EXPERT OPINION

Emerging trends in regenerative medicine: a scientometric analysis in *CiteSpace*

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Introduction: Regenerative medicine involves research in a number of fields and disciplines such as stem cell research, tissue engineering and biological therapy in general. As research in these areas advances rapidly, it is critical to keep abreast of emerging trends and critical turns of the development of the collective knowledge.
Areas covered: A progressively synthesized network is derived from 35,963 original research and review articles that cite 3875 articles obtained from an initial topic search on regenerative medicine between 2000 and 2011. CiteSpace is used to facilitate the analysis of the intellectual structure and emerging trends.
Expert opinion: A major ongoing research trend is concerned with finding alternative reprogramming techniques as well as refining existing ones for induced pluripotent stem cells (iPSCs). A more recent emerging trend focuses on the structural and functional equivalence between iPSCs and human embryonic stem cells and potential clinical and therapeutic implications on regenerative medicine in a long run. The two trends overlap in terms of what they cite, but they are distinct and have different implications on future research. Visual analytics of the literature provides a valuable, timely, repeatable and flexible approach in addition to traditional systematic reviews so as to track the development of new emerging trends and identify critical evidence.

Keywords: CiteSpace, co-citation analysis, induced pluripotent stem cells, regenerative medicine, scientometrics

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1. Introduction

Regenerative medicine is a rapidly growing and fast-moving interdisciplinary field of study, involving stem cell research, tissue engineering, biomaterials, wound healing and patient-specific drug discovery [1-3]. The potential of reprogramming patients' own cells for biological therapy, tissue repairing and regeneration is critical to regenerative medicine. It has been widely expected that regenerative medicine will revolutionize medicine and clinical practices far beyond what is currently possible. Mesenchymal stem cells (MSCs), for example, may differentiate into bone cells, fat cells and cartilage cells. Skin cells can be reprogrammed into induced pluripotent stem cells (iPSCs). The rapid advance of the research has also challenged many previous assumptions and expectations. Although iPSCs resemble embryonic stem cells (ESCs) in many ways, comparative studies have found potentially profound differences [4-6].

The body of the relevant literature grows rapidly. In this article, unless stated otherwise, the literature is reviewed as of November 2011. The Web of Science has 4295 records between 2000 and 2011 based on a topic search of the term 'regenerative medicine' in titles, abstracts or indexing terms. If we include records that are relevant to regenerative medicine, but do not use the term 'regenerative

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Table 1. Major clusters of co-cited references.

Cluster ID	Size	Silhouette	Label (TFIDF)	Label (LLR)	Label (MI)	Year Ave.
9	97	0.791	Evolving concept	Mesenchymal stem cell	Cardiac progenitor cell	1999
17	71	0.929	Somatic control	Drosophila spermatogenesis	Drosophila	1994
6	67	0.980	Mcf-7 cell	Intestinal-type gastric cancer	Change	2001
12	62	0.891	Midkine	Human embryonic stem cell	Dna	2002
5	53	0.952	Grid2ip gene	Silico	Gastric cancer	2002
19	42	0.119	Bevacizumab	Combination	Cartilage	2004
7	40	0.960	Monogenic disease treatment	Induced pluripotent stem cell	Clinic	2008
15	25	0.930	Tumorigenic melanoma cell	Cancer stem cell	Cancer prevention	2003

Clusters are referred in terms of the labels selected by log-likelihood ratio test method (LLR).

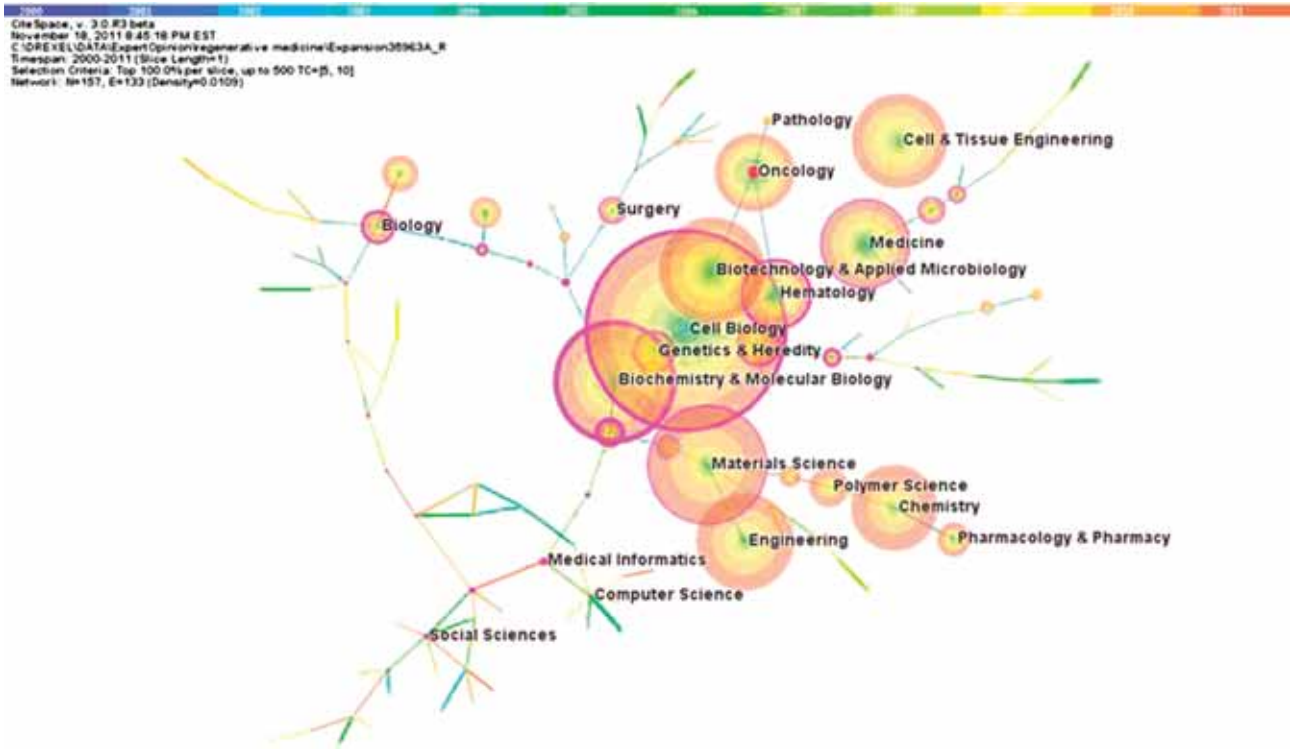

Figure 1. Disciplines involved in regenerative medicine, shown as a Pathfinder network of subject categories.

medicine' explicitly, the number could be as 10 times higher. Stem cell research plays a substantial role in regenerative medicine. There are more than 2 million publications on stem cells on Google Scholar. There are 167,353 publications specifically indexed as related to stem cell research in the Web of Science. Keeping abreast the fast-moving body of literature is critical not only because new discoveries emerge from a diverse range of areas but also because new findings may fundamentally alter the collective knowledge as a whole [7].

