Article

Induced Pluripotent Stem Cells: Inventors turning into competitors. Can a competitive patent combat yield better inventions in stem cell research?

Pratap Devarapalli
is an Intellectual Property Professional at the CSIR Unit for Research and Development of Information Products

Swapnil Laxman Bhalke
is an Intellectual Property Professional at the CSIR Unit for Research and Development of Information Products

Neelam Sudhir Dharmadhikari
is an Intellectual Property Professional at the CSIR Unit for Research and Development of Information Products

Vandana Mishra
was a Research Associate at the CSIR Unit for Research and Development of Information Products

Neha Mago
was a Project Fellow at the CSIR Unit for Research and Development of Information Products

Nishad Deshpande
is a Scientist at the CSIR Unit for Research and Development of Information Products

Rajkumar Hirwani
is Head, CSIR Unit for Research and Development of Information Products

ABSTRACT

Induced Pluripotent Stem Cells (IPSCs) are a kind of adult cells that have been genetically reprogrammed to become different cell types. Differentiated cells can be reprogrammed to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with embryonic stem cells. IPSCs technology was pioneered by Shinya Yamanaka from Kyoto University. This breakthrough had inspired researchers to start working around IPSCs technology. James Thomson from University of California had developed IPS cell lines derived from Human Somatic Cells. Subsequently, he had established a large scale human IPSC manufacturing company called Cellular Dynamics International. Increasing interests in the commercial exploitation of IPSCs patents have driven us to look into the patent portfolios of top three patent assignees in IPSC technology. In this study, we have discussed technological patent trends and multiple factors which reflected the competitive scenario in between the top assignees of IPSC technology. Our conclusions suggest that Kyoto Univtersity led by inventor Shinya Yamanaka is found to be the leader of IPSC technology. However, patent-product linkage analysis suggest that Cellular Dynamics International led by inventor James Thomson may surpass Kyoto University in near future.

Journal of Commercial Biotechnology (2016) 22(4), 19–26. doi: 10.5912/jcb756
Keywords: IPSC, Induced Pluripotent Stem Cells, Patents, Competitive Intelligence.

Correspondence:
Nishad Deshpande, CSIR Unit for Research and Development of Information Products, India. Email: nishad@urdip.res.in

INTRODUCTION

Induced Pluripotent Stem Cells (IPSCs) are a kind of adult cells that have been genetically reprogrammed to become different cell types. Differentiated cells can be reprogrammed to an embryonic-like state by transfer of nuclear contents into oocytes or by fusion with embryonic stem (ES) cells. IPSCs technology was pioneered by Shinya Yamanaka from Kyoto University, Japan. He was awarded Nobel Prize in the year 2012 for the achievement of same. This innovative technology was first reported in mouse in the year 2006 [1]. Yamanaka, the pioneer of IPSC technology has filed a patent in the year 2009 claiming "a method for preparing an induced pluripotent stem cell by nuclear reprogramming of a somatic cell from a mammalian species" which was granted in the year 2011 [2]. Yamanaka's patent [2] is one of the dominant and strong patents standing for IPSC technology in Kyoto University patent portfolio of IPSCs. In the subsequent years, researchers had made use of this technology and developed IPSCs from adult human fibroblasts [3] and also generated germline-competent IPSCs [4].

Researchers started working around the IPSCs technology and in the year 2007 James Thomson from University of Wisconsin and University of California, US had developed Induced Pluripotent Stem Cell Lines derived from Human Somatic Cells [5]. James Thomson, one of the key inventors in IPSC technology has established a large scale human IPSC manufacturing company called Cellular Dynamics International in the year 2004. Since then, commercial exploration of IPSC technology has stated all over the world where intellectual property rights came in to picture [6]. Increasing interests in the commercial exploitation of IPSCs patents have driven us to look into the patent portfolios of major patent assignees in IPSC technology. Kyoto University (KU) is found to be conquering first place with 202 patents in relation to IPSC technology followed by Cellular Dynamics International (CDI) with 77 and University of California (UC) with 72.

TECHNOLOGY MAPPING

Induced Pluripotent Stem Cell technology research has been diversified into multiple subgroups due to its vast applications in medicine. Our patent analysis had identified that most of the IPSC research has been carried out on Nuclear Reprogramming, Gene Therapy, Cell Culturing and Pluripotency Assays (Suppl. Fig. 1). IPSC technology has multiple applications in medicine. Specifically, diseases such as Cancer, Cardiovascular, Diabetes, Spinal Injury and Multiple Sclerosis have been identified to be treated and cured using IPSC technology (Suppl. Fig. 1). IPSCs patent portfolios of leading assignees majorly deals with nuclear reprogramming, gene therapy, cell culturing and pluripotency assays (Table 1). Comparatively, KU patent portfolio has more patents dealing with nuclear reprogramming technology leaving CDI and UC far back. KU continued its lead in gene therapy patents as well as patents discussing about cell culturing. UC and CDI patent portfolios has almost similar no. of patents dealing with gene therapy and cell culturing.

