Science System Assessment

Regenerative Medicine: an Emerging Research Field

Peter van den Besselaar and Thomas Gurney

Rathenau Instituut

Regenerative Medicine: an Emerging Research Field

Peter van den Besselaar & Thomas Gurney

Regenerative Medicine: an Emerging Research Field

Peter van den Besselaar & Thomas Gurney

Rathenau Instituut
Anna van Saksenlaan 51

Postal address:
Postbus 95366
2509 CJ Den Haag

Tel: +31 (0)70-342 15 42
Fax: +31 (0)70-363 34 88
E-mail: info@rathenau.nl
Website: www.rathenau.nl

Publisher: Rathenau Instituut

Preferred citation:
Peter van den Besselaar & Thomas Gurney, *Regenerative medicine: an emerging research field*.
Den Haag, Rathenau Instituut, 2009.

Science System Assessment Report 0912

June 2009

Table of Contents

1 Introduction

This report analyzes the knowledge dynamics of a new research field, *Regenerative Medicine*. The study is part of the forecasting exercise of the Council for Medical Research (RMW) of the Royal Netherlands Academy of Science (KNAW). The aim of these forecasts is to create an overview of the developments in a discipline or research field. What are the promising developments, what is the position of the Netherlands in the field, and what agenda setting policies, funding instruments and organizational forms can be used to stimulate the development of the research field under study? These forecasts can be done for existing disciplines, but also for new and emerging research fields.

Regenerative Medicine (RM) is such a new and emerging field of research. This report answers a set of questions with respect to its early development.

- What is the nature of the field of RM?
- What is the size of the research field, in terms of research papers in international journals? What is its rate of growth? In what research fields do papers on regenerative medicine (RM) appear? What are the specific RM journals?
- What is the focus of current regenerative medicine research and has this changed over time?
- Where does the field emerge from - on what research traditions is it based?
- In which direction is the research field moving? Is it emerging as a identifiable research field, different from other and related fields? Or is RM a set of different research questions, combining together in a multidisciplinary program - spread over a heterogeneous set of specialties? Or, is it a label covering a heterogeneous set of activities, without any meaningful strong connection.
- What is the social and organizational environment of regenerative medicine?
    - What is the position of different countries and research organizations in the research field and in the various subfields?
    - What are the collaboration networks of the Dutch universities in the Netherlands and internationally?

In this report[1] we will try to answer these questions, mainly by using bibliometric methods.[2] In order to do this, we adopt an analytical framework in which research fields are described in three dimensions: growth, the nature of scientific change, and the knowledge dependencies.[3] The analysis is done at the level of networks of scholarly journals, as this shows the development of RM as a research field in connection with other relevant research fields in its environment. As a methodological exercise, we present in annex 2 an analysis of the development of research topics within RM. Although the annex has mainly a methodological focus, the results support the findings at the higher (journal) level.

As the report shows, RM is a combination of tissue engineering and stem cell research. It therefore is highly subjected to ethical debates. In annex 1, we map the ethical discussion around RM, as reflected in the scholarly literature.

---

1 This study is included as annex 4 in the final report of the forecast committee: Opportunities for regenerative medicine in the Netherlands. Amsterdam, KNAW, 2009 (in Dutch).

2 Peter van den Besselaar, Loet Leydesdorff, The development of Artificial Intelligence. *JASIS* **47**, 1996. Peter van den Besselaar & Gaston Heimeriks, Disciplinary, Multidisciplinary, Interdisciplinary: Concepts and Indicators. In M. Davis & C.S. Wilson (eds), *Proceedings 8th International Conference on Scientometrics and Informetrics - ISSI 2001*. Sydney: UNSW 2001. 705-716. Peter van den Besselaar, Gaston Heimeriks, Mapping research topics using word-reference co-occurrences. *Scientometrics* **68** (2006) pp 377-393.

3 Peter van den Besselaar, Antoine Schoen, Louise Herrera, Philippe Laredo, *Knowledge dynamics, the case of chemistry* (forthcoming).

2 Method and data

2.1 Introduction

The analysis in this report is based on the theory that research specialties consist of a densely connected (communication) network of journals. Journals that have similar positions in the scholarly communication network are considered to belong to the same specialty.

Research fields can be mapped on different levels of aggregation. Studying the structure of a *discipline* or a sub-discipline (a research field) can best be done at the level of the specialist journals.[4] This is also true for interdisciplinary fields.[5] However, when mapping the research fronts within a delineated research field, scholarly articles within a predetermined journal context are the correct data form choice. Additionally, the phase of development of a research field is important. In the early phases of development, specialized journals do not yet exist, or are only coming into existence. In such situations of *emerging research fields*, there is no other option than to delineate a research field in terms of papers - selected through keywords and/or citation relations. If this is done, we can test whether a set of core journals is emerging in the field, and eventually these can be used to map the research field as a network of journals. This mapping approach is followed in this report as this enables us to identify the 'invisible college' of core researchers and their institutional affiliations; and it enables us to study whether a research field in terms of a journal is emerging at all.