Scientometrics is a branch of informatics that quantitatively analyzes patterns in scientific literature in order to understand emerging trends and the knowledge structure of a research field. Science mapping tools typically take scientific publications in the literature as an input and generate interactive visual representations of complex structures for statistical analysis and interactive visual exploration. An increasing number of science mapping tools are available [8]. Science mapping tools resemble their counterparts in biomedicine research such as Cytoscape [9] and Ingenuity Pathway Analysis [10]. Many science mapping techniques are originated from the idea of co-citation analyses, which characterize the structure of intellectual knowledge in terms of networks of co-cited references [11]. An array of science mapping tools are made widely available to researchers and analysts,

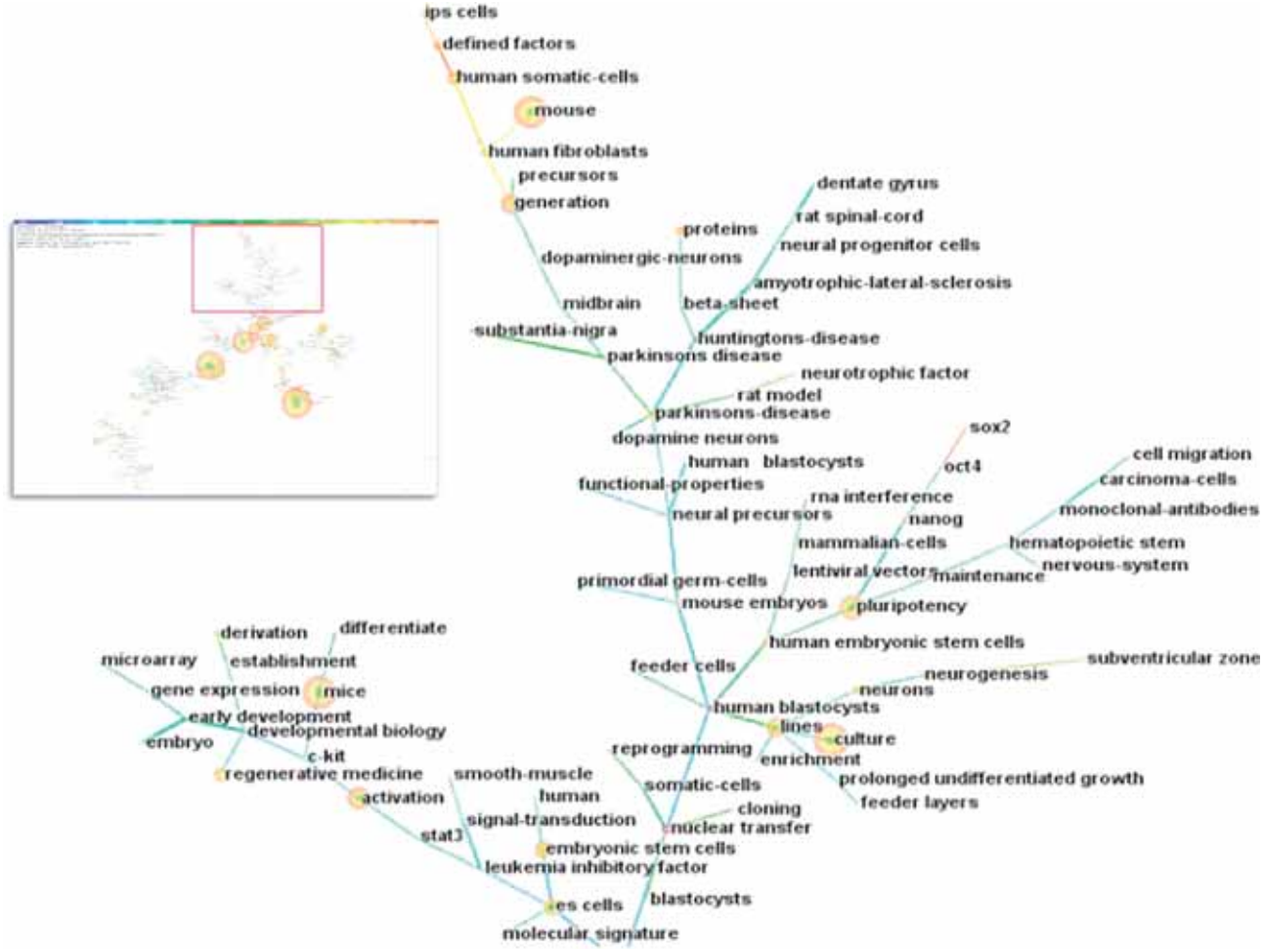

Figure 2. Part of a minimum spanning tree of a 641-keyword network based on articles published between 2000 and 2011.

notably including *HistCite* [12], *VOSviewer* [13], *Network WorkBench* [14], *DIVA* [15], Loet Leydesdorff's software [16] and CiteSpace [7,17-20].

In fact, a recent citation network analysis [21] identified future core articles on regenerative medicine based on their positions in a citation network derived from 17,824 articles published before the end of 2008. In this review, we demonstrate a scientometric approach and use CiteSpace to delineate the structure and dynamics of the regenerative medicine research. CiteSpace is specifically designed to facilitate the detection of emerging trends and abrupt changes in scientific literature. Our study is unique in several ways. First, our dataset contains relevant articles published between 2000 and 2011. We expect that it will reveal more recent trends emerged within the last 3 years. Second, we use a citation index-based expansion to construct our dataset, which is more robust than defining a rapidly growing field with a list of predefined keywords. Third, emerging trends are identified based on indicators computed by CiteSpace without domain experts' intervention or prior working knowledge of the topic. This approach makes the analysis repeatable with new data and verifiable by different analysts.

2. CiteSpace

CiteSpace is used to generate and analyze networks of co-cited references based on bibliographic records retrieved from the Web of Science. An initial topic search for 'regenerative medicine' resulted in 4295 records published between 2000 and 2011. After filtering out less representative record types such as proceedings papers and notes, the dataset was reduced to 3875 original research articles and review articles.

The 3875 records do not include relevant publications if the term 'regenerative medicine' does not explicitly appear in the titles, abstracts or index terms. We expanded the dataset by citation indexing. If an article cites at least one of the 3875 records, then the article will be included in the expanded dataset based on the assumption that citing a regenerative medicine article makes the citing article relevant

Table 2. Cited references and citing articles of Cluster #17 drosophila spermatogenesis.

Cluster #17 drosophila spermatogenesis			
Cited References		Citing Articles	
Cites	Author (Year) Journal, Volume, Page	Coverage %	Author (Year) Title
260	Schofield R (1978) Blood Cells, V4, P7	34	Tran J (2000) somatic control over the germline stem cell lineage during **drosophila spermatogenesis**
192	Xie T (2000) SCIENCE, V290, P328	25	Spradling A (2001) stem cells find their niche
151	Xie T (1998) CELL, V94, P251	23	Shinohara T (2001) remodeling of the postnatal mouse testis is accompanied by dramatic changes in stem cell number and niche accessibility
149	Kiger AA (2001) SCIENCE, V294, P2542	20	Kiger AA (2001) stem cell self-renewal specified by jak-stat activation in response to a support cell cue
147	Tulina N (2001) SCIENCE, V294, P2546	14	Tulina N (2001) control of stem cell self-renewal in **drosophila spermatogenesis** by jak–stat signaling

Cluster label terms are bold.

Table 3. Cited references and citing articles of Cluster #9 mesenchymal stem cell.

Cluster #9 mesenchymal stem cell			
Cited references		Citing articles	
Cites	Author (Year) Journal, Volume, Page	Coverage %	Author (Year) Title
2486	Pittenger MF (1999) Science, V284, P143	40	Blau, HM (2001) the evolving concept of a stem cell: entity or function?
1061	Jiang YH (2002) Nature, V418, P41	15	Bianco, P (2001) stem cells in tissue engineering
705	Orlic D (2001) Nature, V410, P701	9	Klich, Izabella (2010) very small embryonic like stem cells (vsels) isolated from adult tissues – an update
662	Prockop DJ (1997) Science, V276, P71	9	Guyette, Jacques P. (2010) strategies for regeneration of heart muscle
596	Asahara T (1997) Science, V275, P964	8	Yi, B. Alexander (2010) pregenerative medicine: developmental paradigms in the biology of cardiovascular regeneration

to the topic. The citation index-based expansion resulted in 35,963 records, consisting of 28,252 (78.6%) original articles and 7711 (21.4%) review articles. The range of the expanded set remains to be 2000 – 2011. Thus, the analysis focuses on the development of regenerative medicine over the last decade. The 35,963-article dataset is used in the subsequent analysis. Incorrect citation variants to the two highly visible references, a 1998 landmark article by Thomson *et al.* [22] and a 1999 article by Pittenger [23], were corrected prior to the analysis.

