] (figure 1).

ESC and iPSC are artificial stem cell species which can ensure pluripotency i.e. able to differentiate into nearly all cells. For industrial application an FDA approval of a Geron Corporation's clinical trial that employ human ESCs (hESCs) in 2009 were major events in terms of accelerating the application of pluripotent stem cells in medicine. That is to say, because the technological characteristics of utilizing fertilized human embryos have caused ethical and political disputes, technological innovation was not considered to have sufficiently progressed until recently. That is why at this time characteristics and issues of pluripotent stem cell-related technology must be analyzed from the viewpoint of commercialization, and technological innovation and measures to be taken towards realization of regenerative medicine must be examined.

In this report we attempted to extract issues regarding formation and application of intellectual property related to the present technology, and will discuss the importance and approach plans for standardization and practitioner's business modelling.

Figure 1 General Procedure of artificial stem cell generation



2 Research design and approach

To analyze scientific activity linkages we applied the methodology of technology mapping and looked at the state of patent landscape and investigated selected key patents at a claim level.

To analyze business model linkages we nominated three bio start-up companies as representative cases of realizing innovation. One is a drug discovery support business employing human and simian ES/iPSCs, and the other runs a regenerative medicine business using somatic stem cells. The businesses were employed as the cases because both are the first to put products on market in Japan with substantial sales records. For each of these cases we demonstrated technology mapping and classification to understand key technology elements and ways of protection.

3 Research results and findings

3.1 Technology and patent analysis

We adopted the ES and iPSC technology for consideration. Stem cell-related technology is generally classified into several categories: basic technology for generation and maintenance of cell lines, technology for application such as differentiation into specific cell types, analysis on their characteristics, modification of cells for medical purposes and administration to the human body [9].

There was a precedent observation for ESCs that intellectual properties related to the basic technology are exclusively possessed by a few organizations whereas intellectual properties related to application technology are possessed by a large number of organizations of various nationalities, and the coverage of each patent are generally narrow [10].

Our exploration to existing and related patents reconfirmed an uneven distribution (figure 2): 63, 53 and 86 out of the related 219 patents are allocated to the technology for cell generation, maintenance and differentiation, respectively whereas only six patents have been dedicated to further applications. Second, in-depth analysis on selected patents revealed that most of them are process patents with narrow claiming limited to specific cell species and/or ways of cell modification thus supposed to be insufficient to compete to new substitutive technologies.

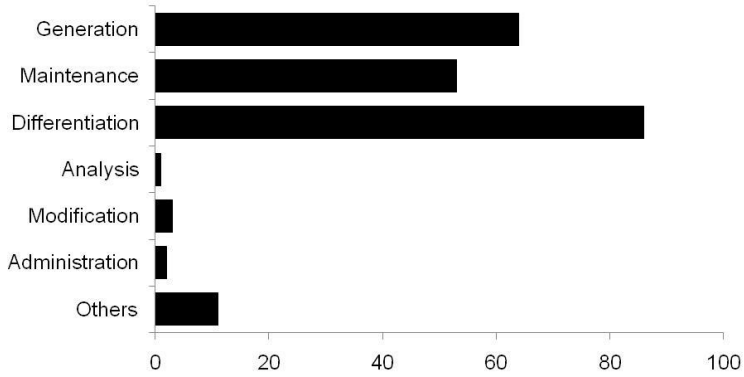
The major patents related to basic technology of ESCs is taken hold by an organization: Wisconsin Alumni Research Foundation (WARF) and this has been debated as a problem on utilization and application of intellectual property of stem cells [10, 11]. Precisely, the fundamental technology for hESCs was established at University of Wisconsin and the patents related to these technologies has been granted to WARF, claiming a product of human and simian ESCs and generation methods of these cells (US Patent 5,843,780 for simian ESCs and its method for isolation, US Patent 6,200,806 for human ESCs and its method for isolation and US Patent 7,029,913 for human ESCs). On July 21, 2005, WARF has further filed an application claiming human pluripotent stem cells (US patent application 20,050,158,854) as a continuing application of said US Patent 6,200,806.

