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# Accounting for the knowledge dynamics process of a science-based innovation

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## Eric Jolivet\*

Université Toulouse 1 Capitole, 2 Rue du Doyen-Gabriel-Marty, 31042  
Toulouse, France.  
E-mail: Eric.Jolivet@univ-tlse1.fr

## Alfonso Ávila Robinson

Kyoto University, Yoshida-honmachi, Sakyo-ku, 606-8501, Kyoto,  
Japan.  
E-mail: aavilarobinson@icems.kyoto-u.ac.jp

## Hiroatsu Nohara

Aix-Marseille university, Laboratoire d'Economie et de Sociologie du  
Travail (CNRS), 35 Avenue Jules Ferry, 13626 Aix-en-Provence,  
France.  
E-mail: hiroatsu.nohara@univ-amu.fr

## Shintaro Sengoku\*

Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro-ku, 182-  
8550, Tokyo, Japan.  
E-mail sengoku@mot.titech.ac.jp

\* Corresponding author

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## 1 Introduction

The evolution, change and transformation of scientific and technological knowledge has been a prevalent topic in the field of innovation research. Due to the higher frequency and intensity of the waves of change disrupting the current economic system, this has been a particularly pressing need for technologies of an emerging nature. Over the years, different conceptualizations have been used to approach the dynamics of technological innovations. A review of the literature shows that these conceptualizations share in common the following three aspects (Van Lente, 2010): a) a framework clustering the heuristics and routines guiding the search processes of innovation, b) trajectories along which these search processes are channeled, and c) time-dependent phases of development. Table 1 provides a summary of some of these approaches.

Reference	Framework	Trajectory	Phases
Foster (1986), Christensen (1992)	-	S-curve	birth, growth, maturity, and demise
Abernathy-Utterback (1978)	dominant design	-	fluid pattern, transition pattern, and specific pattern
Dosi (1982)	technological paradigm	technological trajectory	pre-paradigmatic, post- paradigmatic
Kuhn (1996)	scientific paradigm	-	pre-paradigmatic science, normal science, crisis, revolution
Geels (2007)	sociotechnical regimes	transition pathways	interactions across three levels: regimes, niches, and landscape
Sahal (1985)	technological guideposts	innovation avenues	-

**Table 1.** Theoretical background of the present study.

This study builds on the work of Abernathy and Utterback (1978), later refined by Anderson and Tushman (1990) and Benner and Tushman (2003). In the Abernathy and Utterback model (A-U model) of technological change, the patterns of innovation are divided into three stages: fluid, transition, and specific stages. The fluid or ferment stage is characterized by the multiplication of product designs and alternative routes in an explorative dynamics. In this stage, variety is created. In the specific stage, the deepening of a established route takes place through incremental and cumulative efforts within the framework of exploitative dynamics. Here, efficiency and economic performance dominate. Of interest for this study is the mechanism through which an formative industry enters into a more mature stage. For Abernathy and Utterback (1978), this transition goes through a process of standardization initiated by the advent of a ‘dominant design’. For industry players, the ‘dominant design’ signals that investments should now be focused in deepening and building up from this first product version. Given their embryonic nature, emerging technologies still lack such social and cognitive rules guiding their research and development (van Merkerk and van Lente, 2008). Actors in emerging fields, van Merkerk and van Lente (2008) argue, rely on speculation and promises. For them, this emerging phase is characterized by negotiation and experimentation. These processes lie at the heart of standardization.

In particular, this paper addresses the study of the standardization phase for science-based innovations. Over the years, Abernathy and Utterback (1978)’s model (A-U model) has been discussed and refined at length by scholars. These research efforts have mainly focused on classical industry cases, such as the automotive industry (Lee and Berente, 2013), the float glass industry (Uusitalo and Mikkola, 2010), the semiconductor industry (Funk, 2008), among others. Far too little attention, however, has been paid to the use of the ‘A-U model’ on emerging science-based industries. It is well-known that the strong sectoral specificities of innovation (Pavitt, 1984; Malerba, 2002) prevent researchers from extrapolating across sectors. Thus, there is a need for assessing the commonalities and specificities, in regards to standardization, between science-based and industry/business-based innovation. For the case of science-based innovations, knowledge dynamics appear

to be more networked and multi-level than in industry-based innovations (Benner and Tushman, 2003; Zuker et al 2002).