Moreover, CDI claims more no. of patents dealing with technologies related to pluripotency assays and most of the CDI patents deal with Essentially Vector

Table 1: List of patents owned by leading assignees in IPSC technology classified according to specific claimed technologies and types of diseases and treatment

Technologies	Kyoto University	University of California	Cellular Dynamics International
Nuclear Reprogramming	178	22	61
Gene Therapy	136	50	49
Cell Culturing	169	66	66
Pluripotency Assays	47	23	59
Disease and Treatment			
Cancer	112	35	57
Cardiovascular	29	31	48
Diabetes	55	15	29
Spinal Injury	46	27	17
Multiple Sclerosis	19	21	5

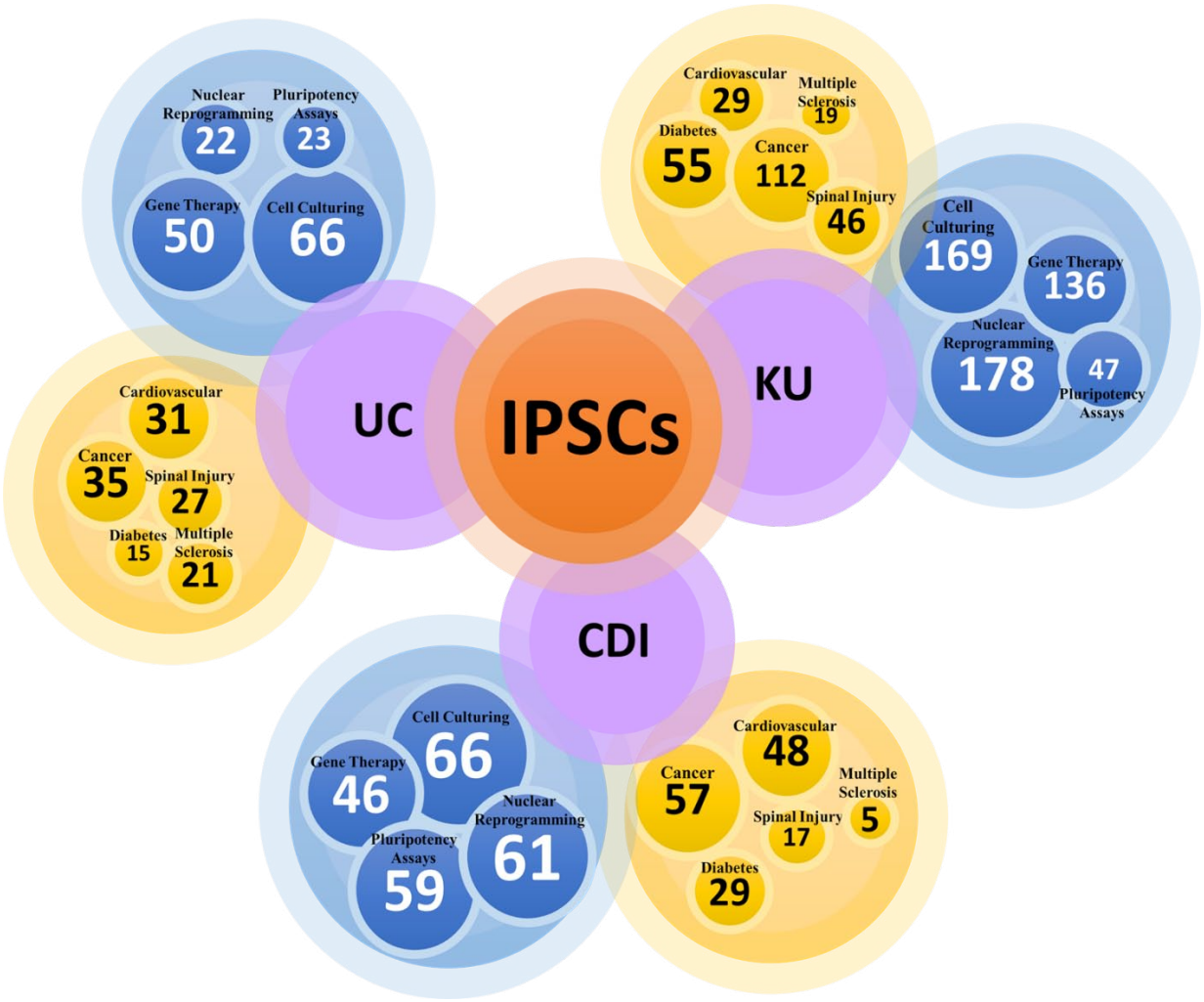


Figure 1: Technology, Disease and Treatment specific patent clusters of leading assignees in Induced Pluripotent Stem Cell technology