3. Disciplines and topics involved in regenerative medicine

Which disciplines are involved in regenerative medicine? Each article indexed by the Web of Science is assigned one or more subject categories. **Figure 1** shows a network of such subject categories after being simplified by Pathfinder network scaling, which retains the most salient connections. The most common category is Cell Biology, which has the largest circle, followed by Biochemistry & Molecular Biology and Materials Science. Oncology, with some of its citation rings in red, is a category in which the number of articles has increased rapidly. Although Medical Informatics, Computer Science and Social Sciences are much smaller, they are marked for reference.

The topics involved in regenerative medicine can be delineated in terms of the keywords assigned to each article in the dataset. **Figure 2** shows a portion of a minimum spanning tree of a network of keywords. Adjacent keywords are often assigned to the same articles. For example, ips cells, defined factors and human somatic cells are near to each other on the top of the diagram.

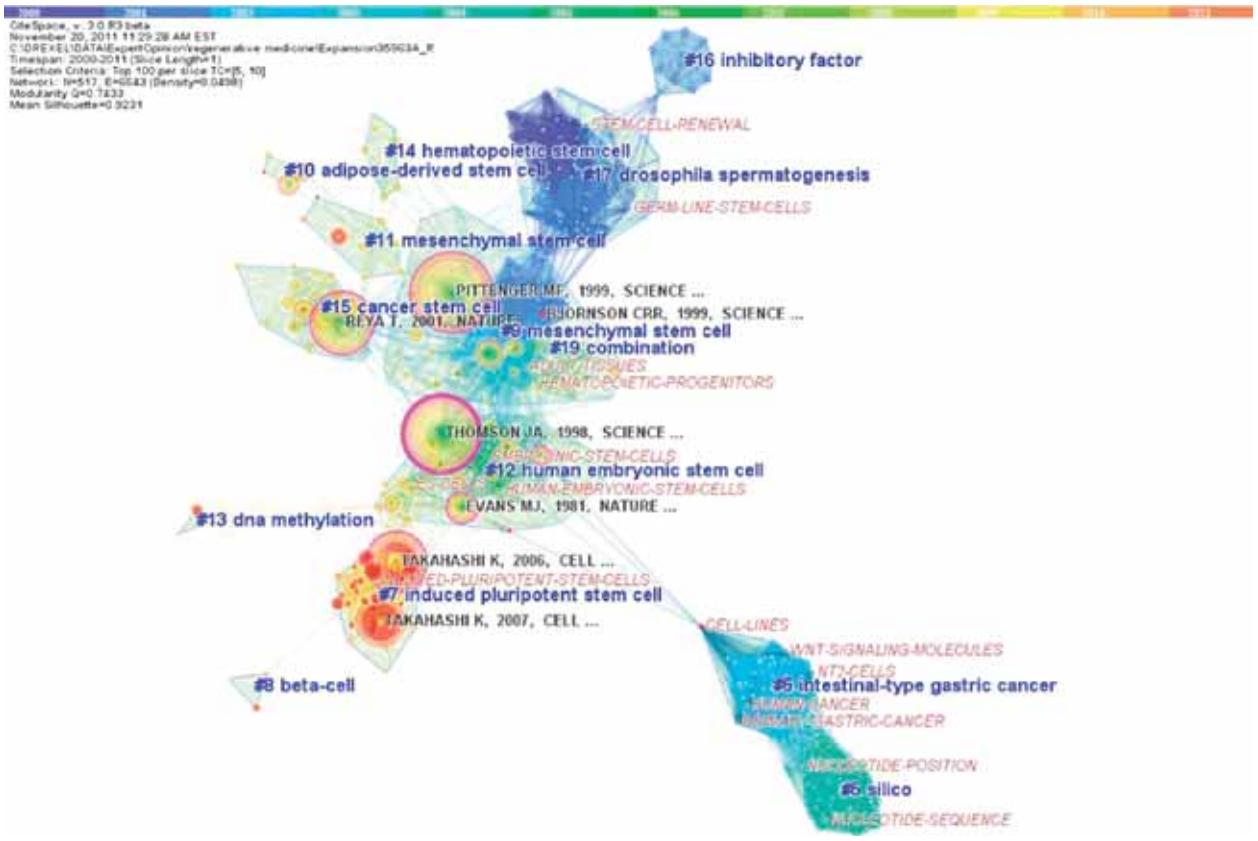

Figure 3. Trajectories of relevant research shown in a hybrid network of co-cited references and burst terms from titles and abstracts. Clusters are labeled in blue text. Landmark articles are labeled in black. Burst terms are shown in light red text. Red circles indicate articles with citation bursts, that is, rapid increases of citation counts.

4. The intellectual structure of regenerative medicine

CiteSpace represents the literature in terms of a network synthesized from a series of individual networks. Each individual network is constructed from articles published in a 1-year time interval, known as a time slice. CiteSpace integrates these individual networks and forms an overview of how a scientific field has been evolving over time.

For this review, an individual network is derived from the 100 most cited articles published in the corresponding time slice, which ranges from 2000 to 2011.

Each research article typically cites a number of references. These references are represented as nodes in a co-citation network. The connectivity between the nodes of such references represents how often they are cited by the same articles. The assumption is that if two references are often cited together, then it is evident that the two references are associated in some ways. The exact nature of the connectivity represents a dual relationship between the cited references and their citing articles. It has been shown that networks formed in this way capture research focuses of the underlying scientific community [7,11,24].

CiteSpace characterizes emerging trends and patterns of change in such networks in terms of a variety of visual attributes. The size of a node indicates how many citations the associated reference received. Each node is depicted with a series of citation tree-rings across the series of time slices. The structural properties of a node are displayed in terms of a purple ring. The thickness of the purple ring indicates the degree of its betweenness centrality, which is a measure associated with the transformative potential of a scientific contribution. Such nodes tend to bridge different stages of the development of a scientific field. Citation rings in red indicate the time slices in which citation bursts, or abrupt increases of citations, are detected. Citation bursts provide a useful means to trace the development of research focus.

CiteSpace divides the co-citation network into a number of clusters of co-cited references such that references are tightly connected within the same clusters, but loosely connected between different clusters. **Table 1** lists eight major clusters by their size, that is, the number of members in each cluster. Clusters with few members tend to be less representative than larger clusters because small clusters are likely to be formed by the citing behavior of a small number of publications. The quality of a cluster is also reflected in terms of its silhouette score, which is

Table 4. Cited references and citing articles of Cluster #12 human embryonic stem cell.

Cluster #12 human embryonic stem cell			
Cited references		Citing articles	
Cites	Author (Year) Journal, Volume, Page	Coverage %	Author (Year) Title
2223	Thomson JA (1998) Science, V282, P1145	32	Witkowska, Anna (2010) **human embryonic stem cells** – regulation of pluripotency and differentiation
1030	Evans MJ (1981) Nature, V292, P154	29	Vazin, Tandis (2010) **human embryonic stem cells:** derivation, culture, and differentiation: a review
735	Martin GR (1981) P Natl Acad Sci-Biol, V78, P7634	27	Schnerch, Angelique (2010) distinguishing between mouse and human pluripotent stem cell regulation: the best laid plans of mice and men
708	Reubinoff BE (2000) Nat Biotechnol, V18, P399	24	Avery, Stuart (2010) the role of smad4 in **human embryonic stem cell** self-renewal and stem cell fate
707	Sato N (2004) Nat Med, V10, P55	23	Ralston, Amy (2010) the genetics of induced pluripotency

Cluster #12 human embryonic stem cells are bold.