2.2 Method and data

We started by consulting members of the *KNAW committee on regenerative medicine* as to relevant journal titles. The request for core journals resulted in a large list of titles, from general biomedical and biochemistry journals to more specialized ones. In terms of journal type, the list contains biomaterial journals, tissue engineering journals, regeneration and transplantation journals, and cell research journals. Apart from these, journals focusing on specific organs/tissues were found on the list as well as fundamental journals of biomedical and biochemical research. In other words, the coverage of regenerative medicine by a set of journals is not straightforward, which is not uncommon in new fields of research. Consequently, a keyword based approach was used for the *exploration* of the structure of regenerative medicine. We took the following steps:

- 1a) Selection of relevant keywords (through an iterative process of retrieving and validating), leading to the
- 1b) delineation of a corpus of relevant papers - from the Web of Science - using 'topic search' which in turn enables the
- 1c) identification of the main journals in which these papers were published.
- 2) The most important journals are used for mapping the field of regenerative medicine in terms of journal sets - using citation relations between journals as reported in the Journal Citation Reports (JCR).
- 3a) Papers and journals networks can be used for identifying the various subfields of regenerative medicine: a knowledge map of the field, which leads us to the
- 3b) identification of relevant research institutions and their collaboration networks.

4 Van den Besselaar, Schoen et al (forthcoming).
5 Van den Besselaar, Heimeriks 2001.

The keywords were used to retrieve publications from the ISI Science Citation Index (WoS edition - updated until December 31, 2008). We used 'topic search' in which the documents were retrieved by the selected keywords (search terms) appearing in either the title, abstract or keyword list. We restricted the search to so-called *citable items*: articles, letters, notes and reviews (ALNR).[6]

For the journals networks we used the Journal Citation Reports (CD Rom version). We used the 2000, 2003, and 2007 versions to make a map for each of these years - in order to investigate the development of RM over time. For analyzing the data we used the Science System Assessment toolbox.[7]

2.3 Identifying the relevant keywords

The identification of keywords was done trough an iterative process of selecting keywords, retrieving the document set, having the document set inspected by specialists, and then adapting the keywords and starting a next cycle. An initial experiment was done with a restricted set of keywords: "regenerative medicin*", "tissue engineer*" and "biomaterial*", using *topic search* in the *Web of Science*. The members of the *KNAW committee on regenerative medicine* were asked to reflect on the obtained papers from which it was then decided to add several additional keywords (Table 1). For the period, 2006-2007, 14981 documents were retrieved. However, using the keywords individually, we retrieved 19436 papers. This implied that 81% of the papers were found through only one keyword. Checking this for the individual keywords, several keywords turned out to be rather disjunctive, like "biomaterial*" (88%), "cell* therap*" (70%) and "remodel* AND tissue*" (89%).

Table 1 General search

Selected key words		Hits 2006-2007	% unique
1	"regenerative medicin*"	614	24%
2	*"tissue engineer*"*	*3816*	*53%*
3	*"cell* therap*"*	*1553*	*70%*
4	*"marrow stromal"*	*1497*	*44%*
5	"mesenchym* stromal"	166	56%
6	*"mesenchym* stem"*	*3138*	*56%*
7	*"biomaterial*"*	*3370*	*88%*
8	"cell transplantation" AND regenerat*	321	55%
9	"tissue transplantation" AND regenerat*	9	44%
10	bioactivity AND biomaterial*	149	0%
11	bioactivity AND scaffold*	132	38%
12	biodegrada* AND scaffold*	624	20%
13	remodel* AND tissue*	2503	89%
14	*"tissue repair*"*	*716*	*65%*
15	"tissue regeneration"	835	45%
	Sum	**19436**	
	Total number of documents	**14981**	**81%**

Topic search: January 3, 2009; Databases: SCI expanded, SSCI, AHCI - all publication types.
Same search for the period 1975-2007: 54086 documents.