Free Pluripotent Stem Cells (Fig. 1). Despite of all, KU patent portfolio is comparatively strong with most no. of patents in major breakthrough technologies of IPSCs research (Fig. 1). Cooperative Patent Classification trends suggest that most no. of patents in IPSC portfolio of all leading assignees are covered under C12N class which deals with microorganisms or enzymes; compositions thereof; followed by C07K, A61K, G01N and C12Q (Suppl. Fig. 2). Sub-classification analysis of CPC classes suggest that KU's research is more focused towards Artificially Induced Pluripotent Stem Cells (C12N50696) and Genetically modified cells (C12N521000). In contrast, UC's research is more focused towards Materials from mammals; Compositions comprising non-specified tissues or cells; Compositions comprising non-embryonic stem cells (A61K3512) and General methods applicable to biologically active non-coding nucleic acids (C12N15111). Similar to KU, CDI's research is more focused towards Genetically modified cells (C12N521000) and Genetic engineering for animal cells (C12N15/85).

DISEASE AND TREATMENT

Research on generating disease specific IPSCs was reported in the year 2008 where cell biologists have generated IPSCs derived from somatic cells of patients with genetic diseases [7]. These disease specific IPSCs offer an unprecedented opportunity to recapitulate both normal and pathologic human tissue formation in vitro, thereby enabling disease investigation and drug development. Most of the IPSCs patent portfolios of leading assignees covers patents related to cancer followed by cardiovascular diseases, diabetes, and multiple sclerosis. However, a cluster of patents in IPSC portfolio deals with treatment of spinal injuries using IPSC technology.

Comparative patent portfolio analysis with regard to disease and treatment suggest that KU patent portfolio has more patents dealing with cancer, diabetes and spinal injury. Nevertheless, most of the patents dealing with cardiovascular diseases are claimed by CDI followed by UC. Patents related to multiple sclerosis are found in all the three portfolios. However, UC is claimed to have more no .of patents related to multiple sclerosis almost with a slight edge lead of two patents against KU (Fig. 1). Yet, KU's patent portfolio had continued its domination in the disease and treatment specific clusters with most patents covered.

CITATION ANALYSIS

Forward citation analysis is one of the measures to assess the quality of a patent [9]. It provides the no. of times a patent has been cited by other patents. Portfolio citation analysis of all the three assignees had provided better insights in evaluating the strengths of IPSC patent portfolios.

Comparative analysis of forward citations suggest that KU portfolio has large no. of forward citations of 544 leaving UC and CDI far back with comparatively very small numbers of 39 and 12. A calculation of Average Citation per Patent (ACP) showed that KU has a value of 2.69 ACP followed by UC with 0.53 and CDI with 0.16 ACP (Fig. 2). KU's patent portfolio stood strong in the field of IPSC technology with overall patent citations of 544 of 202 patents. However, patent citations of the recent patents of other two leading assignees suggest that they may surpass KU is the upcoming years [9, 10].

FILING TRENDS

As KU is the pioneer of IPSC technology, its journey of patent filing has started a bit earlier than the other two leading assignees. KU has an average filing frequency of 22 patents per year whereas UC and CDI has an average filing frequencies of 9 and 11 patents per year. However, overall filing trends of leading assignees suggest that there is a gradual decrease in patent filings from the year 2012 (Fig. 3). These statistics may reflect that the research interests of leading assignees are getting shifted away from IPSC technology.

Publication trends of applications and grants of patents related to IPSCs of leading assignees suggest that KU has 50 patent grants of 202 applications, UC has 8 patent grants of 77 applications and CDI has 31 patent grants of 77 applications. However, calculated Patent Grant Percentages (PGP) suggest that CDI has a major PGP of 67.3% followed by KU with 33.7 % and UC with 12.5% PGP. KU has the strongest patent portfolio with 50 granted patents in the field of IPSC technology.