Table 5. Cited references and citing articles of Cluster #7 on induced pluripotent stem cells (iPSCs).

Cluster #7 induced pluripotent stem cell			
Cited references		Citing articles	
Cites	Author (Year) Journal, Volume, Page	Coverage %	Author (Year) Title
1841	Takahashi K (2006) Cell, V126, P663	95	Stadtfeld, Matthias (2010) induced pluripotency: history, mechanisms, and applications
1583	Takahashi K (2007) Cell, V131, P861	80	Kiskinis, Evangelos (2010) progress toward the clinical application of patient-specific pluripotent stem cells
1273	Yu JY (2007) Science, V318, P1917	77	Masip, Manuel (2010) reprogramming with defined factors: from induced pluripotency to induced transdifferentiation
762	Okita K (2007) Nature, V448, P313	77	Sommer, Cesar A. (2010) experimental approaches for the generation of **induced pluripotent stem cells**
640	Wernig M (2007) Nature, V448, P318	73	Lowry, William E. (2010) roadblocks en route to the clinical application of **induced pluripotent stem cells**
615	Park IH (2008) Nature, V451, P141	73	Archacka, Karolina (2010) **induced pluripotent stem cells** – hopes, fears and visions
501	Nakagawa M (2008) Nat Biotechnol, V26, P101	73	Yoshida, Yoshinori (2010) recent stem cell advances: **induced pluripotent stem cells** for disease modeling and stem cell-based regeneration
445	Okita K (2008) Science, V322, P949	73	Rashid, S. Tamir (2010) **induced pluripotent stem cells** – alchemist's tale or clinical reality? rid c-6368-2011
391	Maherali N (2007) Cell Stem Cell, V1, P55	68	Kun, Gabriel (2010) gene therapy, gene targeting and **induced pluripotent stem cells:** applications in monogenic disease treatment
348	Stadtfeld M (2008) Science, V322, P945	65	Robbins, Reiesha D. (2010) **inducible pluripotent stem cells:** not quite ready for prime time?

Cluster #7 on induced pluripotent stem cells (iPSCs) are bold.

an indicator of its homogeneity or consistency. Silhouette values of homogenous clusters tend to close to 1. Most of the clusters in **Table 3** are highly homogeneous, except Cluster #19 with a low silhouette score of 0.119. Each cluster is labeled by noun phrases from titles of citing articles of the cluster [24]. Using terms from citing articles is in part due to the limitation of source data. Titles of cited references may not be always available in records from the Web of Science. Labels chosen by the log-likelihood ratio test method (LLR) are used in the subsequent discussions [24].

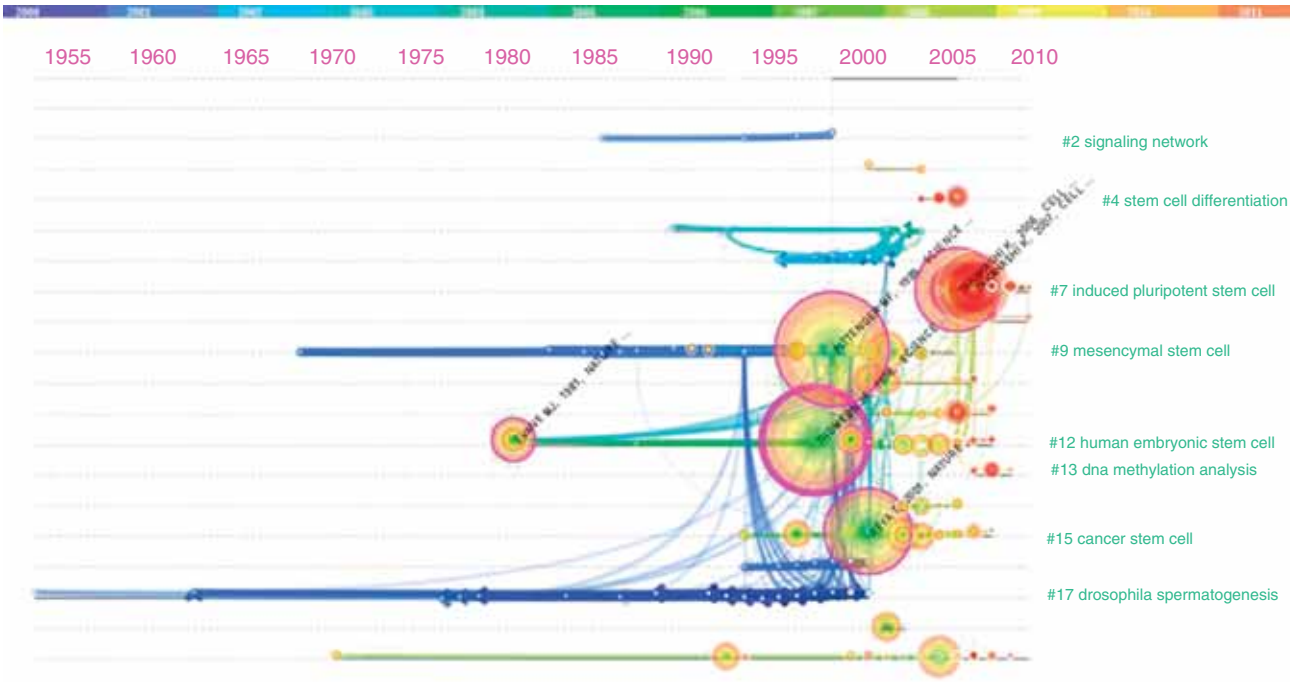

Figure 4. Timelines of co-citation clusters. Major clusters are labeled on the right. Landmark articles are labeled.

Table 6. Cited citations with the highest betweenness centrality.

Rank	Centrality	References	Cluster #
1	0.55	Thomson JA, 1998, Science, V282, P1145	12
2	0.32	Bjornson CRR, 1999, Science, V283, P534	9
3	0.18	Evans MJ, 1981, Nature, V292, P154	12
4	0.17	Reya T, 2001, Nature, V414, P105	15
5	0.15	Kiger AA, 2000, Nature, V407, P750	17
6	0.13	Pittenger MF, 1999, Science, V284, P143	9
7	0.11	Takahashi K, 2006, Cell, V126, P663	7
8	0.11	Reubinoff BE, 2000, Nat Biotechnol, V18, P399	12
9	0.10	Martin GR, 1981, Proc Natl Acad Sci-Biol, V78, P7634	12

They are central in connecting the network's components.

The average year of publication of a cluster indicates its recentness. For example, Cluster #9 on MSC has an average year of 1999. The most recently formed cluster, Cluster #7 on iPSCs, has an average year of 2008.

Cluster #7 contains numerous nodes with red rings of citation bursts. The visualized network also shows highly burst terms found in the titles and abstracts of citing articles to the major clusters. For example, terms *stem-cell-renewal* and *germ-line-stem-cells* are not only used when articles cite references in Cluster #17 drosophila spermatogenesis, but also used with a period of rapid increase. Similarly, the term *induced-pluripotent-stem-cells* is a burst term associated with Cluster #7, which is consistently labeled as iPSC by a different selection mechanism, the LLR. We will particularly focus on Cluster #7 in order to identify emerging trends in regenerative medicine.

Figure 3 shows an overview of a network of co-cited references and burst terms on regenerative medicine. Each cluster involves citing articles as well as cited references. The following tables list key players of four major clusters #17, #9, #12 and #7 to indicate their critical research focuses. Five citing articles that the most references in a cluster are selected, whereas five cited references that have the most citations are highlighted. Clusters #5 and #6 appear to be almost exclusively formed by the publications of Katoh M.