With this in mind, the empirical case of induced pluripotent stem cells (iPS cells) is used in this study. iPS cells are a novel, science-intensive technology first discovered in 2006 by a group of Japanese researchers at Kyoto University. The value chain of iPS cells encompasses a complex and interrelated set of technologies (Roberts et al, 2014). This value chain runs from the upstream generation of iPS cells through the use of reprogramming technologies to their downstream conversion into other cells and their use in application domains as different as drug screening, toxicity testing, cell therapies, etc. (Sengoku et al, 2011). Within this formative biomanufacturing system, the production of high-quality iPS cells at a high volume and low cost is a crucial requirement for the commercialization of iPS cell-derived products (Silva et al, 2015). By focusing on the alternative methods for the generation of iPS cells, this study addresses the following questions: What are the dynamics of knowledge evolution followed by science-based innovations as iPS cell generation technologies? In particular, how are the trajectories and paradigms of the dominant technological approaches selected? Moreover, What is the structure and evolution of the networks surrounding this knowledge? Is the structure conducive to domination? Besides this, the reasons for choosing a living cell-based process to the present study are: i) this a novel case of a science-based innovation, ii) this technology is expected to give rise to a wide range of innovations including medical and pharmaceutical uses, and iii) the dynamics of knowledge transfer and innovation have hardly been studied systematically to date.

This paper is structured as follows. Section 2 provides a description of the case study under focus and the materials and methods used in this research. Section 3 continues with the results of this study. Section 4 concludes with discussions and conclusions.

## **2 Research design**

### *The case and scope*

In order to test these research questions in an empirical manner we selected stem cells, particularly induced pluripotent stem (iPS) cells, as a case of novel biomedical technology (Sengoku et al, 2011). As a pluripotent stem cell species, iPS cells have the ability to proliferate indefinitely and to differentiate into almost any other cell type in the body. iPS cells were first discovered in 2006 by Shinya Yamanaka and colleagues at Kyoto University. Since their discovery, iPS cells have been regarded as a promising, potentially disruptive technology for the fields of drug discovery and development and regenerative medicine (Sengoku et al, 2011; Barfoot et al, 2013). Given these potentials and the possibility to circumvent the ethical and political debates surrounding embryonic stem (ES) cells, the field of iPS has experienced an exponential growth in the recent years (Barfoot et al, 2013).

Different approaches have been proposed to generate pluripotent stem cells from mature cells (Table 2). Generally, these approaches are referred as nuclear reprogramming, as they attempt to reverse mature cells into a state of pluripotency. In particular, iPS cells are generated by the introduction of defined genetic or chemical factors, also defined as transcription or inducing factors. Over the years, different methods have been demonstrated

to generate iPS cells. Basically, these iPS cell reprogramming methods differ in terms of the ‘vehicle’ used to deliver these pluripotency-related transcription factors into the cell nuclei. These ‘reprogramming vehicles’ could be as different as DNA or RNA molecules, protein, nanomaterials, bacteria, among others. Later sections provide a more detailed description of the different iPS cell reprogramming methods.