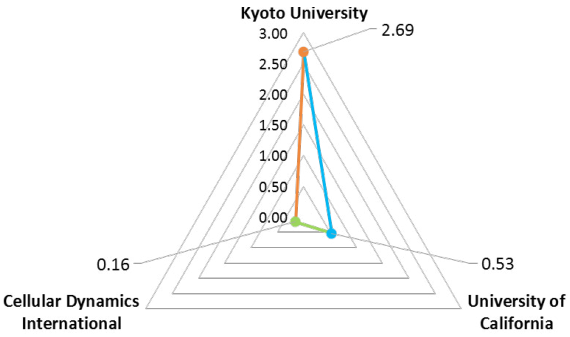


Figure 2: Delta visualization of Average Citation per Patent of patent portfolios of leading assignees in Induced Pluripotent Stem Cell technology

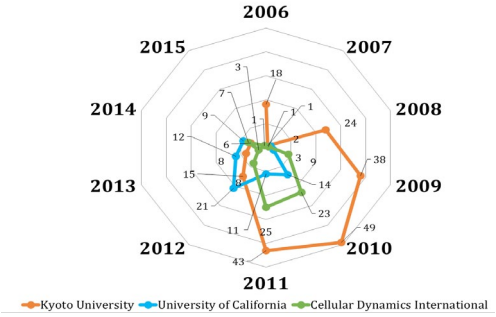


Figure 3: Line graph visualization of patent filing trends of leading assignees in Induced Pluripotent Stem Cell technology

Nevertheless, patent grant percentages reflect that CDI may overtake KU in future.

COUNTRY COVERAGE

Country coverage of a patent portfolio is one of the best value indicators of all the available patent evaluating tools [11]. It has been known that patent portfolios having a broad country coverage are much stronger than the ones which have less country coverage.

Country coverage analysis of the leading assignees in IPSC technology have shown that KU has a better country coverage in vital jurisdictions like US, Europe, China and Japan. CDI stood in the second place with second major filings in US, Europe and China (Fig. 4). These country coverage insights suggest that there is a better market for IPSC technology in US, Europe and China in comparison with other countries (Fig. 4). According to portfolio country coverage analysis KU can be considered having the strongest patent portfolio with major no. of filings in various jurisdictions.

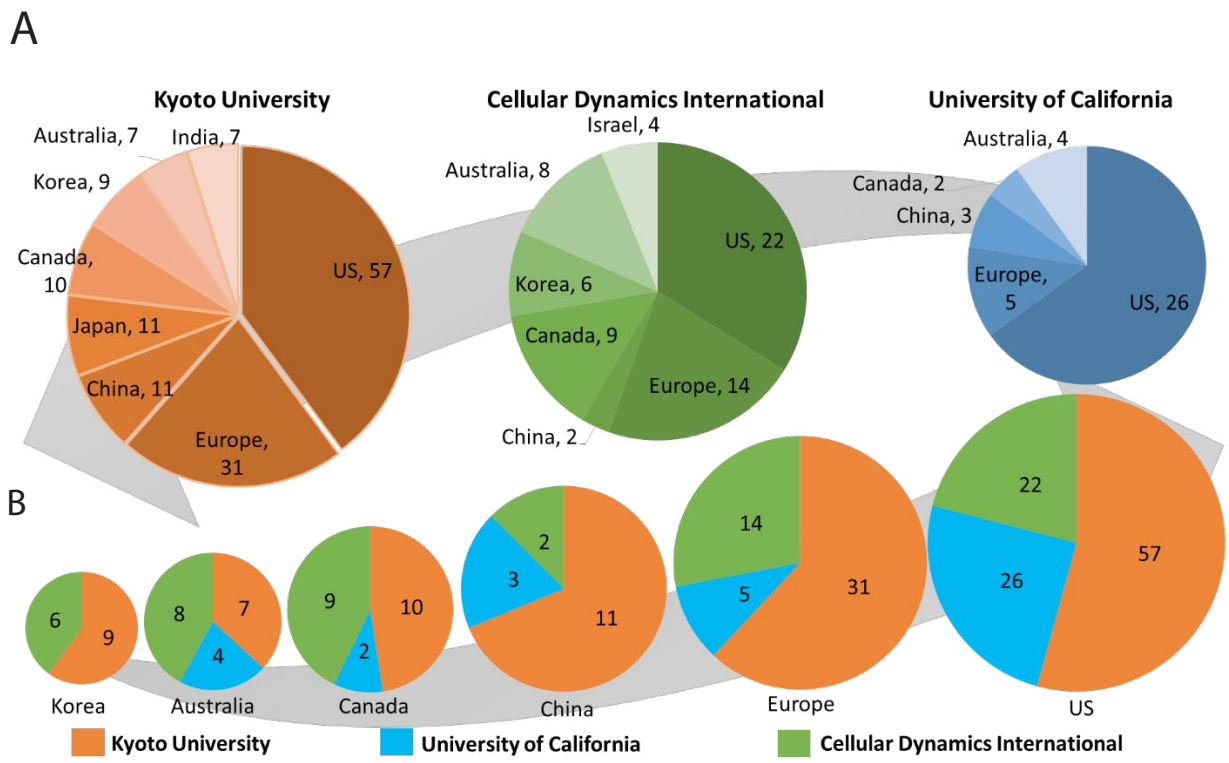


Figure 4: Ascending pie graph visualization of country coverage of patent portfolios of leading assignees in Induced Pluripotent Stem Cell technology. A. Assignee wise country coverage view patents in IPSC technology B. Country wise categorized leading assignee patents in IPSC technology