The core members of Cluster #9 represent major milestones in relation to MSCs, notably Pittenger *et al.*'s article on *Multilineage Potential of Adult Human Mesenchymal Stem Cells* [23] and an article by Jiang *et al.*, entitled *Pluripotency of mesenchymal stem cells derived from adult marrow* [25].

Cluster #12, human hESCs, contains further milestones in stem cell research. The second most highly cited work in this

Table 7. Most cited references.

Citation counts	References	Cluster #
2486	Pittenger MF, 1999, Science, V284, P143	9
2223	Thomson JA, 1998, Science, V282, P1145	12
2102	Reya T, 2001, Nature, V414, P105 [Review]	15
1841	Takahashi K, 2006, Cell, V126, P663	7
1583	Takahashi K, 2007, Cell, V131, P861	7
1273	Yu JY, 2007, Science, V318, P1917	7
1145	Jain RK, 2005, Science, V307, P58	19
1061	Jiang YH, 2002, Nature, V418, P41	9
1030	EVANS MJ, 1981, Nature, V292, P154	12
945	Al-Hajj M, 2003, Proc Natl Acad Sci USA, V100, P3983	15

Table 8. References with the strongest citation bursts.

Citation bursts	References	Cluster #
124.73	Takahashi K, 2006, Cell, V126, P663	7
121.36	Takahashi K, 2007, Cell, V131, P861	7
81.37	Yu JY, 2007, Science, V318, P1917	7
71.24	Okita K, 2008, Science, V322, P949	7
66.23	Meissner A, 2008, Nature, V454, P766	13
63.12	Vierbuchen T, 2010, Nature, V463, P1035	8
62.54	Zhou HY, 2009, Cell Stem Cell, V4, P381	7

cluster is the 1981 article by Evans and Kaufman (**Table 4**) [26]. Their work pioneered the establishment of pluripotent cell lines in tissue culture from mouse blastocysts. The predominant member of the cluster is the 1998 landmark article by Thomson *et al.* As of November 2011, it has 2223 citations in the Web of Science. Their work reported the establishment of pluripotent cell lines from human blastocysts and opened up new grounds for human developmental biology, drug discovery and transplantation medicine.

The five major citing articles, in terms of their citation coverage, are all published in 2010, more than 10 years later after the human blastocyst-derived pluripotent cell lines and 20 years since the first mouse blastocyst-derived pluripotent cell lines.

Cluster #7 is the most recently formed cluster. We selected 10 most cited references in this cluster and 10 citing articles (**Table 5**).

The most cited article in this cluster, Takahashi 2006 [27], demonstrated how pluripotent stem cells can be directly generated from mouse somatic cells by introducing only a few defined factors as opposed to transferring nuclear contents to oocytes or egg cells. Their work is a major milestone. The second most cited reference [28], from the same group of researchers, further advanced the state of the art by demonstrating how differentiated human somatic cells can be reprogrammed into pluripotent stem cells using the same factors identified in their previous work.

Cluster #7 consists of 40 co-cited references. The 10 selected citing articles are all published in 2010. They cited 65 – 95% of these references. The one that has the highest citation coverage of 95% is an article by Stadtfeld *et al.* Unlike works that aim to refine and improve the ways to produce iPSCs, their primary concern was whether iPSCs are equivalent, molecularly and functionally, to blastocyst-derived ESCs. The Stadtfeld article itself belongs to the cluster. Other citing articles also seem to question some of the fundamental assumptions or call for more research before further clinical development in regenerative medicine.

Figure 4 shows a timeline visualization of how the network is divided into distinct co-citation clusters. It is evident that Cluster #7 has a high concentration of nodes with citation bursts, which echoes the fact that this is the most recently formed cluster. Clusters #9 and #17 do not appear to have much current high-profile publications. In addition to Cluster #7, Clusters #11 – #13 appear to have recent publications with citation bursts.

4.1 Betweenness centrality

The betweenness centrality of a node in the network measures the importance of the position of the node in the network. Two types of nodes may have high betweenness centrality scores:

1) Nodes that are highly connected to other nodes such as hubs.
2) Nodes that are positioned between different groups of nodes.

We are particularly interested in the second type because they are more likely to lead to insights into emerging trends than the first type of nodes.

Table 6 shows nine structurally essential references in the synthesized network. These references are important in terms of not only how they connect individual nodes in the network but also how they connect aggregated groups of nodes, such as co-citation clusters. Three of these nodes are in Cluster #12 and two in Cluster #2. These works can be seen as landmark works in the context of our broadly defined area of regenerative medicine.

4.2 Most cited articles

The most cited articles are usually regarded as the landmarks due to their groundbreaking contributions. Cluster #7 has 3 articles in the top 10 landmark articles. Each of Clusters #9, #12 and #15 has two. The most cited article in our dataset is Pittenger MF (1999) with 2486 citations, followed by

Table 9. Structurally and temporally significant references.

Sigma	Burst	Centrality	Citations	References	Cluster #
377340.46	124.73	0.11	1841	Takahashi K, 2006, Cell, V126, P663	7
29079.18	37.38	0.32	202	Bjornson CRR, 1999, Science, V283, P534	9
195.15	121.36	0.04	1583	Takahashi K, 2007, Cell, V131, P861	7
58.91	81.37	0.05	1273	Yu JY, 2007, Science, V318, P1917	7
15.97	19.53	0.15	130	Kiger AA, 2000, Nature, V407, P750	17

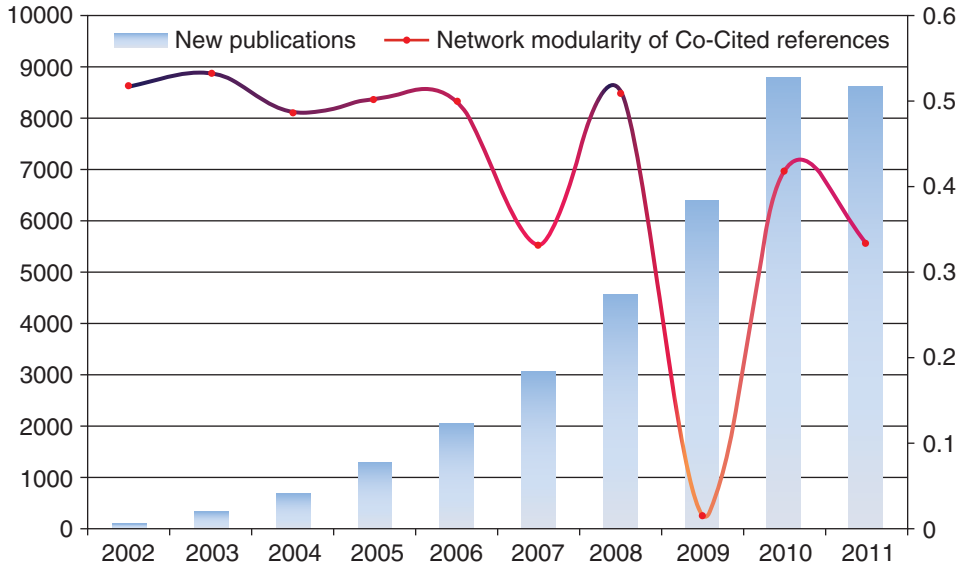

Figure 5. The modularity of the network dropped considerably in 2007 and even more in 2009, suggesting that some major structural changes took place in these 2 years in particular.