Methods	Experimental approach	Machanistic insights
Nuclear transfer	Reproducible cloning: functional test for reprogramming to totipotency Somatic cell nuclear transfer: efficient deviation of genetical matched ES cells with normal potency	Allows epigenetic changes to be distinguished from genetic changes
Cell fusion	Nuclear reprogramming of somatic genome in hybrids generated with pluripotent cells	Allow study of genetics of reprogramming
Cell extract	Exposure of somatic nuclei or permeabilised cells to extracts from oocytes or pluripotent cells	Allows biochemical and kinetic analysis of reprogramming
Cell explanation	Explanation in nuclear selects for pluripotent, reprogrammed cells	Allows study of genetics of reprogramming
Direct reprogramming by defined factors	Generation of pluripotent cells by the introduction of defined genetic or chemical factors	Cells generated are autologous to donour Technically straightforward

**Table 2.** Representative approaches for nuclear reprogramming (Hochedlinger and Jaenisch, 2006; Qi et al, 2014).

### *Material and method*

To capture the dynamics of knowledge evolution in the field of iPS cells, this study retrieved scientific publications from the Thomson Reuters’ Web of Science (WoS) database. In order to obtain the iPS cell-related publications, a broad search query was used: TS=((induc\* NEAR/25 pluripoten\* NEAR/25 stem) OR ((IPS OR IPSC) AND (stem NEAR/5 cell\*))), where \* is a wildcard. A total of 2, 283 publications were collected, which were manually evaluated in order to identify those documents relevant for the field of iPS cells. A total of 1,535 articles and conference proceedings published from 2006 to 2012 were collected after this procedure. Subsequently, the set of iPS cell-relevant publications were evaluated to select those publications directly related to the reprogramming of iPS cells. By this, it is meant only those publications focusing on the development or enhancement of an iPS cell generation technology were selected for this study. At the end, 581 publications were found to be directly related to this subfield of iPS cell research. Each of these publications were assessed to define the specific reprogramming method(s) involved in their studies. This was done through the evaluation of the titles, abstracts, and/or experimental/materials sections of these publications. For this purpose, as shown in Table 3, a taxonomy of iPS reprogramming methods was developed in this study.

No	Delivery system	Brief description
I	Viral-based methods	Use of viral vectors to reprogram mature cells into iPS cells. It includes retroviral, lentiviral, Sendai viral, adenoviral, and baculoviral vectors.
II	Transposon-based methods	Non-viral approach involving the delivery of genes through transposons, such as piggyBac (PB) and Sleeping Beauty (SB)
III	Plasmid-based methods	Non-viral delivery approach making use of episomal plasmids, minicircle DNA, and conventional transient plasmids
IV	Protein-based methods	Non-viral, non-integrative delivery approach based on proteins
V	Chemical-based methods	Non-viral, non-integrative delivery approach conducted through chemical methods, particularly small molecules. It also involves the improvement of reprogramming methods through chemicals
VI	RNA-based methods	Non-viral, non-integrative approach based on the delivery of reprogramming genes through different RNA types: RNA virus (Sendai virus), synthetic mRNA, miRNA, and RNA replicon. It also involves the improvement of reprogramming performance through RNA
VII	Other methods	Non-viral reprogramming approaches making use nanoparticles, bacteria, human artificial chromosomes (HAC), among others

**Table 3.** Taxonomy of delivery systems for iPS cell generation/reprogramming.

The construction of the taxonomy of reprogramming methods relied on an exhaustive review of the technical literature and additional sources of information, such as on-line resources and expert advice. There appears to be a consensus among researchers about the classification of iPS cell reprogramming approaches. Two trajectories are crucial for discerning among the different reprogramming methods are the nature of the reprogramming vehicle and its integration/excisibility. The former relates to the usage or not usage of viruses as carriers for the delivery of the iPS cell-related genes. Relatedly, the latter refers to the deleterious integration of material into the genome of the host cell. Different problems for integrating genetic materials: cell death, residual expression and re-activation of reprogramming factors, immunogenicity, uncontrolled silencing of transgenes, and insertional mutagenesis (Hu, 2014). For the case of excisable vectors, the integrated materials can be removed from the genome through the use of specific enzymes.