PATENT-PRODUCT LINKAGE

Patent-Product Linkage (PPL) helps to determine the number of patents linked to a product. Technology complexity of the product is directly proportional to the number patents linked to the product. Patent-Product Linkage analysis of KU's patent portfolio has provided some new insights of competitive strategies of KU. KU's had licensed out most of its IPSC patents to different firms around the globe. Country wise patent-product linkage analysis suggested that different companies of different jurisdictions have developed IPSC products based on patents licensed from KU. Stemgent, a US stem cell company has an IPSC product in market named Mouse Priamry iPS cells-WP5 which is linked to 118 patents of KU. A network of different companies and their products linked to KU's patents is visualized in Fig. 5.

CDI, a major competitor of KU in IPSC technology had developed some of their products and patents based on patents licensed from KU (Suppl. Fig. 3). Patent-Product Linkage of CDI's patents and products suggest that a product named iCell Hematopoietic Progenitor Cells has been linked to 29 patents.

CONCLUSION

As a pioneer of IPSC technology, KU has dominated the patent sector of IPSC technology with 202 patents. Comparatively, KU had a better technological coverage with 178 patents dealing with nuclear reprogramming, 169 patents in cell culturing and 136 patents dealing with gene therapy. Disease and treatment specific patent portfolio analysis had shown that KU is the major player in research related to different dreadful diseases like Cancer and Diabetes but was not able to maintain its lead in cardiovascular diseases. Yamanaka, the major inventor of KU has started commercializing IPSCs technology by licensing out patents to more than 150 entities worldwide. As James Thomson (University of California) had turned into entrepreneur from inventor and established CDI, the technology trends of UC have fallen down with subsequent rise of CDI in IPSCs. KU's patent portfolio is comparatively strong with most no. of patents & ACP value of 2.69 in major breakthrough technologies of IPSCs research. Country coverage analysis of the leading assignees in IPSC shown that KU has a better country coverage in vital jurisdictions like US, Europe, China and Japan. Patent – Product linkage shows that KU's patents are comparatively more licensed out and