6 In the remainder of the report, the term 'papers' will be used for these document types.

7 Andre Somers, Thomas Gurney, Edwin Horlings, Peter van den Besselaar, *A bibliometric toolbox for analyzing knowledge dynamics.* (forthcoming)

Is the selection of keywords correct? Two issues are at stake here: recall and precision. Firstly, what is the quality of the *recall* of publications, that is do we find all or most articles belonging to the field of regenerative medicine? Secondly, is the *precision* of the retrieved set high enough? That is, does the search not include many irrelevant papers? Obviously, there is a trade off between recall and precision - the more precise we try to be, the higher the risk that relevant papers are excluded, and the better the recall we try to get, the lower the precision generally is. If the keywords are too general, it is useful to combine them with other words thus increasing precision.

Inspection of a sample of the retrieved papers suggested that the recall indeed was too large - and precision too low. For example, a large amount of non-RM papers on molecular cell research were included. Therefore, we refined the search by replacing keywords with a large percentage 'unique hits' (> 60% of the retrieved documents by such keywords were only retrieved through one keyword), or with a large recall (>1500 papers), by composite keywords (Table 2). This was done for the keywords "tissue engineer*", "mesenchym* stem", "tissue repair*", "marrow stromal", "cell* therap*", "biomaterials" and remodel* AND tissue*.

Table 2 Refined search with composite keywords: the example of tissue engineering

("tissue engineer*" AND biomaterial*) OR
("tissue engineer*" AND medica*) OR
("tissue engineer*" AND health*) OR
("tissue engineer*" AND scaffold*) OR
("tissue engineer*" AND repair) OR
("tissue engineer*" AND cell*) OR
("tissue engineer*" AND "extracellular matrix") OR
("tissue engineer*" AND bioreactor*) OR
("tissue engineer*" AND "mechanical properties" AND biomate* AND tissue*) OR
("tissue engineer*" AND "in-vivo*") OR
("tissue engineer*" AND "in-vitro*") OR
("tissue engineer*" AND "bone marrow") OR
("tissue engineer*" AND "stromal cell*") OR
("tissue engineer*" AND regeneration) OR
("tissue engineer*" AND biocompab*) OR
("tissue engineer*" AND implants)

For the keywords, "tissue engineer*", "mesenchym* stem", "tissue repair*", and "marrow stromal" the refined set resulted in more or less the same set of papers as with the general search (Table 3).

For the remaining three keywords, "biomaterial*", "cell* therap*" and remodel* AND tissue*, the picture is different. The refined search resulted in much smaller sets of papers. For "biomaterial*", 29% of the papers found in the general search, are not included anymore. This suggests that the general search is not precise enough. Inspection of the retrieved set indeed showed documents that are not medicine-related, but belong to, for example, chemistry, materials science, neuroscience, and nanotechnology. The same holds true for "cell* therap*" (25%) and for 'remodel* AND tissue' (19%).
In conclusion, the refined search was used for "biomaterials*", "cell* therap*", remodel* AND tissue*, and the general search was used for the other keywords. The final search string is in table 4.

Table 3 Comparing the general and refined search

Keyword	Period	General search	Refined search (difference)	
"mesenchym* stem",	2006-2007	3138	3134	(0%)
"tissue repair*"	2006-2007	716	714	(0%)
"marrow stromal"	2006-2007	1498	1498	(0%)
"tissue engineer*"	2007	1924	1842	(-4%'
remodel* AND tissue	2006-2007	2503	2025	(-19%)
"cell* therap*"	2007	873	653	(-25%)
biomaterial*	2007	1836	1297	(-29%)