The collected 581 publications together with their respective allocated reprogramming approach(es) formed the basis for the results to be presented in the following sections. To test the research questions proposed in this study, a series of bibliometric methods and social network approaches, supported by a series of interviews with domain experts, were devised (Table 4). For the case of the dynamics of knowledge creation, a series of longitudinal bibliometric analyses were conducted to trace the trajectories of knowledge accumulation for each iPS cell generation/reprogramming method. Additionally, citation networks were built with the software CitNetExplorer (van Eck and Waltman, 2014) in order to evaluate the evolution of this sub-field of research and their underpinning reprogramming paradigms (de Nooy et al, 2011). To obtain a clearer visualization of the citation networks, this study set a threshold of eight or more citations on the network nodes. Due to the restrictions of the software, up to 100 nodes were able to be displayed on the network.

Topic	Research questions	Research Methods
Knowledge creation dynamics	What are the dynamics of knowledge evolution for science-based innovations?	Longitudinal methods, citation networks, interviews
	How are the trajectories and paradigms of dominant theories selected?	
Social dynamics	How individuals or groups of actors make objects for the efficient collective action of a community? What is the structure of networks on which dominant designs are grounded and how it has evolved?	Two-mode networks (delivery systems and organizations), interviews

**Table 4.** Summary of research method

On the other hand, two-mode networks were constructed to evaluate the dynamics of the groups engaged in the scientific development of the field of iPS cell reprogramming/generation. These networks relate the different delivery systems with the co-authoring organizations of the relevant publication sub-set. A threshold equal or greater than three was set on the network edges. Moreover, three periods of time are studied in this analysis: 2006-2009, 2010-2012, and 2006-2012. The results of both research methods were validated through the conduction of a series of interviews with experts in the field of iPS cell generation/reprogramming.

### 3 Result

This section presents the results of the two analyses of this study: dynamics of knowledge creation and social dynamics. A total of 1,537 publications relevant for the field of iPS cells between 2006-2012 were identified. From these, as previously mentioned, 581 (around 38%) were found to be directly related to the reprogramming of iPS cells.

#### *Dynamics of knowledge creation*

Figure 1 presents the general longitudinal trends in the total number of publications collected for the field of iPS cells as a whole and those related to iPS cell reprogramming approaches.

On Figure 1a (left), it can be readily seen that the year 2010 marked the transition of the field of iPS cells from an upstream- to a downstream-dominated path of knowledge accumulation. By downstream-dominated knowledge paths, it is referred to activities such as the differentiation of iPS cells into other types of body cell or the use of these differentiated iPS cells into any of the potential application domains. This does not imply that the imminent problems revolving around the search processes in the field of iPS cell reprogramming have already been solved. They are still highly relevant. However, in terms of the number of publications, iPS cell reprogramming appears to be outweighed by downstream activities. Figure 1b (right) shows that knowledge in this subfield has been mainly accumulated in viral-based reprogramming approaches. This is not surprising, as these approaches were used in the pioneering studies of the field of iPS cells. Nevertheless, as shown in Figure 1b, a series of alternative reprogramming approaches have been demonstrated in the recent years. This is directly related to the on-going efforts aiming at

the development of the most suitable and efficient methods of iPSC cell generation (Roberts et al, 2014).

**Figure 1.** The cumulative number of publications related to the iPSC reprogramming: a) total number of publications, and b) by type of delivery system.