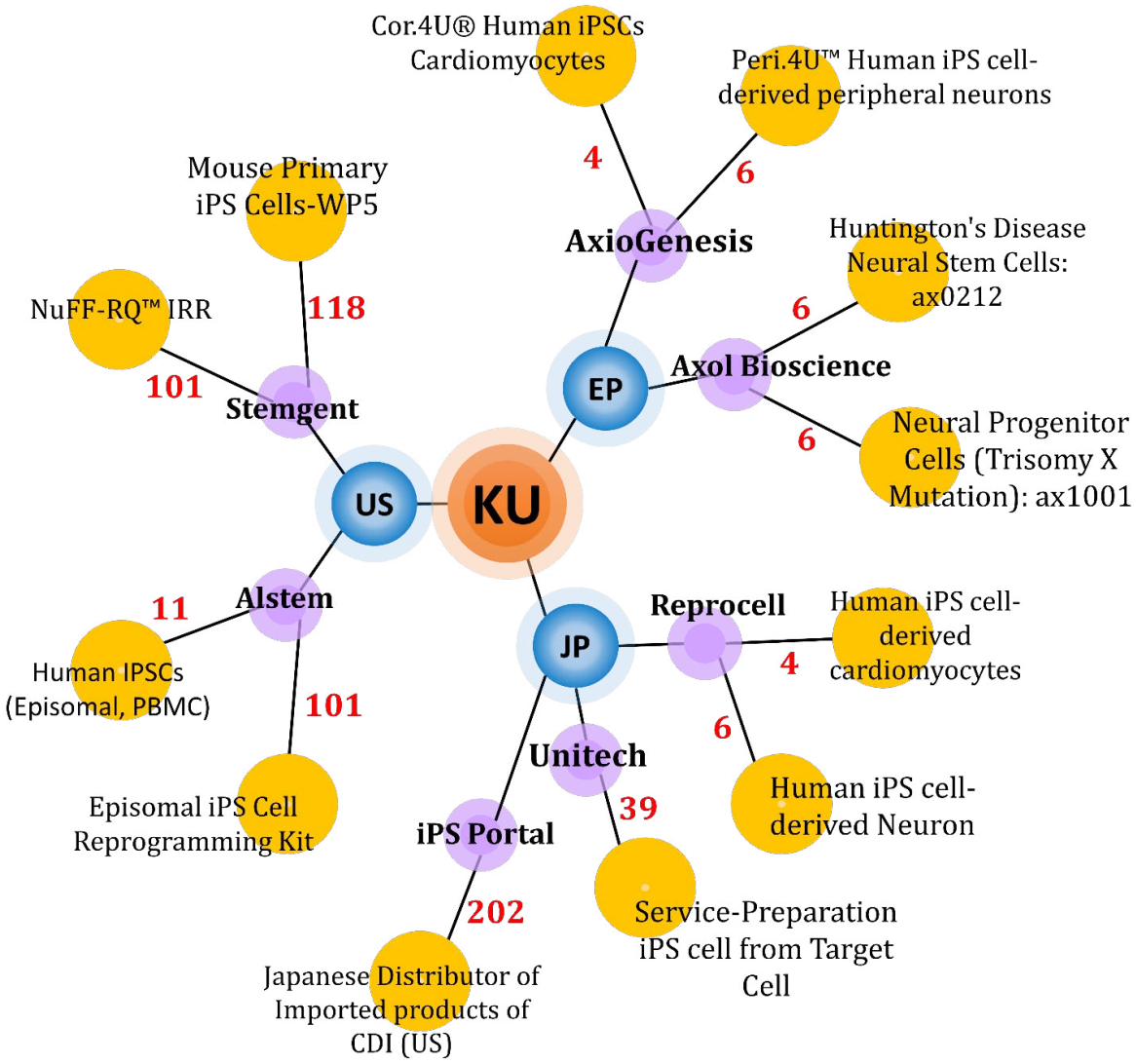


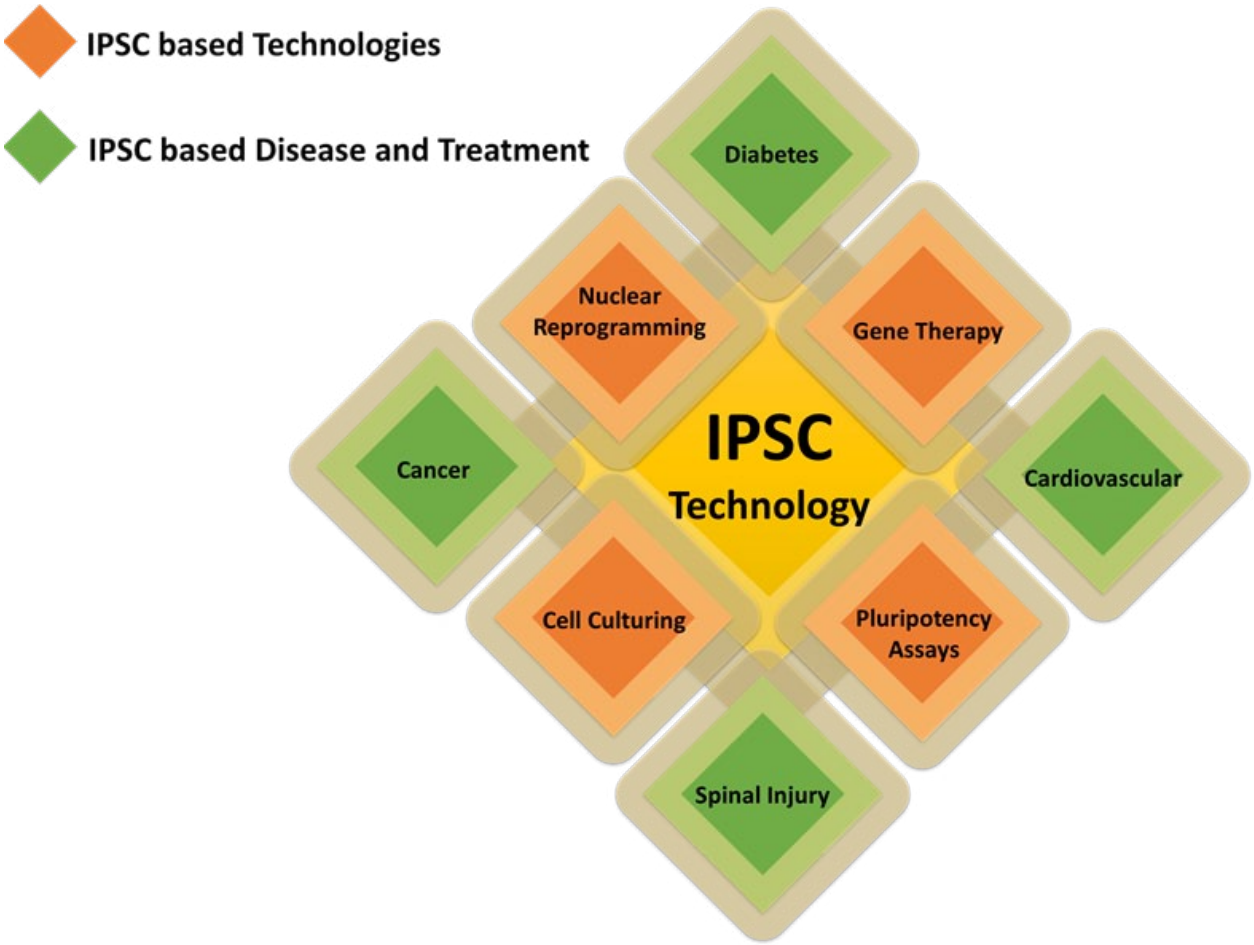
Figure 5: Network Visualization of products of different jurisdictions linked to Kyoto University's patents. Blue Circles: Countries, Purple circles: Companies, Yellow Circles: Products, Number in Red Color: Patents

