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

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**Abstract:** Understanding the underlying waves of progress in scientific and technological (S&T) knowledge that allow innovative companies to generate value is vital for innovation managers. Established models have shown that the pathways of S&T advances are not random: a) they follow cumulative processes of coopetitive learning; b) knowledge accumulation occurs through two major modes, namely, exploration and optimisation; c) knowledge infrastructure channels the direction and the mode of learning. The Abernathy-Utterback model (A-U model) encapsulates these insights and their implications for management. This model has been validated by extensive empirical studies in a number of traditional industries. However, this model seems to be less relevant in explaining the recent S&T dynamics observed in science-based industries such as the biomedical industry. This calls for a critical assessment of the model and a research programme to complement the model. This study aims to address this gap in the literature.

**Keywords:** This is; an example; of the style; for keywords. Please use about 10 keywords and separate them with semi-colons.

## 1 Introduction

The evolution, change, and transformation of scientific and technological knowledge constitute a topic that is commonly explored in the field of innovation research. This is because science and technology is a major source of innovation and industrial transformation, as Schumpeter's seminal work established. As Bower and Christensen stated, company strategy mainly involves 'catching the wave'.

Because of the higher frequency and intensity of the waves of change disrupting the current economic system, there has been a particularly pressing need for technologies of an emerging nature. Over the years, different conceptualisations have been used to approach the knowledge dynamics of technological innovations. A review of the literature shows that these conceptualisations have three aspects in common (Van Lente, 2010): a framework that clusters the heuristics and routines guiding the search processes of innovation; trajectories along which these search processes are channelled; and time-dependent phases of development. Table 1 summarises some of these prior approaches.

| Reference | Framework | Trajectory | Phases |
|---|---|---|---|
| Foster (1986), Christensen (1992) | Technology life cycle | S-curve | Birth, growth, maturity, and demise |
| Abernathy-Utterback (1978) | Dominant design | Product vs. process innovation | Fluid pattern, transition pattern, and specific pattern |
| Nelson & Winter | Technology search and selection mechanisms | Heuristics, routines, trajectories | - |
| Dosi (1982) | Technological paradigm | Technological trajectory | Pre-paradigmatic, post-paradigmatic |
| 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) that was subsequently 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 characterised by the multiplication of product designs and alternative routes in an explorative dynamics framework. In this stage, variety is created. In the specific stage, an established route is deepened through incremental and cumulative efforts within the framework of exploitative dynamics. In this stage, efficiency and economic performance dominate. Of particular interest for this study is the mechanism through which

a formative industry enters a more mature stage (transition stage). For Abernathy and Utterback (1978), this transition involves a process of standardisation initiated by the introduction 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.

The underlying knowledge dynamics proposed by the model are key to this study. According to this model, knowledge dynamics follows two very different, successive patterns: 1) an exploratory pattern, during which the basic potential of the technology and the market are assessed, and the possible technological routes are discovered; and 2) a cumulative one, during which the main players agree about the trajectory to be followed and rush to capture the value of successive generations of innovations along the path. This model is consistent with March's observation about the patterns of organisational learning.

Managers of innovation are particularly interested in understanding the current knowledge regime and its implications, as well as the mechanism of transition from explorative to exploitative knowledge dynamics. Tushman et al. (1990 and 2003) argued that these aspects greatly conditioned the nature of their investments and their returns on investment. According to the A-U model, the transition from explorative to exploitative knowledge dynamics relies on design freeze, i.e. the establishment of a dominant design. This is consistent with Van Lente's idea of irreversibility and the findings of the economics of standards that such standardisation might take the form of a lock-in (David, 1985). The questions of how and when an industry freezes a dominant design thus form a central consideration while investing in new products and processes.

Given their nascent nature, emerging technologies lack such social and cognitive rules that guide their research and development (van Merkerk and van Lente, 2008). van Merkerk and van Lente (2008) argue that the actors in emerging fields rely on speculation and promises. For them, this emerging phase is characterised by negotiation and experimentation. These processes lie at the heart of standardisation.