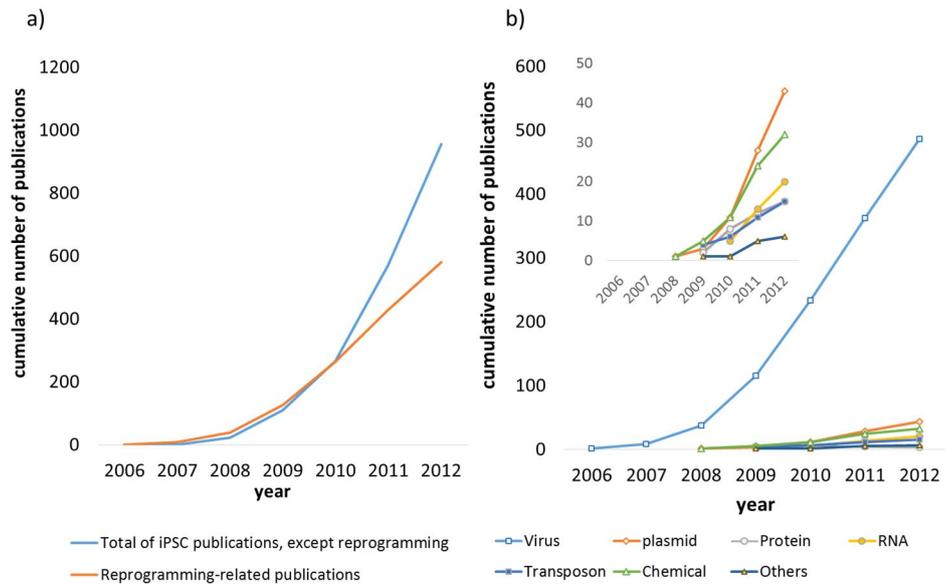
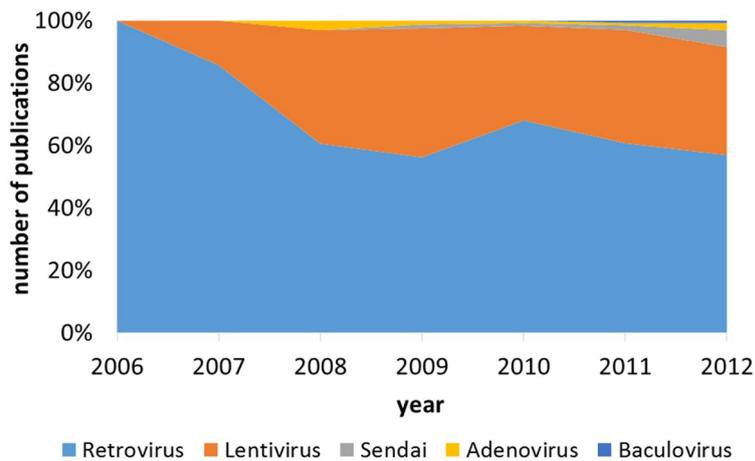


Figure 2 assesses the proportions of publications across the different viral-based reprogramming methods over the years. The pioneering retroviral approaches used by Yamanaka and colleagues appear to be gradually giving way to alternative viral-based methods. Here, lentiviral, Sendai viral, and adenoviral-based reprogramming methods stand out. This shift is highly related to the potentially non-integrating nature, i.e. the viral vectors do not integrate into the genome, of these viral approaches. As such, these approaches appear to be attracting the interest of researchers as potential processes for the generation of clinical-grade iPSC cells.



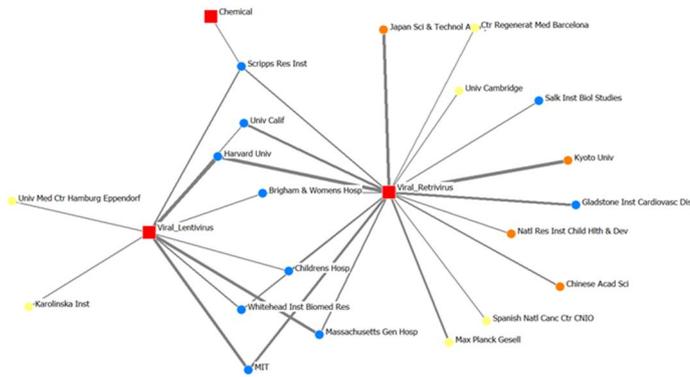
**Figure 2.** The number of publications over time by the type of viral vectors.