linked with different IPSCs products around the globe. In essence, the overall analysis using multiple indicators reflects the lead of KU in IPSCs technology.

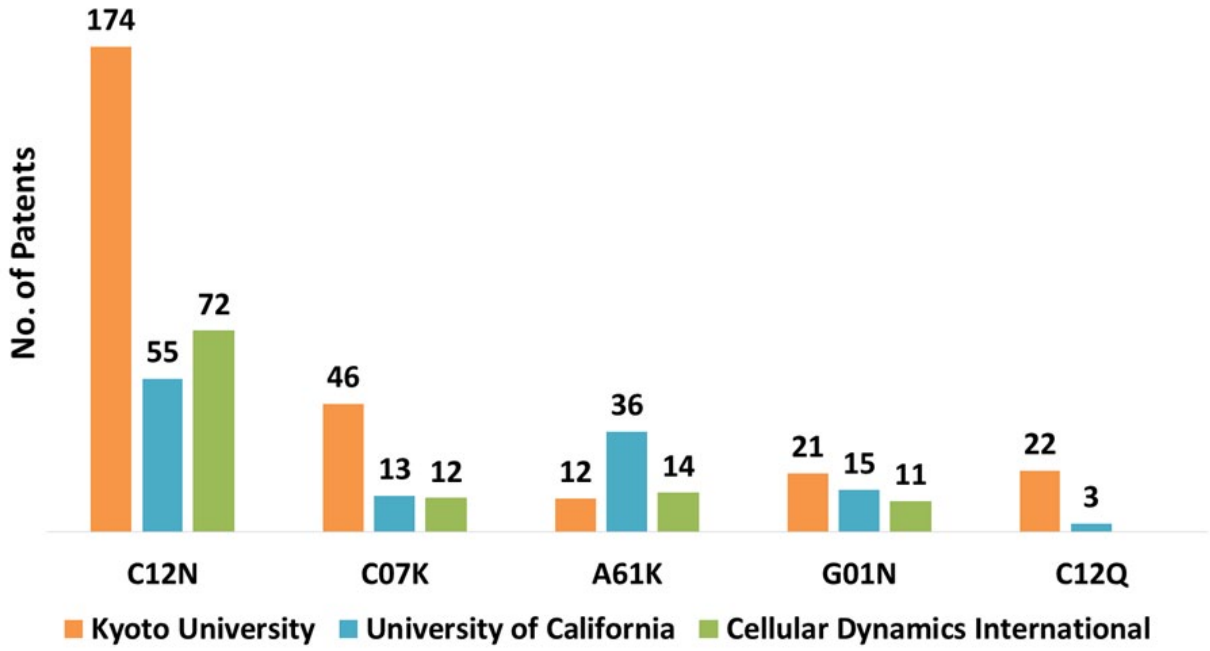
REFERENCES

1. Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, *126*(4), 663–676.
2. Yamanaka, S., & Takahashi, K. (2011). Oct3/4, Klf4, c-Myc and Sox2 produce induced pluripotent stem cells. *US8058065 B2*. Washington DC: United States Patent and Trademark Office.
3. Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., & Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*, *131*(5), 861–872.
4. Okita, K., Ichisaka, T., & Yamanaka, S. (2007). Generation of germline-competent induced pluripotent stem cells. *Nature*, *448*(7151), 313–317.
5. Yu, J., Vodyanik, M. A., Smuga-Otto, K., Antosiewicz-Bourget, J., Frane, J. L., Tian, S., & Thomson, J. A. (2007). Induced pluripotent stem cell lines derived from human somatic cells. *Science*, *318*(5858), 1917–1920.