This study explores the standardisation phase of science-based innovations. Over the years, Abernathy and Utterback's (1978) model (the A-U model) has been discussed and refined at length by scholars. These research efforts have mainly focused on cases involving traditional industries such as the automotive industry (Lee and Berente, 2013), the float glass industry (Uusitalo and Mikkola, 2010), and the semiconductor industry (Funk, 2008), among others. Far too little attention has been paid to the use of the A-U model in the 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 to assess the commonalities and specificities related to standardisation of science-based innovation and those of industry/business-based innovation. The knowledge dynamics of science-based innovations appear to be more networked and multi-level than the knowledge dynamics of industry-based innovations (Benner and Tushman, 2003; Zuker et al., 2002).

Given this context, 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 bio-manufacturing system, the production of high-quality iPS cells at a high volume and low cost is a crucial requirement for the commercialisation 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 that are followed by science-based innovations such as iPS cell generation technologies? In particular, how are the trajectories and paradigms of the dominant technological approaches selected? Moreover, what are the pathways of the structure formation and evolution of the networks surrounding this knowledge? Is the structure conducive to domination? The reasons for choosing a living cell-based process for the present study are: i) this is a novel case of a science-based innovation; ii) this technology is expected to give rise to a wide range of innovations, including those related to medical and pharmaceutical uses; and iii) few extant studies have systematically explored the dynamics of knowledge transfer and innovation.

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

## 2 Research design

*Case study and scope of research*

In order to test the research questions in an empirical manner, we selected stem cell technology, specifically, induced pluripotent stem (iPS) cells, as a case of innovative 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 by Takahashi and Yamanaka (2006) at Kyoto University. Since their discovery, iPS cells have been regarded as a promising, potentially disruptive technology for 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 exponential growth in the recent years (Barfoot et al., 2013).

Different approaches have been proposed by prior researchers to generate pluripotent stem cells from mature cells (Table 2). These approaches are generally called 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 known as transcription or inducing factors. Over the years, different methods of generating iPS cells have been reported. These iPS cell (iPSC) reprogramming methods mainly 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, and bacteria. The different iPS cell reprogramming methods are discussed in detail later.

| Methods | Experimental approach | Machanistic insights |
|---|---|---|

| | | |
|---|---|---|
| Nuclear transfer | Reproducible cloning: functional test for reprogramming to totipotency<br>Somatic cell nuclear transfer: efficient deviation of genetically 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 | Allows study of the genetics of reprogramming |
| Cell extraction | 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 the genetics of reprogramming |
| Direct reprogramming by defined factors | Generation of pluripotent cells by the introduction of defined genetic or chemical factors | Generated cells are autologous to donor<br>Technically straightforward |

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

## *Material and method*

To explore the dynamics of knowledge evolution related to iPS cells, this study retrieved scientific publications from Thomson Reuters' Web of Science (WoS) database. In order to obtain 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 obtained from the search; these were manually evaluated in order to identify the documents relevant to the field of iPS cells. A total of 1,535 articles and conference proceedings published from 2006 to 2012 were retained after this procedure. Subsequently, the set of publications relevant to iPS cell were further evaluated to select those publications directly related to the reprogramming of iPS cells. Thus, only those publications focusing on the development or enhancement of an iPS cell generation technology were selected for this study. Finally, 581 publications were found to be directly related to this subfield of iPS cell research. Each of these publications was assessed to define the specific reprogramming method(s) involved in the research. This was done by evaluating the titles, abstracts, and/or experimental/materials sections of these publications. For this purpose, a taxonomy of iPS reprogramming methods was developed in this study (see Table 3).

| No. | Delivery system | Brief description |
|---|---|---|
| I | Viral vector-based methods | Use of viral vectors to reprogram mature cells into iPS cells. The viral vectors used include 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) transposons. |
| III | Plasmid-based methods | Non-viral delivery approach involving 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, especially using 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 using nanoparticles, bacteria, and 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 online resources and expert advice. There appears to be consensus among researchers about the classification of iPS cell reprogramming approaches. Two trajectories that are crucial for distinguishing the different reprogramming methods are the nature of the reprogramming vehicle and its integration/excisability. The former relates to whether viruses are used as the carriers for the delivery of the iPS cell-related genes. The latter refers to the deleterious integration of material into the genome of the host cell. There are different problems associated with the integration of genetic materials: cell death, residual expression and reactivation of reprogramming factors, immunogenicity, uncontrolled silencing of transgenes, and insertational mutagenesis (Hu, 2014). In the case of excisable vectors, the integrated materials can be removed from the genome using specific enzymes.