*Social dynamics*

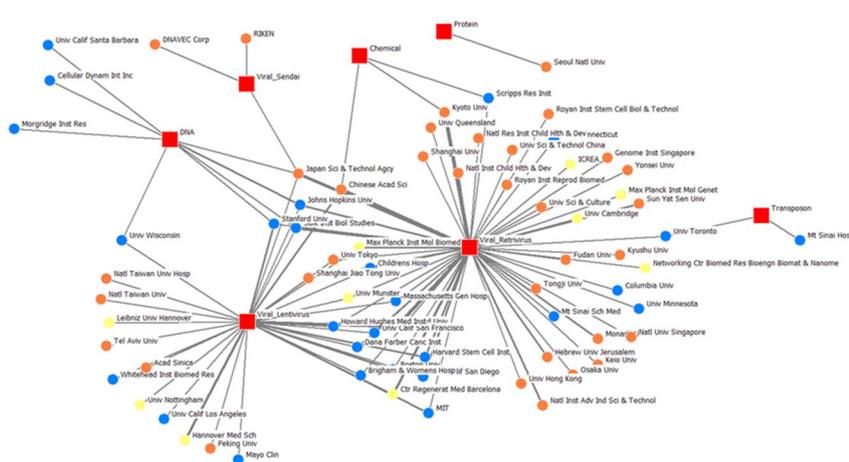
This section describes the dynamics of change among the communities involved in the development of the field of iPS cell reprogramming approaches. For that purpose, a series of two-mode networks were built to relate the different iPS cell reprogramming approaches with the affiliated co-authoring organizations of the collected publications (Figure 3). Three time periods are displayed in this figure: 2006-2009, 2010-2012, and 2006-2012.

In these networks, the location of a particular organisation denotes their patterns of usage of iPS cell reprogramming methods. By analysing the spread of nodes in terms of their geographical region, it can be seen that Asian organizations tend to focus on either retroviral or lentiviral approaches. In contrast, American organizations, and partly European organizations, tend to make use of both approaches. Moreover, American organizations appear to be more willing to make use of alternative iPS cell reprogramming methods, such as plasmid-, transposon-, chemical-, RNA-, or protein-based approaches. Exceptions are some Japanese organizations, such as Riken or Kyoto University. This closely resonates to the strong downstream competences of American and European organizations compared to their Asian counterparts.