Thomson JA (1998) with 2223 citations. The third one is a review article by Reya T (2001). Articles at the fourth to sixth positions are all from Cluster #7, namely Takahashi K (2006), Takahashi K (2007) and Yu JY (2007). These three are also the more recent articles on the list, suggesting that they have inspired intense interest in iPSCs.

4.3 Citation bursts

A citation burst has two attributes: the intensity of the burst and how long the burst status lasts. **Table 8** lists references with the strongest citation bursts across the entire dataset during the period of 2000 – 2011. The first four articles with strong citation bursts are from Cluster #7 on iPSCs. Interestingly, one 2009 article (again in Cluster #7) and one 2010 article (in Cluster #8, a small cluster) are detected to have considerable degrees of citation burst.

4.4 Sigma

The Sigma metric measures both structural centrality and citation burstness of a cited reference. If a reference is strong in both measures, it will have a higher Sigma value than a reference that is only strong in one of the two measures (**Table 9**).

The pioneering iPSCs article by Takahashi (2006) has the highest Sigma of 377340.46, which means it is structurally essential and inspirational in terms of its strong citation burst. The second highest work by this measure is a 1999 article in Science by Bjornson *et al.* [29]. They reported an experiment in which neural stem cells were found to have a wider differentiation potential than previously thought because they evidently produced a variety of blood cell types.

5. Emerging trends

The modularity of a network measures the degree to which nodes in the network can be divided into a number of groups such that nodes within the same group are connected tighter than nodes between different groups. The collective intellectual structure of the knowledge of a scientific field can be represented as associated networks of co-cited references. Such networks evolve over time. Newly published articles may introduce profound structural variation or have little or no impact on the structure.

Figure 5 shows the change of modularity of networks over time. Each network is constructed based on a 2-year sliding

Table 10. Articles published in 2007 with subsequent citation bursts in descending order of local citation counts.

Ref.	Local citations	Title	Burst	Duration	Range (2000 – 2011)
Takahashi 2007 [28]	1583	Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors	121.36	2009 – 2011	
Yu 2007 [39]	1273	Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells	81.37	2009 – 2011	
Wernig 2007 [40]	640	In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state	26.70	2008 – 2009	
O'Brien 2007 [41]	438	A human colon cancer cell capable of initiating tumour growth in immunodeficient mice	18.13	2008 – 2009	
Ricci-Vitiani 2007 [42]	427	Identification and expansion of human colon-cancer-initiating cells	8.83	2008 – 2009	
Li 2007 [43]	299	Identification of Pancreatic Cancer Stem Cells	9.78	2008 – 2008	
Mikkelsen 2007 [44]	283	Genome-wide maps of chromatin state in pluripotent and lineage-committed cells	19.59	2010 – 2011	
Laflamme 2007 [45]	265	Cardiomyocytes derived from human embryonic stem cells in pro-survival factors enhance function of infarcted rat hearts	16.48	2010 – 2011	
Gimble 2007 [46] [R]	247	Adipose-Derived Stem Cells for Regenerative Medicine	25.19	2010– 2011	
Phinney 2007 [47] [R]	229	Concise Review: Mesenchymal Stem/ Multipotent Stromal Cells: The State of Transdifferentiation and Modes of Tissue Repair—Current Views	16.52	2010 – 2011	
Khang 2007 [48] [In Korean]	90	Recent and future directions of stem cells for the application of regenerative medicine	35.25	2008 – 2009	

window. The number of publications per year increased considerably. It is noticeable that the modularity dipped in 2007 and bounced back to the previous level before it dropped even deeper in 2009. Based on this observation, it is plausible that groundbreaking works appeared in 2007 and 2009. We will, therefore, specifically investigate potential emerging trends in these 2 years.

Which publications in 2007 would explain the significant decrease in the modularity of the network formed based on publications prior to 2007? If a 2007 publication has a subsequent citation burst, then we expect that this publication played an important role in changing the overall intellectual structure. Eleven publications in 2007 are found to have subsequent citation bursts (**Table 10**). Notably, Takahashi 2007 and Yu 2007 top the list. Both of them represent pioneering investigations of reprogramming human body cells to iPSCs. Both of them have current citation bursts since 2009. Other articles on the list address the pluripotency of stem cells related to human cancer, including colon cancer and pancreatic cancer. Two review articles on regenerative medicine and tissue repair are published in 2007 with citation bursts since 2010. These observations suggest that the modularity change in 2007 is an indication of an emerging trend in the human iPSC research. The trend is current and active as shown by the number of citation bursts associated with publications in 2007 alone.

If the modularity change in 2007 indicates an emerging trend in human iPSCs research, what caused the even more profound modularity change in 2009? The cluster that is responsible for the 2009 modularity change is Cluster #7 iPSC. On the one hand, the cluster contains Takahashi 2006 and Takahashi 2007, which pioneered the human iPSC trend. On the other hand, the cluster contains many recent publications. The average age of the articles in this cluster is 2008. Therefore, we examine the members of this cluster closely, especially focusing on 2009 publications.

The impact of Takahashi 2006 and Takahashi 2007 is so profound that their citation rings would overshadow all other members in Cluster #7. After excluding the display of their overshadowing citation rings, it becomes apparent that this cluster is full of articles with citation bursts, which are shown as citation rings in red. We labeled the ones published in 2009 and also two 2008 articles and one 2010 article (**Figure 6** and **Table 11**).

The pioneering reprogramming methods introduced by Takahashi 2006 and Takahashi 2007 modify adult cells to obtain properties similar to ESCs using a cancer-causing oncogene c-Myc as one of the defined factors and a virus to

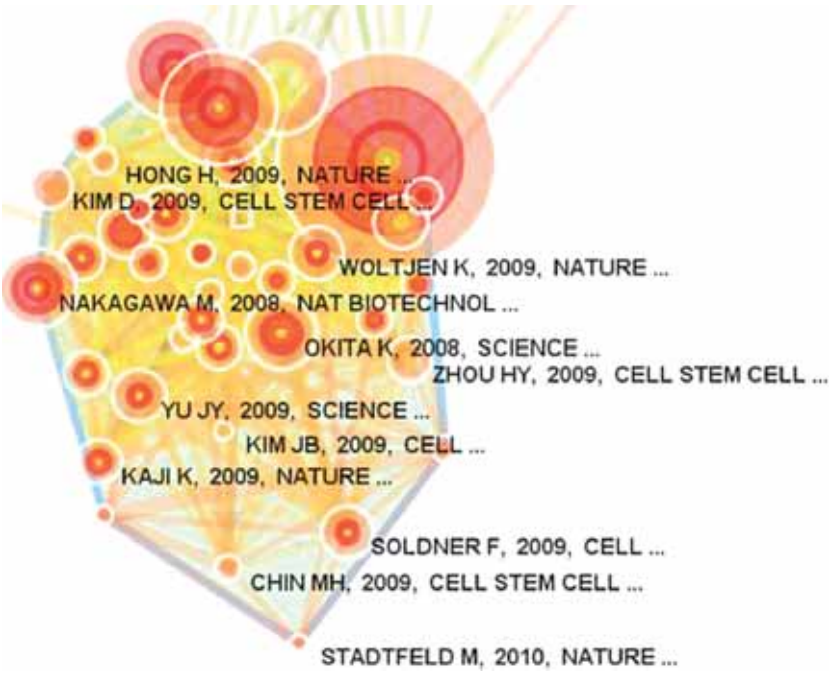

Figure 6. Many members of Cluster #7 are found to have citation bursts, shown as citation rings in red. Chin MH 2009 and Stadtfeld M 2010 at the bottom area of the cluster represent a theme that differs from other themes of the cluster.

deliver the genes into target cells [30]. It was shown later on that c-Myc is not needed. The use of viruses as the delivery vehicle raised safety concerns of its clinical implications in regenerative medicine because viral integration into target cells' genome might activate or inactivate critical host genes. Searching for virus-free techniques motivated a series of such studies, leading by an article [31] appeared on 9 October 2008.