The 581 publications that were collected from the WoS database together with their respective allocated reprogramming approach(es) formed the basis for the results that are presented in the following section. 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 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 using the software CitNetExplorer (van Eck and Waltman, 2014) in order to evaluate the evolution of this subfield of research and the reprogramming paradigms used in the studies (de Nooy et al., 2011). To obtain a clearer visualisation of the citation networks, this study set a threshold of eight or more citations for the network nodes. Because of the restrictions of the software, up to 100 nodes could be displayed on the network.

| Topic | Research questions | Research Methods |
|---|---|---|
| Knowledge creation dynamics | What are the dynamics of knowledge evolution for science-based innovations? How are the trajectories and paradigms of the dominant theories selected? | Longitudinal methods, citation networks, interviews |

| | | |
|---|---|---|
| Social dynamics | How do individuals or groups of actors define the objectives 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 organisations), interviews |

**Table 4.** Summary of research method.

Further, two-mode networks were constructed to evaluate the dynamics of the groups engaged in scientific development in the field of iPS cell reprogramming/generation. These networks relate the different delivery systems with the co-authoring organisation of the relevant publication subset. A threshold equal to or greater than three was set for the network edges. The analysis spanned over three periods: 2006–2009, 2010–2012, and 2006–2012. The results of the two research methods were validated through a series of interviews with experts in the field of iPS cell generation/reprogramming.

## 3 Results

This section presents the results of the two analyses of this study related to the dynamics of knowledge creation and social dynamics. As discussed in the previous sections, 1,537 publications relevant to the field of iPS cells published between 2006 and 2012 were identified from the WoS database. Of these publications, 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 for the total number of publications collected related to the field of iPS cells as a whole (Figure 1a) and for those related to iPS cell (iPSC) reprogramming approaches in particular (Figure 1b).

Figure 1a shows that the year 2010 marked a transition in the field of iPS cells from an upstream- to a downstream-dominated path of knowledge accumulation. Downstream-dominated knowledge paths involve activities such as the differentiation of iPS cells into other types of body cells or the use of these differentiated iPS cells in any of the potential application domains. This does not imply that the immanent problems related to the search processes in the field of iPS cell reprogramming have already been solved. These problems remain highly relevant. However, in terms of the number of publications, the iPS cell reprogramming publications appear to be outweighed by those on downstream activities. Figure 1b shows that the accumulated knowledge in this subfield is mainly related to viral vector-based reprogramming approaches. This is not surprising, since these approaches were used in the pioneering studies on iPS cells. Nevertheless, as shown in Figure 1b, a series of alternative reprogramming approaches have been demonstrated in recent years.

This is directly related to the on-going efforts aimed at developing more suitable and efficient methods of iPS cell generation (Roberts et al., 2014).