2006-2009, n=125



2010-2012, n=456



2006-2012, n=581

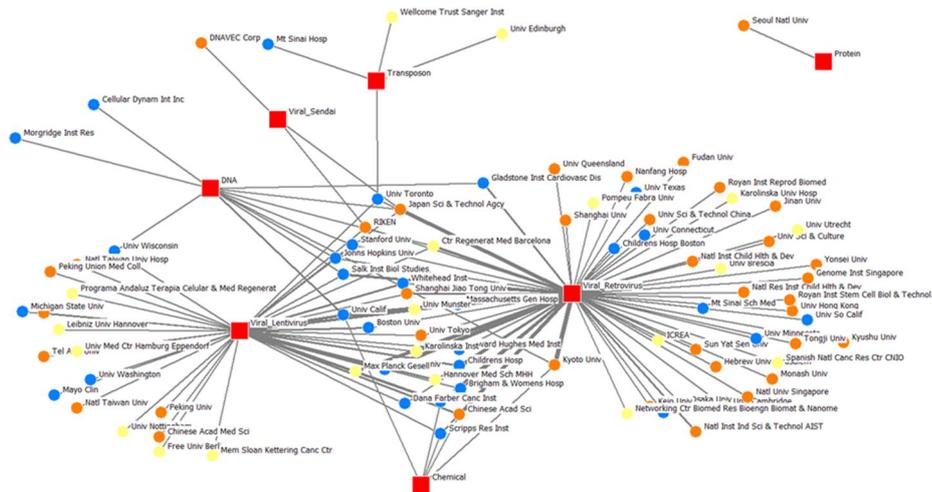
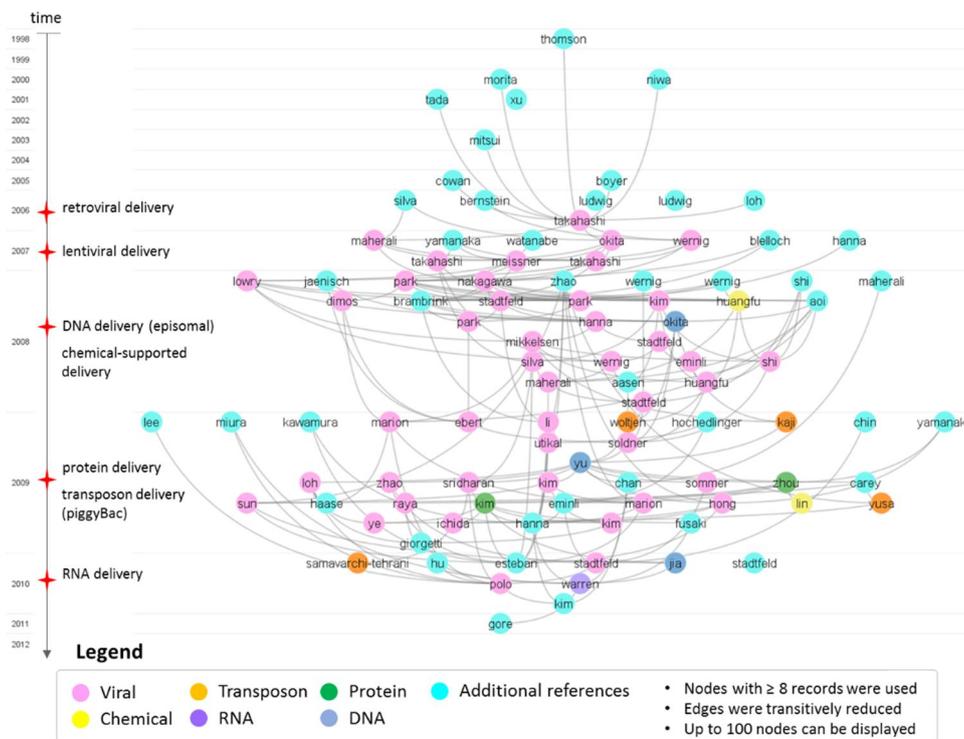


Figure 3. Two-mode networks on organization and delivery method over time.

An alternative way to trace the dynamics of knowledge accumulation is through the construction and analysis of citation networks. As described above, the iPS cell reprogramming-related publications together with their list of references were used to construct the citation network shown in Figure 4. For this purpose, the software CitNetExplorer was used. In this network, nodes are arranged by their publication year on the y-axis. Moreover, the network nodes are colored according to the type of reprogramming approach used. As these networks include the whole list of cited references, those nodes not included in the list of iPS cell reprogramming-related documents are colored in light blue in Figure 4. In line with the previous discussions, the pathways of knowledge accumulation are dominated by viral-based reprogramming approaches. From the years 2009-2010, alternative reprogramming approaches have been demonstrated, but their influence is still not significant enough for them to build their own specific paths of knowledge evolution.



**Figure 4.** A citation network of publications related to the iPSC reprogramming.

## 4 Discussion

### *The question of knowledge creation dynamics*

Our observation shown in Figure 3 confirmed the separation of research institutions according to differences in delivery methods, and that this tendency is particular with methods located in the periphery in the map. For instance, there have been few overlaps of research institutions across methods using a Sendai virus, a transposon, chemicals and proteins, whereas most of these institutions have been interrelated for viral-based methods. We also observed that the emergence of these peripheral methods does not mean a takeover from the central ones although those at the periphery such as transposon or chemicals hold substantial superiority in a clinical usage (Sengoku, in press). These results strongly suggest that the agreement to form a dominant design has never been a general trend but limited inside each of representative academic groups.