These situations were expected to change by establishment of human iPSCs in 2007, but all the same, intense competition broke out. One of the reasons for this is the fact that

claiming iPSCs as a composition of matter claim is difficult. The characteristics of iPSCs are so difficult to discriminate from formerly established ESCs, both from physical (e.g. surface antigens or gene expression patterns) and functional characteristics that the novelty of iPSCs per se is difficult to prove.

In fact, human iPSCs were filed in a PCT application (WO2007/069666) by the inventor and affiliated organization Kyoto University as a relatively wide range of generation methods and their products. However, in Japan as of today, only the minimal claims of this application, which were the generation methods utilizing *oct4*, *sox2*, *klf4* and *c-myc* genes, were filed as divisional applications in 2008 and patented (Japanese Patent No. 4183742). Moreover, patents related to establishment of iPSCs are filed from multiple organizations, each with different methods of production [12]. The scope of rights of these patents claiming method of production will be relatively narrow because they will be limited to the specific method of production.

Figure 2 Number of patent applications for ES/iPSC technologies (as of April 2010)



3.2 Case study

3.2.1. Drug Discovery Fundamental Technology: ReproCELL Inc.

ReproCELL Inc. is a biotech company founded in February 2003 in Tokyo [13]. ReproCELLwas established with the objective to return to the society the accomplishments of stem cell researches at the Institute for Frontier Medical Sciences, Kyoto University and The Institute of Medical Sciences, The University of Tokyo. Currently, the company's operations include, for example, sales of research reagents for ES/iPSCs, drug discovery screening and toxicity tests using stem cells, and clinical diagnostics services.

As a drug discovery screening support business using stem cells, QT prolongation test service "QTempo" employing ESC-derived cardiomyocyte has been developed. Because QT prolongation phenomenon in the myocardium is correlated with the expression of myocardial toxicity, this is set as a mandatory item in the reviewing of new drugs by regulating authorities such as FDA. Hearts resected from animal individuals or cells isolated therefrom are currently used for QT prolongation tests. However, due to their nature of being derived from individuals, they cannot be stably provided in large amounts, and this has been the cause of the cost and test period remaining high. The company

therefore developed "QTempo" that employs simian ESC-derived cardiomyocytes. Preparation of cell samples in this test system is easier compared to the conventional system, and screening of large amounts of drug candidates can be efficiently carried out. A system employing hES/iPSCs has now been introduced, providing successful construction of a system closer to the therapeutic reality.

Of the technology categories listed in section 3.1, the business process of "QTempo" falls under four categories which are generation, maintenance, differentiation, and analysis (Figure 3).

Focusing on patents, a composition patent is granted to the media for maintenance culture technology, but this is sold as a commercial product and is thus available to anyone without a licence. Currently, there are also proposed multiple means of differentiation induction methods from ESC into cardiomyocytes. It is only that high-throughput in analysis by a unique technology is attempted. In other words, contribution to value by protection of rights by patents is limited.

Rather, the origin of value of "QTempo" can be found in the improvement of quality of measurement by organic linkage and integration of each of the elemental technologies of generation, maintenance, differentiation, and analysis. In fact, in the operation of "QTempo," when the measurement results are unfavorable, it is not so rare that verification will extend not only to improvement of method of analysis, but to maintenance culture and differentiation method, and further to selection or method of establishment of appropriate ESC strains.

Figure 3 Business system of ReproCELL's "QTempo"

	Receiving patient tissue	Generation of pluripotent cell strains	Differentiation into cardiomyocyte	Measurement and analysis of cardio-toxicity
Patent		• Composition of culture medium		• High throughput measurement instrument • Composition of measurement medium
Tangible asset		• Standard protocol • Culture reagents such as medium, detachment solution, and stock solution	• Standard protocol	• Measurement instrument (generic) • Analysis software (generic)
Know-how	• Patient tissue collection and inspection • Biological product safety management	• Characterization of obtained hES/iPSCs • Cell strain selection method • Undifferentiated cell culturing method	• Strain-dependent differentiation method	• Differentiated cell seeding method
External network		• Supply agreement of hESC strains • Licensing agreement with two academic institutions	• Licensing relationship (differentiation method) • Advisory contract with four experts	• Patent / tangible asset licensing agreements from business partners

3.2.2. Regenerative Medicine: Japan Tissue Engineering Co., Ltd.

Japan Tissue Engineering Co., Ltd. (J-TEC) is a biotech company founded in February 1999 in Aichi [14]. The business of J-TEC can be categorized into regenerative medicine business (cultured autologous epidermis, cultured autologous cartilage, and cultured autologous corneal epithelium) and research and development support business (cultured human tissue for research).