Table 4 The final set of keywords

"regenerative medicin*" OR "tissue engineer*" OR "marrow stromal" OR "mesenchym* stromal" OR "mesenchym* stem" OR ("cell transplantation" AND regenerat*) OR ("tissue transplantation" AND regenerat*) OR (bioactivity AND biomaterial*) OR (bioactivity AND scaffold*) OR (Biodegrade* AND scaffold*) OR "tissue repair*" OR "tissue regeneration" OR	(biomaterial* AND "tissue engineer*") OR (biomaterial* AND medica*) OR (biomaterial* AND health*) OR (biomaterial* AND scaffold*) OR (biomaterial* AND repair) OR (biomaterial* AND cell*) OR (biomaterial* AND "extracellular matrix") OR (biomaterial* AND bioreactor*) OR (biomaterial* AND "mechanical properties" AND tissue*) OR (biomaterial* AND "in-vivo*") OR (biomaterial* AND "in-vitro*") OR (biomaterial* AND "bone marrow") OR (biomaterial* AND "stromal cell*") OR (biomaterial* AND regeneration) OR (biomaterial* AND biocompab*) OR (biomaterial* AND implants) OR
("cell* therap*" AND biomaterial*) OR ("cell* therap*" AND "tissue engineer *") OR ("cell* therap*" AND medica*) OR ("cell* therap*" AND health*) OR ("cell* therap*" AND scaffold*) OR ("cell* therap*" AND repair) OR ("cell* therap*" AND cell*) OR ("cell* therap*" AND "extracellular matrix") OR ("cell* therap*" AND bioreactor*) OR ("cell* therap*" AND "mechanical properties" AND biomate* AND tissue*) OR ("cell* therap*" AND "in-vivo*") OR ("cell* therap*" AND "in-vitro*") OR ("cell* therap*" AND "bone marrow") OR ("cell* therap*" AND "stromal cell*") OR ("cell* therap*" AND regeneration) OR ("cell* therap*" AND biocompab*) OR ("cell* therap*" AND implants) OR	(remodel* AND tissue* AND "tissue engineer*") OR (remodel* AND tissue* AND biomaterial*) OR (remodel* AND tissue* AND medica*) OR (remodel* AND tissue* AND health*) OR (remodel* AND tissue* AND scaffold*) OR (remodel* AND tissue* AND repair) OR (remodel* AND tissue* AND cell*) OR (remodel* AND tissue* AND "extracellular matrix") OR (remodel* AND tissue* AND bioreactor*) OR (remodel* AND tissue* AND "mechanical properties" AND biomate*) OR (remodel* AND tissue* AND "in-vivo*") OR (remodel* AND tissue* AND "in-vitro*") OR (remodel* AND tissue* AND "bone marrow") OR (remodel* AND tissue* AND "stromal cell*") OR (remodel* AND tissue* AND regeneration) OR (remodel* AND tissue* AND biocompab*) OR (remodel* AND tissue* AND implants)

2.4 Validation of the keywords

In order to validate the keywords, we randomly drew 80 papers from the set of papers and had them inspected by the members of the *KNAW committee on regenerative medicine*. All papers were recognized as relevant for the field of regenerative medicine. In addition, we investigated the most cited papers by the document set from the years 2005, 2006, 2007. These papers were not necessarily in the document set generated by the selected keywords, as every research field cites not only from within but also from outside.

Table 5 shows the top 25 cited papers. The members of the *KNAW committee on regenerative medicine* confirmed that these papers are part of the core of the intellectual base of the field of regenerative medicine. Finally, we retrieved all papers with authors from one of the Dutch universities, and confirmed whether they did indeed feature as RM-researchers. This check also resulted in a satisfactory outcome. In conclusion, the selection of the keywords is correct.

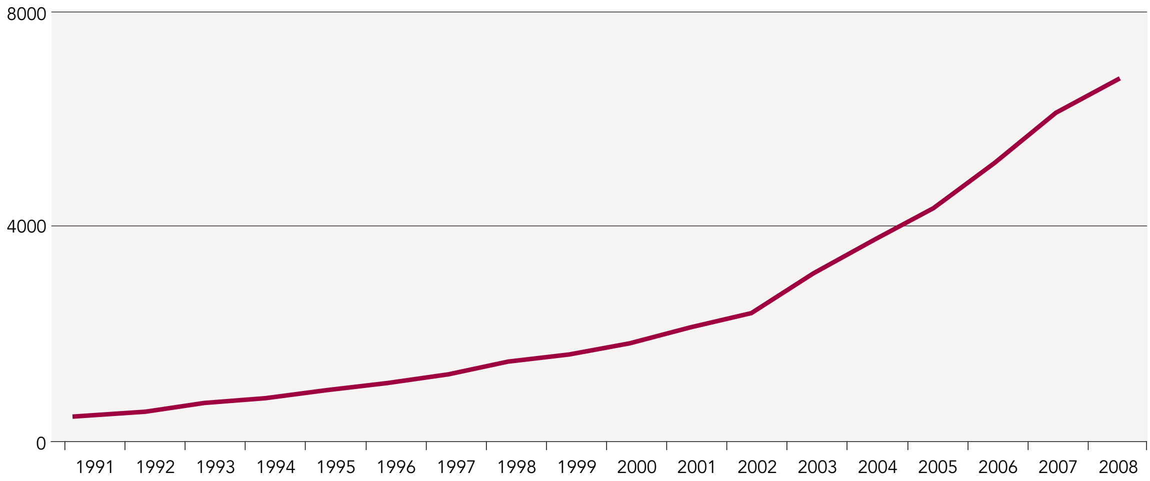
Table 5 Top cited references in the document set