What many of these 2009 articles have in common appear to be the focus on improving previous techniques of reprogramming human somatic cells to regain a pluripotent state. It was realized that the original method used to induce pluripotent stem cells has a number of possible drawbacks associated with the use of viral reprogramming factors. Several subsequent studies investigated alternative ways to induce pluripotent stem cells with lower risks or improved certainty. These articles were published within a short period of time. For instance, Woltjen 2009 demonstrated a virus-independent simplification of iPSC production. On 26 March 2009, Yu *et al.*'s article demonstrated that reprogramming human somatic cells can be done without genomic integration or the continued presence of exogenous reprogramming factors. On 23 April 2009, Zhou *et al.*'s article demonstrated how to avoid using exogenous genetic modifications by delivering recombinant cell-penetrating reprogramming proteins directly into target cells. Soldner 2009 reported a method without using viral reprogramming factors. Kaji reported a virus-free pluripotency induction method. On 28 May 2009, Kim *et al.*'s article introduced a method of direct delivery of reprogramming proteins.

Vierbuchen 2010 is one of the few most recent articles that are found to have citation bursts. The majority of the 2009 articles with citation bursts focused on reprogramming human somatic cells to an undifferentiated state. By contrast, Vierbuchen 2010 expanded the scope of reprogramming by demonstrating the possibility of converting fibroblasts to functional neurons directly.

Two articles of particular interest appear at the lower end of Cluster #7, Chin *et al.* 2009 [4] and Stadtfeld *et al.* 2010. Chin *et al.*'s article has 158 citations within the dataset. A citation burst was detected for Chin 2009 since 2010. Chin *et al.* questioned whether iPSCs are indistinguishable from ESCs. Their investigation suggested that iPSCs should be considered as a unique subtype of pluripotent cell.

The co-citation network analysis has identified several articles that cite the work by Chin *et al.* In order to establish whether Chin *et al.* represents the beginning of a new emerging trend, we inspect these citing articles listed in **Table 12**. Stadtfeld 2010 is the most cited citing article by itself with 134 citations. Similar to Chin *et al.*, Stadtfeld 2010 addresses the question whether iPSCs are molecularly and functionally equivalent to blastocyst-derived ESCs. Their work identified the role of Dlk1–Dio3 gene cluster in association with the level of induced pluripotency. In other words, these studies focus on mechanisms that govern induced pluripotency, which can be seen as a distinct trend from the earlier trend on improving reprogramming techniques. **Table 12** includes two review articles cited by Stadtfeld 2010.

Table 11. Articles published in 2009 with citation bursts.

Ref.	Local citations	Title	Burst	Burst duration	Range (2000 – 2011)
Woltjen 2009 [49]	320	piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells	52.65	2009 – 2011	
Yu 2009 [50]	300	Human Induced Pluripotent Stem Cells Free of Vector and Transgene Sequences	59.97	2010 – 2011	
Zhou 2009 [51]	293	Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins	62.54	2010 – 2011	
Soldner 2009 [52]	288	Parkinson's Disease Patient-Derived Induced Pluripotent Stem Cells Free of Viral Reprogramming Factors	53.94	2010 – 2011	
Kaji 2009 [53]	284	Virus-free induction of pluripotency and subsequent excision of reprogramming factors	46.71	2009 – 2011	
Kim 2009 [54]	235	Generation of Human Induced Pluripotent Stem Cells by Direct Delivery of Reprogramming Proteins	56.03	2010 – 2011	
Ebert 2009 [55]	211	Induced pluripotent stem cells from a spinal muscular atrophy patient	41.91	2010 – 2011	
Kim 2009 [56]	194	Oct4-Induced Pluripotency in Adult Neural Stem Cells	31.87	2009 – 2011	
Vierbuchen 2010 [57]	193	Direct conversion of fibroblasts to functional neurons by defined factors	63.12	2010 – 2011	
Lister 2009 [58]	161	Human DNA methylomes at base resolution show widespread epigenomic differences	51.93	2010 – 2011	
Chin 2009 [4]	158	Induced Pluripotent Stem Cells and Embryonic Stem Cells Are Distinguished by Gene Expression Signatures	45.39	2010 – 2011	
Discher 2009 [59]	149	Growth Factors, Matrices, and Forces Combine and Control Stem Cells	43.14	2010 – 2011	
Hong 2009 [60]	138	Suppression of induced pluripotent stem cell generation by the p53–p21 pathway	43.71	2010 – 2011	
Slaughter 2009 [61]	97	Hydrogels in Regenerative Medicine	31.68	2010 – 2011	

The new emerging trend is concerned with the equivalence of iPSCs and their hESC counterparts in terms of their short- and long-term functions. The new trend has critical implications on the therapeutic potential of iPSCs. In addition to the works by Chin *et al.* and Stadtfeld *et al.*, an article published on 2 August 2009, by Boland *et al.* [32] reported an investigation of mice derived entirely from iPSCs. Another article [5] appeared on 12 February 2010, investigated abnormalities such as limited expansion and early senescence found in human iPSCs. The Stadtfeld 2010 article [6] we discussed earlier appeared on 13 May 2010.

Some of the more recent citing articles of Chin *et al.* focused on providing resources for more stringent evaluative and comparative studies of iPSCs. On 7 January 2011, an article [33] reported a study of genomic stability and abnormalities in pluripotent stem cells and called for frequent genomic monitoring to assure phenotypic stability and clinical safety. On 4 February 2011, Bock *et al.* [34] published genome-wide reference maps of DNA methylation and gene expression for 20 previously derived human ES lines and 12 human iPS cell lines. In a more recent article [35] published on 11 February 2011, Boulting *et al.* established a robust resource that consists of 16 iPSC lines and a stringent test of differentiation capacity.

iPSCs are characterized by their self-renewal and versatile ability to differentiate into a wide variety of cell types. These properties are invaluable for regenerative medicine. However, the same properties also make iPSCs tumorigenic or cancer prone. In a review article published in April 2011, Ben-David and Benvenisty [36] reviewed the tumorigenicity of human embryonic and iPS cells. Zhao *et al.* challenged a generally held assumption concerning the immunogenicity of iPSCs in an article [37] on 13 May 2011. The immunogenicity of iPSCs has clinical implications on therapeutically valuable cells derived from patient-specific iPSCs.

In summary, a series of more recent articles have re-examined several fundamental assumptions and properties of iPSCs with more profound considerations for clinical and therapeutic implications on regenerative medicine [38].

Table 12. Articles that cite Chin *et al.*'s 2009 article [4] and their citation counts as of November 2011.

Article	Citations	Title
Stadtfeld 2010 [6]	134	Aberrant silencing of imprinted genes on chromosome 12qF1 in mouse induced pluripotent stem cells
Boland 2009 [32]	109	Adult mice generated from induced pluripotent stem cells
Feng 2010 [5]	72	Hemangioblastic Derivatives from Human Induced Pluripotent Stem Cells Exhibit Ltd Expansion and Early Senescence
Kiskinis 2010 [62] [R]	59	Progress toward the clinical application of patient-specific pluripotent stem cells
Laurent 2011 [33]	48	Dynamic Changes in the Copy Number of Pluripotency and Cell Proliferation Genes in Human ESCs and iPSCs during Reprogramming and Time in Culture
Bock 2011 [34]	31	Reference Maps of Human ES and iPS Cell Variation Enable High-Throughput Characterization of Pluripotent Cell Lines
Zhao 2011 [37]	22	Immunogenicity of induced pluripotent stem cells
Boulting 2011 [35]	17	A functionally characterized test set of human induced pluripotent stem cells
Young 2011 [63] [R]*	16	Control of the Embryonic Stem Cell State
Ben-David 2011 [36] [R]*	11	The tumorigenicity of human embryonic and induced pluripotent stem cells

*Cited by Stadtfeld 2010 [6].
[R]: Review articles.