Regenerative medicine therapy by cultured autologous epidermis is performed by collecting normal epidermal tissue from a burn patient, separating the contained somatic

stem cells, culturing for three weeks to obtain the epidermal tissue, and grafting this onto the patient. J-TEC's cultured autologous epidermal product acquired manufacturing approval by the Japanese Health, Labour and Welfare Ministry in October 2007 as the first product in Japan that utilizes human cells and tissues. It is currently sold by the commercial name "JACE (J-TEC Autologous Cultured Epidermis)," with indication targeted to severe and extensive burns.

Of the technologies listed in section 3.1, the business process of "JACE" falls under four categories which are generation, differentiation and modification, and administration (Figure 4).

Regarding patents, patents filed thus far include efficient manufacturing methods of "JACE" and peripheral patents, but a product patent does not exist. A basic patent was granted for the method of generating cultured skin sheet but duration of rights has already expired.

Rather, measures are taken for promotion of efficiency of preparation of samples, product manufacture process, or quality assurance process, as well as capability to deal with irregular situation. This has been considered to the origin of strongpoint by the J-TEC management.

Physical assets also contribute to the formation of business value of "JACE." In this business, for each of the collected cells that differ among patients, it is required that the product be generated reproducibly while securing quality and safety. A fully equipped manufacturing facility is therefore a prerequisite condition for approval, and J-TEC has a manufacturing facility in order that is suitable for manufacture of "JACE" and also complying to GMP. Further, in terms of delivery of "JACE" to medical institutions, because the expiration limit after preparation is 56 hours, and temperature management during delivery is essential due to these being living cells, a transportation system appropriate for the product needed to be in place. In this regard as well, J-TEC had handled this by constructing its own distribution network.

Figure 4 Business system of J-TEC's "JACE"

	Receiving patient tissue	Manufacturing of cultured epidermal sheet	Delivery and application of JACE	Regulatory compliance
Patent		• Skin culture method • Production method • Quality inspection method (culture)	• Transportation container & packaging method	
Tangible asset	• Customized made-to-order system	• Production facility and hardware complying to GMP	• Transportation device • Treatment guidelines (for physician and for patient)	• Storage facility of final product (store for at least 30 years) • Monitoring systems after manufacturing and distribution
Know-how	• Tissue inspection • Biological product safety management	• Patient tissue validation technology • Methods for operations of tissue culturing, production and quality inspection	• Quality assurance method • Treatment method	• Regulatory correspondence
External network	• Network with medical institutions capable of appropriate treatment of severe burn cases	• Consulting contract regarding appropriate tissue differentiation and culturing • License for a feeder cell	• In-house distribution network	• Post-marketing surveillance targeting all cases during reexamination period (seven years)