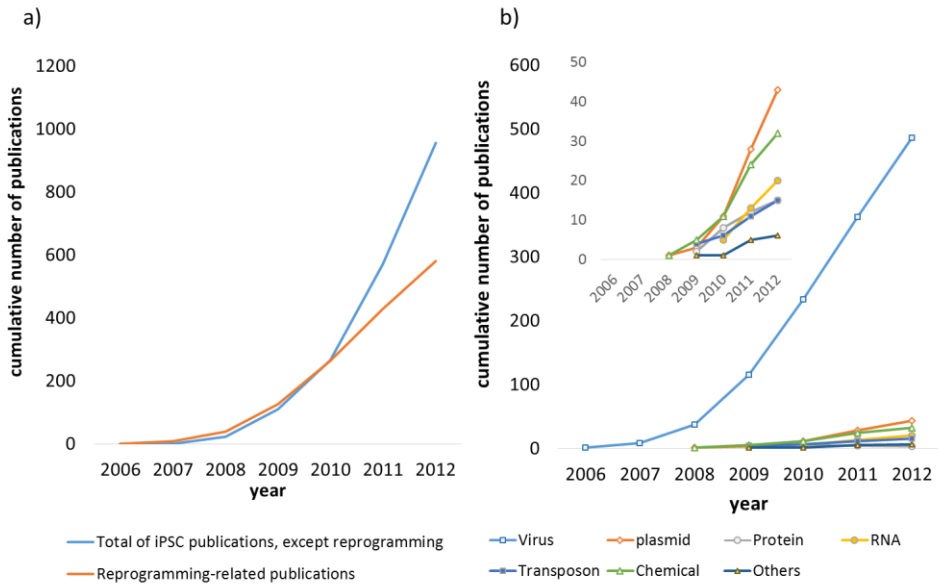


**Figure 1.** Cumulative number of publications related to iPSC reprogramming: a) by total number of publications, and b) by type of delivery system.

Figure 2 assesses the proportion of publications across the different viral-based reprogramming methods over the years. The pioneering retroviral approaches used by Takahashi and Yamanaka (2006) appear to be gradually giving way to alternative viral-based methods. The most common alternative viral vector-based methods are the lentivirus-, Sendai virus-, and adenovirus-based reprogramming methods. This shift is significantly related to the potentially non-integrating nature of these viral approaches, i.e. the viral vectors do not integrate into the genome. Thus, these approaches appear to be attracting the interest of researchers as potential processes for the generation of clinical-grade iPS cells.

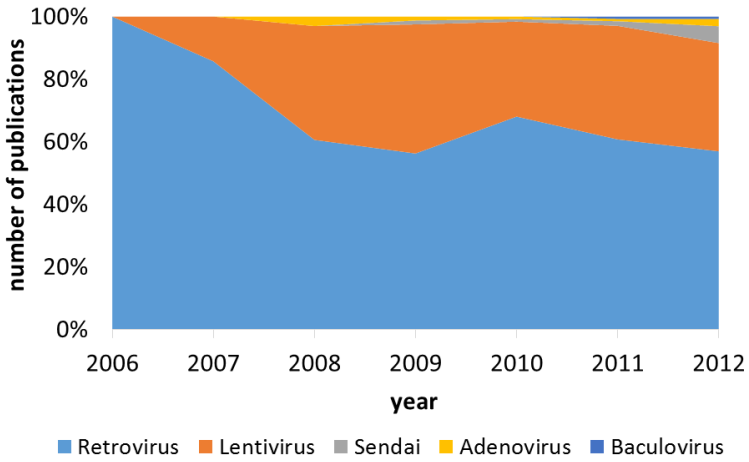


**Figure 2.** Number of publications over time according to the type of viral vectors.

*Social dynamics*

This section describes the dynamics of change among the scientific communities involved in the development of iPS cell reprogramming approaches. A series of two-mode networks was built to relate the different iPS cell reprogramming approaches with the affiliated co-authoring organisations of the collected publications (Figure 3). Three time periods are displayed in Figure 3: 2006–2009, 2010–2012, and 2006–2012.

In these networks, the location of a particular organisation denotes the patterns of usage of iPS cell reprogramming methods. The analysis of the spread of the nodes in terms of their geographical region shows that Asian organisations tend to focus on either retroviral or lentiviral approaches. In contrast, American organisations and some European organisations tend to use both approaches. Moreover, American organisations appear to be more willing to use alternative iPS cell reprogramming methods, such as plasmid-, transposon-, chemical-, RNA-, or protein-based approaches. Some Japanese organisations, such as Riken University or Kyoto University, are exceptions to this trend. This finding reflects the strong downstream competences of American and European organisations compared to those of their Asian counterparts.