These results are identical to observations in precedent studies, which show a clear separation through the innovation process even in the identical methodological category, in particular, three groups which had succeeded the generation of human iPS cells (Roberts 2014). Each of these cell lines thus trajectories were protected by an individual set of patents, produced at a commercial base by an individual affiliated biotech firms, and translated into clinic by a part of the individual academic group.

### *The question of knowledge content codification and incorporation: technology*

Development was taken place individually with very few cooperative interactions for integration, however, there are scientific conditions which affect each of these actors to participate in a coding and institutionalization process with institutional realm.

Figure 4 shows knowledge interrelations in the course of the development reprogramming methods as citing-cited networks, where the integration of precedent additional references was achieved by Takahashi's study on the discovery of the iPS cell in 2006 (Takahashi and Yamanaka, 2006). This study was widely diversified by following studies across regions, and notably, the development process the intensive interrelations of knowledge through citing-cited complex interactions. This result implies that the condition in terms of intensive knowledge transfer at the scientific research level has made representative groups compartmentalize with one another and concentrated into a specific methodology, resulting in the existence of multiple designs for the iPS reprogramming.

### *The question of social dynamics on which dominant designs are grounded*

The present observation is strongly supporting the projection of scientific research networks of cooperation and also constraints, which is well comprehended to be the nature of science-based industry. As shown in Figure 3 and 4, we confirmed a multi-layer situation of cooperation and competition: separation in methodological development (figure 3) whereas intensive interrelation through the citation of scientific papers in the knowledge creation (figure 4), and competition in the product development and marketing [reference].

This feature has a good accordance to previous studies. One representative case is a study on a constraint between collaboration and competition (Bubela et al, 2010). Their

bibliometric research showed that technological development at the patenting level negatively impacts collaboration patterns in scientific research, suggesting the co-existence of collaboration and commercialisation in this case of science-driven industry.

### *Contribution*

Science-based innovations have increasingly contributed to the renewal and creation of novel businesses and industries recently. Classical models of technological dynamics and evolution have however been designed mainly on the basis of industry-based innovations. Thus our question: how do these classical tools apply to science-based innovations? How can we adapt them to make them more accurate instruments for managers?

In this paper we applied the classical Abernathy-Utterback Model, later refined by Tushman on the case of a novel science-based biomedical industry, iPS cells. We found the distinction between explorative and exploitative dynamics of knowledge accurate, but the classical models needed to be adapted to more multi-level and networked environment along three dimensions of source, mechanism, and the effects of standardisation.

Acknowledging for these findings and differences from classical industry cases led us to extend the Abernathy-Utterback model into the development of both science-based and classical industries.

### *Practical implication, limitation and future perspectives*

Throughout the present study we obtained the following practical implications

- The overall framework set by Abernathy-Utterback model holds when it comes to analysing science-based industry development as we retrieved the exploratory versus exploitative staging in the innovation journey of the iPS cells. The model was, however, much less accurate in the crucial phase of standardization and transition in the science-based case. In the regard, 'classical industries' and contemporary 'science-based industries' differ along the three dimensions - technological sourcing, the mechanism and the effect of standardisation.
- In science-based cases, the horizontal and inter-organizational emergence of standards and technological trajectory is further complicated by a vertical and inter-institutional imperative of bridging the two world of science and industry.

We also found there are limitations not to be addressed in the present research. First, the bibliometric analysis was limited to publications, not fully expanded to other indicators. Particularly, patent issues appear to be more closely related to the present discussion. The authors can argue that the analysis based on the scientific articles constitutes a rough indicator of model competition or evolution, as the patent issues in the life sciences are tightly linked to new knowledge in the scientific articles. This however has to be verified in a later study.

Second, In the present paper we does not distinguish the usage of iPS cells. As mentioned previously, iPS cells has a technology platform potential which can be applied not for therapeutic uses, but also basic research and drug discovery purposes. Considering the characteristics and the pros/cons of each reprogramming method, the choice of methods may be affected with the orientation of usages, in which quality standards and the

production process could vary according to one or another. This type of moves should be integrated in a following study.

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