4 Practical implications

4.1 Limitation of a simple pro-patent approach

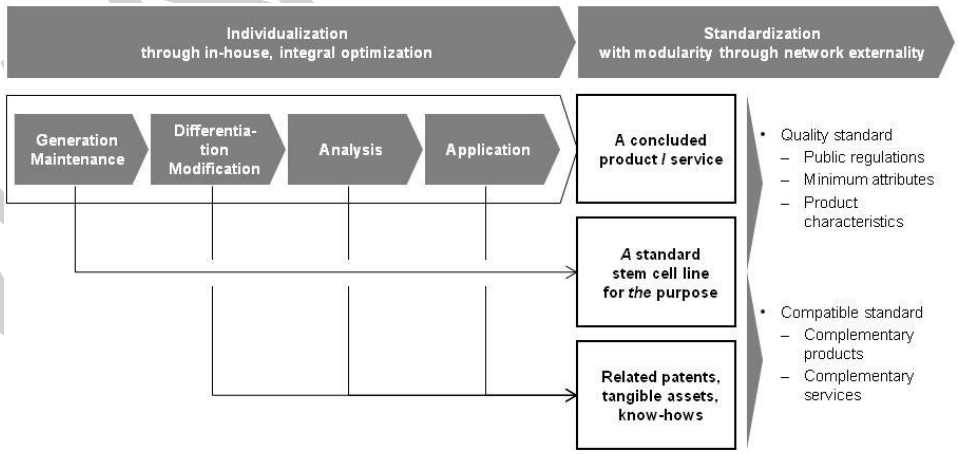
From the patent analysis we observed possible bias in terms of the numbers of patents (figure 1). Moreover, two cases studies suggested that there suppose to be many technological areas where know-how not shown in the patent is more important in terms of operation than the patent itself hence claiming the right thereof may not always be the first choice.

Large number of patent in stem cell technology exists in generation, maintenance or differentiation technology of stem cells. However, because minor variations of these technologies (e.g. differences in the cell line employed, the cell type to be induced, culture condition) significantly affect the characteristics of the final product, claims related to them are to be narrow. In addition, most of these are process patents. Product patents are effective as long as the products are used. In contrast, process patents have the possibility of being substituted by emergence of a different procedure outside of the claims of the patents themselves, and the possibility of a drastic technological innovation which would deny the necessities of the process cannot be dismissed. Of course, there is a possibility that a relatively strong product patent is formed if useful pluripotent stem cell lines is invented by making use of cell modification technology, but no cell line that would be of interest exists so at this time.

4.2 Suggested pro-innovative business modelling

In general, the determinants of innovation are technological opportunity and appropriability, and improvements of both will accelerate innovation [15,16]. Summarizing the results in section 3 the business opportunity of stem cells technology will be secured in the two steps of (i) in-house optimization of the target product and service, and then (ii) standardization of this product and service (and related technology elements) through a common interface (Figure 5.)

Figure 5 Proposed key success factor (KFS) for stem cell business modelling



For the first step, the in-house optimization process, the so-called integral build-in is thought to be effective. Both companies of ReproCELL and J-TEC each uniquely and self-sufficiently had the coherency to take responsibility for the entire business process and the comprehensiveness to cover diverse technology elements. Moreover, in each case the experienced CTO is placed to take charge of integration and management of the entire process. As a result, it is thought that the unifying power of tuning the combination of process and technology element from the standpoint of optimizing the whole is exerted, thus achieving competitive advantage.

For the second step, the standardization process, opening up that has its roots in modularity and exertion of network externalities are required. The main reason is the fact that requirements for product quality, safety and efficacy are predefined by the regulatory authority in the region and these must be cleared to obtain an approval and licence. All of these requirements correspond to quality standards for the product or service.

4.3 Implications to the technology standardization

Technology standards are rules for smoothly and widely circulating a particular technology or products and services based on that technology, consisting of criteria for quality and safety, test methods and user interfaces [17]. The background behind the enhanced interest in standardization is the recent activation of partnering between companies and public organizations, and promotion of research and development activities based on open innovation [18].

In recent years, a movement towards standardization of stem cells is progressing worldwide [19]. One particular example is establishment of standard cell lines: currently there are thought to be approximately more than 60 human ESC lines established, and their functional properties are reported to be significantly diverse [20]. The situations are supposed to be much more complex in the case of hiPSCs. To apply a series of technology established with formerly developed ES cells, lateral comparability between ES and iPS cell species is extremely important [21] but as far as the verification in our studies it is difficult for one universal standard strain to exist.

A hint to address standardization issues is that qualitative demands differ depending on the difference in the purpose of commercialization. In such, a practical approach is that only when the provided products and services satisfy the desired qualitative standard, the cell strain and related technologies used will obtain the status as a standard in the field. When that product or service is successfully approved and gained a leading position in the market, means including patents, physical assets, know-hows necessary to secure the defined quality standard will form de facto standard.

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