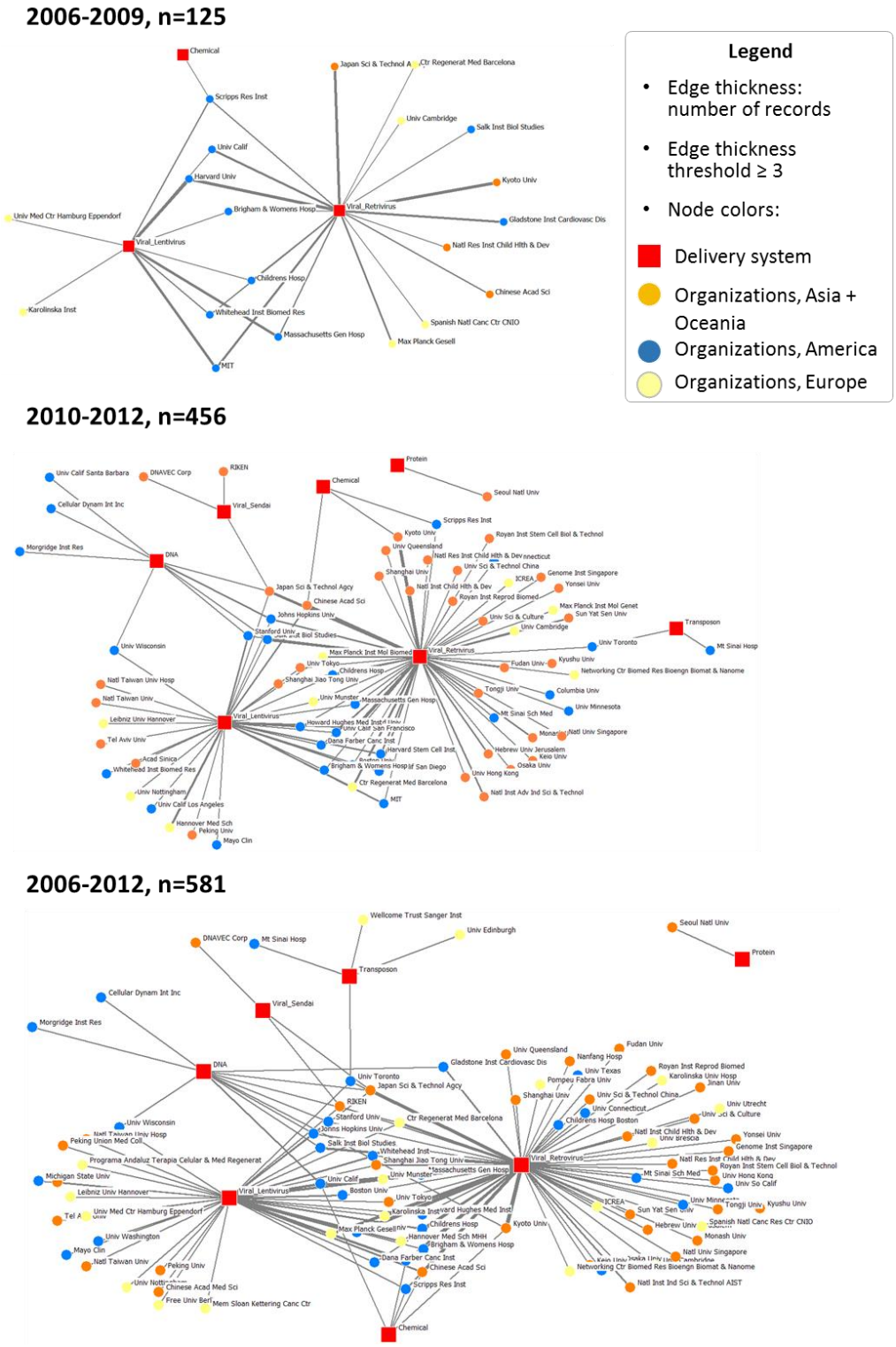


**Figure 3.** Two-mode networks of organisations and delivery methods over time.

An alternative way of tracing the dynamics of knowledge accumulation is through the construction and analysis of citation networks. As described earlier, the publications related to iPS cell reprogramming obtained from the WoS database together with their list of references were used to construct the citation network shown in Figure 4. The software CitNetExplorer was used to construct the citation network. In this network, the nodes are arranged by the year of publication on the y-axis. Moreover, the network nodes are coloured according to the type of reprogramming approach used in each study. As these networks include the entire list of cited references, those nodes that are not included in the list of iPS cell reprogramming-related documents are coloured in light blue in Figure 4. In line with the previous findings, the pathways of knowledge accumulation are dominated by viral-based reprogramming approaches. While alternative reprogramming approaches were used during 2009–2010, their influence was not significant enough for them to build their own specific paths of knowledge evolution.