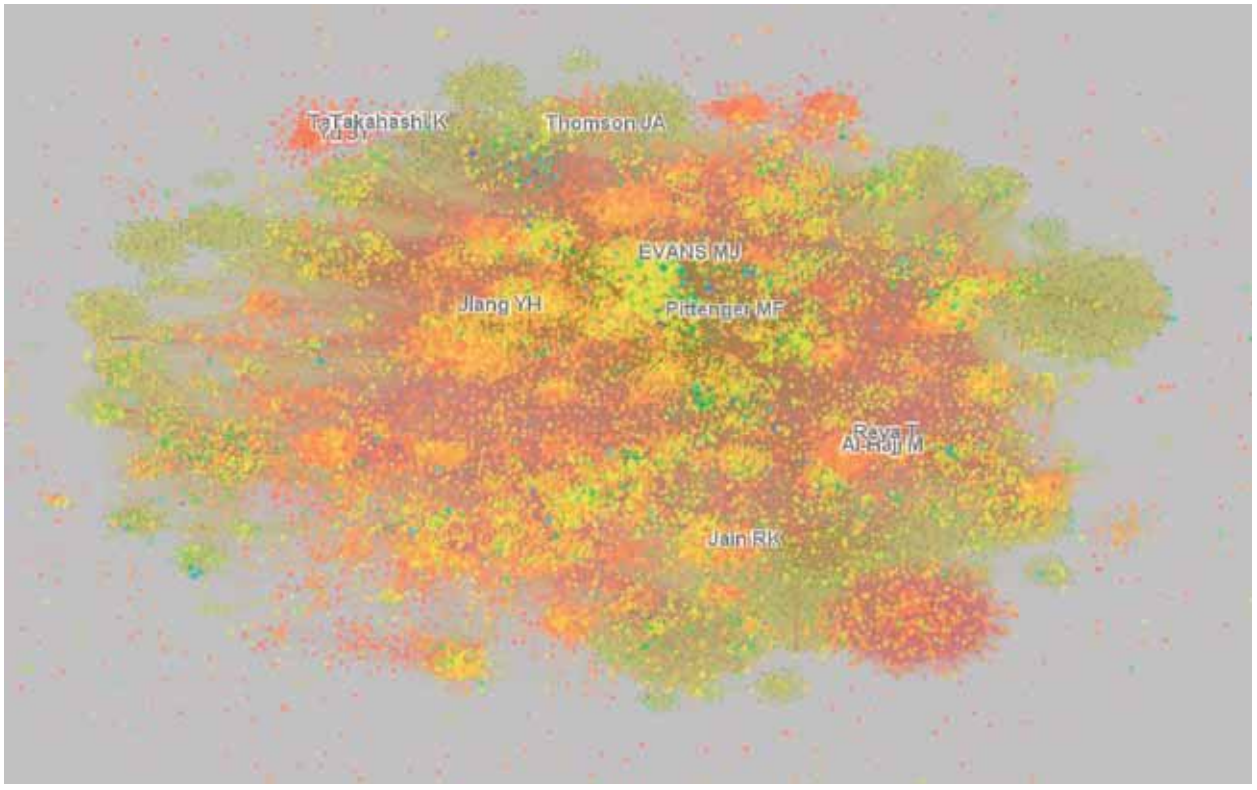

Figure 7. An extensive network of 18,811 references cited by 4000 publications in regenerative medicine each year from 2000 till 2011.

It is also possible to place the analysis in a broader context by taking into account the citation behavior of more publications each year. For example, **Figure** 7 shows an extensive network of 18,811 references shaped by the citation behavior of 4000 publications each year from 2000 till 2011 in relation to regenerative medicine. The colors indicate the time of publication. Early publications are in darker colors, whereas more recent ones are in yellow and orange colors. Labels on the map highlight the names of authors of the most highly cited references. The area that corresponds to the iPSC cluster is located at the upper left corner of the network in orange, where the names of Takahashi and Yu are

labeled. Networks visualized at this level may provide a good starting point to make sense of the dynamics of the evolving field. On the other hands, the devils are in the details. Differentiating topics, hypotheses and findings at document and predicate is essential to the study of an evolving scientific field.

6. Conclusion

In conclusion, the analysis of the literature of regenerative medicine and a citation-based expansion has outlined the evolutionary trajectory of the collective knowledge over the last decade and highlighted the areas of active pursuit. Emerging trends and patterns identified in the analysis are based on computational properties selected by CiteSpace, which is designed to facilitate sense-making tasks of scientific frontiers based on relevant domain literature.

Regenerative medicine is a fascinating and a fast-moving subject matter. As information scientists, we have demonstrated a scientometric approach to tracking the advance of the collective knowledge of a dynamic scientific community by tapping into what experts in the domain have published in the literature and how information and computational techniques can help us to discern patterns and trends at various levels of abstraction, namely, cited references and clusters of co-cited references.

7. Expert opinion

It is worth noting that this expert opinion is solely based on scientometric patterns revealed by CiteSpace without prior working experience in the regenerative medicine field. Based on the analysis of structural and temporal patterns of citations and co-citations, we have identified two major emerging trends. The first one started in 2007 with pioneering works on human iPSCs, including subsequently refined and alternative techniques for reprogramming. The second one started in 2009 with an increasingly broad range of examinations and reexaminations of previously unchallenged assumptions with clinical and therapeutic implications on regenerative medicine, including tumorigenicity and immunogenicity of iPSCs.

The referential expansion of the original topic search of regenerative medicine has revealed a much wider spectrum of intellectual dynamics. The visual analysis of the broader domain outlines the major milestones throughout the extensive period of 2000 – 2011. Several indicators and observations converge to the critical and active role of Cluster #7 on iPSCs. By tracing interrelationships along citation links and citation bursts, visual analytic techniques of scientometrics are able to guide our attention to some of the most vibrating and rapidly advancing research fronts and identify the strategic significance of various challenges addressed by highly specialized technical articles. The number of review articles on relevant topics is rapidly increasing, which is also a sign that the knowledge of regenerative medicine has been advancing rapidly. We expect that visual analytic tools as we utilized in this review will play a more active role in supplement to traditional review and survey articles. Visual analytic tools can be valuable in finding critical developments in the vast amount of newly published studies.

The key findings of the regenerative medicine and related research over the last decade have shown that regenerative medicine has become more and more feasible in many areas and that it will ultimately revolutionize clinical and healthcare practice and many aspects of our society. On the other hand, the challenges ahead are enormous. The biggest challenge is probably related to the fact that human beings are a complex system in that a local perturbation may lead to unpredictable consequences in other parts of the system, which in turn may affect the entire system. The state of the art in science and medicine has a long way to go to handle such complex systems in a holistic way. Suppressing or activating a seemingly isolated factor may have unforeseen consequences.

The two major trends identified in this review have distinct research agendas as well as different perspectives and assumptions. In our opinion, the independencies of such trends at a strategic level are desirable at initial stages of these emerging trends so as to maximize the knowledge gain that is unlikely to be achieved by a single line of research alone. In a long run, more trends are expected to emerge from probably the least expected perspectives. Existing trends may be accommodated by new levels of integration. We expect that safety and uncertainty will remain to be the central concern of regenerative medicine.

Declaration of interest

H Tseng works at NIAMS/NIH, his view expressed here is personal and not representing any official policy of NIAMS/NIH. None of the other authors have any conflicts of interest to disclose.

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