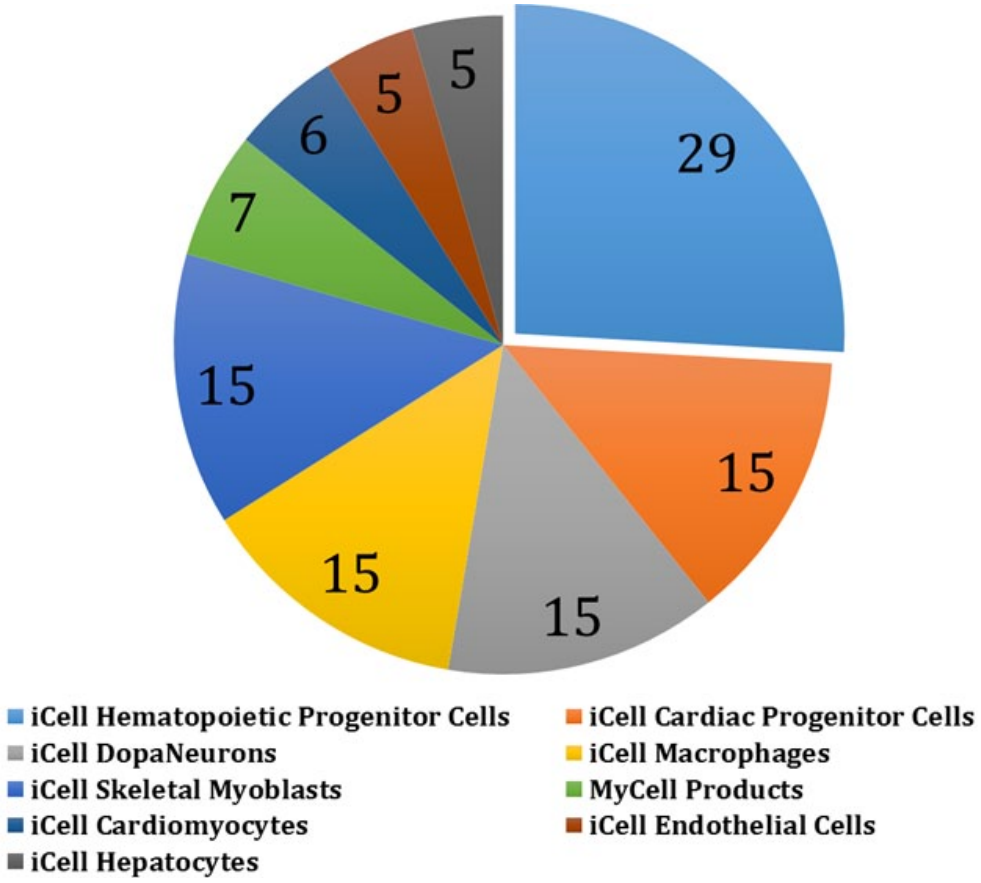
6. Smith, D. (2010). Commercialization challenges associated with induced pluripotent stem cell-based products. *Regenerative medicine*, *5*(4), 593–603.
7. Park, I. H., Arora, N., Huo, H., Maherali, N., Ahfeldt, T., Shimamura, A., & Daley, G. Q. (2008). Disease-specific induced pluripotent stem cells. *Cell, 134*(5), 877–886.
8. Brinn, M. W., Fleming, J. M., Hannaka, F. M., Thomas, C. B., & Beling, P. (2003, April). Investigation of forward citation count as a patent analysis method. In *Systems and Information Engineering Design Symposium, 2003 IEEE* (pp. 1–6). IEEE.
9. Yu, J., Chau, F. K., Jiang, J., Jiang, Y., & Vodyanyk, M. A. (2013). *U.S. Patent No. 8,481,317.* Washington, DC: U.S. Patent and Trademark Office.
10. Cost, G. J., Holmes, M. C., Kasahara, N., Laganiere, J., Miller, J. C., Paschon, D., & Zhang, L. (2015). *U.S. Patent No. 9,222,105.* Washington, DC: U.S. Patent and Trademark Office.
11. Neuhäusler, P., & Frietsch, R. (2013). Patent families as macro level patent value indicators: applying weights to account for market differences. *Scientometrics*, *96*(1), 27–49.



Supplementary Fig. 1. Quadrangular visualization of IPSC based technologies and diseases treated using IPSC technology



Supplementary Fig. 2. Visualization of major CPC's cited for Induced Pluripotent Stem Cell patent portfolios of leading assignees



Supplementary Fig. 3. Pie chart visualization of patents linked to Cellular Dynamic International's products