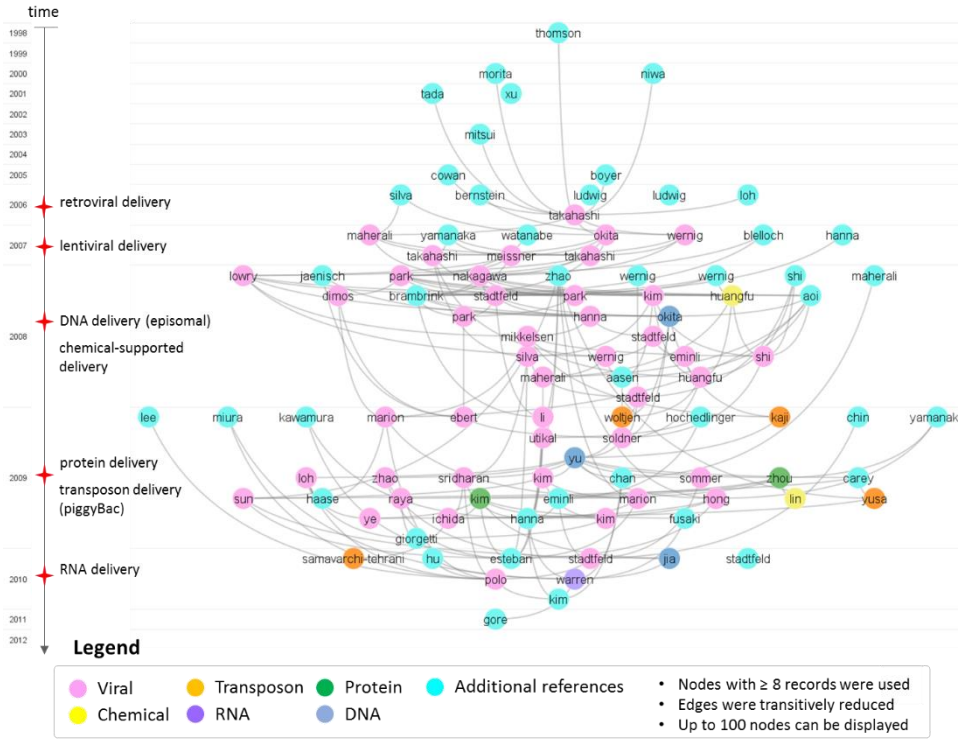


**Figure 4.** Citation network of publications related to iPS cell reprogramming.

## 4 Discussion

### *The question of knowledge creation dynamics*

Our observation related to Figure 3 confirmed the differences among research institutions according to the different delivery methods used; this tendency is particularly evident in the case of the methods located at the periphery of the network. For instance, while there were a few overlaps in the methods of the research institutions using Sendai virus, transposons, chemicals, and proteins, most of these institutions were interrelated in terms of viral-based methods. Further, we observed that the emergence of these peripheral methods does not mean a takeover from the central ones, although those at the periphery (such as transposons or chemicals) are substantially superior in clinical usage (Sengoku, in press). These results strongly suggest that the agreement to form a dominant design has never been a general trend but is limited to each representative academic group.

These results are similar to the findings reported in prior studies, which showed a clear difference among organisations according to the innovation process used, even in categories using the same methodology, especially in the context of the three groups that had succeeded in the generation of human iPS cells (Roberts 2014). For each of these cell lines, the trajectories were protected by separate sets of patents that were produced at a commercial base by an individual biotech firm or affiliated biotech firms and were translated into clinic use by a part of the individual academic group.

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

Development was found to take place individually, with very few cooperative interactions for integration. However, there were scientific conditions that motivated each of these actors to participate in a coding and institutionalisation process within the institutional realm.

Figure 4 presents the knowledge interrelations in the course of the development of reprogramming methods as citing-cited networks, where prior additional references were integrated in Takahashi's study on the discovery of the iPS cells in 2006 (Takahashi and Yamanaka, 2006). This study was extended across regions by subsequent studies; notably, the intensive interrelations of knowledge were developed through citing-cited compiling interactions. This result implies that the conditions related to intensive knowledge transfer at the scientific research level led to the compartmentalisation of the groups, which then concentrated on a specific methodology, resulting in the existence of multiple designs for iPSC reprogramming.

### *The question of social dynamics: Which dominant designs are grounded?*

Our findings strongly support the projection of scientific research networks of cooperation as well as the associated constraints, which are understood to be the nature of the science-based industry. As shown in Figures 3 and 4, we configured a multi-layer situation of cooperation and competition: differences in methodological development (Figure 3) with intensive interrelation through the citation of scientific publications used in knowledge creation (Figure 4).

This finding conforms to what was reported in prior studies. One representative case is the study of the conflict between collaboration and competition conducted by Bubela et al. (2010). Their bibliometric research showed that technological development at the patenting level negatively affects collaboration patterns in scientific research, suggesting the co-existence of collaboration and commercialisation in the science-driven industry.

### *Contribution*

Science-based innovations have increasingly contributed to the renewal and creation of innovative businesses and industries recently. However, classical models of technological dynamics and evolution were mainly designed based on industry-based innovations. This leads to the questions: How do these classical tools apply to science-based innovations? How can we adapt these models to turn them into more accurate instruments for managers?

In this study, we applied the classical Abernathy-Utterback model that was later refined by Tushman to the case of the innovative science-based biomedical industry, specifically to iPS cells. We found the distinction between the explorative and exploitative dynamics of knowledge to be accurate. However, the classical model needed to be adapted to suit a more multi-level and networked environment along three dimensions of source, mechanism, and the effects of standardisation.

Based on these findings and the differences between the studied case of a science-based industry and the classical industry cases, we extended the Abernathy-Utterback model to account for the development of science-based as well as traditional industries.

### *Practical implications, limitations, and future research*

This present presents the following practical implications.

- The overall framework proposed by the Abernathy-Utterback model holds for the analysis of the development of the science-based industry; we were able to confirm the exploratory versus exploitative staging in the innovation journey of the iPS cells. However, the model was much less accurate in the crucial phase of standardisation and transition in the science-based case. Thus, ‘classical industries’ and contemporary ‘science-based industries’ differ along three dimensions: technological sourcing, the mechanism of standardisation, and the effect of standardisation.
- In science-based cases, the horizontal and inter-organisational emergence of standards and technological trajectories is further complicated by a vertical and inter-institutional imperative of bridging the two worlds of science and industry.

This study has some limitations. First, the bibliometric analysis was limited to publications; it was not fully expanded to other indicators. Patent issues in particular appear to be more closely related to the present discussion. It could be argued that the analysis based on the scientific articles constitutes a rough indicator of model competition or evolution, as the patent-related issues in the life sciences are tightly linked to new knowledge in the scientific articles. However, this claim has to be verified in future research.

Second, in the present study, we do not distinguish the intended uses of iPS cells. As mentioned earlier, the iPS cell technology can be applied not only for therapeutic uses but also for basic research and drug discovery purposes. Based on the characteristics and the pros/cons of each reprogramming method, the choice of methods may be affected by the orientation of the usages, in which the quality standards and the production process could vary. These aspects should be integrated in future research.

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