Cited reference	Times cited	Cited reference	Times cited
Pittenger Mf, 1999, Science, V284, P143	1409	Assmus B, 2002, Circulation, V106, P3009,	251
Jiang Yh, 2002, Nature, V418, P41	570	Wollert Kc, 2004, Lancet, V364, P141	249
Langer R, 1993, Science, V260, P920	550	Hutmacher Dw, 2000, Biomaterials, V21, P2529	247
Orlic D, 2001, Nature, V410, P701	481	Asahara T, 1997, Science, V275, P964	242
Prockop Dj, 1997, Science, V276, P71	445	Makino S, 1999, J Clin Invest, V103, P697	226
Zuk Pa, 2001, Tissue Eng, V7, P211	293	Toma C, 2002, Circulation, V105, P93	225
Woodbury D, 2000, J Neurosci Res, V61, P364	280	Caplan Ai, 1991, J Orthop Res, V9, P641	220
Thomson Ja, 1998, Science, V282, P1145	275	Balsam Lb, 2004, Nature, V428, P668,	219
Murry Ce, 2004, Nature, V428, P664,	272	Krause Ds, 2001, Cell, V105, P369	219
Zuk Pa, 2002, Mol Biol Cell, V13, P4279,	263	Brittberg M, 1994, New Engl J Med, V331, P889	218
Strauer Be, 2002, Circulation, V106, P1913,	254	Kocher Aa, 2001, Nat Med, V7, P430	211
Ferrari G, 1998, Science, V279, P1528	253	Orlic D, 2001, P Natl Acad Sci Usa, V98, P10344	210
		Johnstone B, 1998, Exp Cell Res, V238, P265	206

3 Some basic characteristics of the RM document set

Utilizing the keywords in a topic search on the period 1975-2008, 42125 papers were retrieved. In the first year under study, we retrieved only 20 papers with similar counts in the following years - which can be expected in an emerging research field. Most of the papers are of a recent date, and after 1990 the field started to grow fast (Fig 1). Around 2002 a second growth impulse can be observed. The average growth rate of papers since the early 1990s is 18% per year. This suggests that regenerative medicine is a highly dynamic field, increasingly attracting many researchers.

Figure 1 Number of 'regenerative medicine' publications (article, letter, note review) by year (WoS)



As biomedical research develops rapidly, we also focused on a more recent period 2000-2008. In this period, 35010 papers were detected. We used this to determined journals in which the papers were published and the so-called subject areas, which are assigned by the WoS to each journal. In addition, we determined the distribution of papers over countries and institutes (Table 6).

Biomedical engineering is the dominant subject area in which RM papers are published, but cell biology, biomaterials, biochemistry and biotechnology are also strongly represented. For the rest, several core medical fields are present, some focusing on medical disciplines (oncology, immunology) and others on specific tissues and organs (heart and vessels, blood, bone, dental).

The journals in which most papers are published are *Biomaterials, J Biomed Mat Res A and Tissue Engineering* and other biomaterial journals (six places among the top eight). Furthermore, papers are published in journals related to hematology and cardiology (*Blood, Circulation, Hematology*), cell therapy (*Cell Transplantation, Stem Cells, Cytotherapy*), and in fields such as dental research and bone research. Low(er) on the list, there are three journals with 'regenerative medicine' in the title.

All three were launched recently: *Regenerative Medicine* (launched in 2006), *Tissue Engineering and Regenerative Medicine* (2007), and the *Journal of Tissue Engineering and Regenerative*

Table 6 Distribution of 35.010 documents* by journals**, countries#, and institutes## (2000-2008)

Subject areas (freq > 900)	Journals (freq > 150)	Countries (>1%)	Institutes (freq > 200)
5777 Engineering, Biomedical	2028 Biomaterials	37.6% USA	977 Harvard
5202 Cell Biology	1034 J Biomed Mat Res A	10.4% Japan	446 U Texas
5114 Materials Science, Biomaterials	954 Tissue engineering (+prtA)	9.3% Germany	410 U Pittsburgh
3482 Biochemistry & Molecular Biology	476 Stem Cells	8.3% UK	403 U Michigan
3155 Biotechnology & Applied Microbiology	368 J Mat in Sci - Mat in Med	7.1% China	381 U Toronto
2598 Hematology	353 Biophys Bioch Res Com	5.5% Italy	349 MIT U
2119 Medicine, Research & Experimental	352 J Biomed Mat Res	4.8% France	340 Kyoto
1886 Surgery	351 J Biomed Mat Res B Appl	4.3% Canada	316 Nat U Singapore
1737 Oncology	343 J Periodontology	3.6% S. Korea	307 U Tokyo
1608 Polymer Science	330 Biomacromolecules	3.0% Netherlands	299 U London
1545 Cardiac & Cardiovascular Systems	319 Blood	2.6% Switzerland	297 U Washington
1526 Dentistry, Oral Surgery & Medicine	288 J Biological Chemistry	2.3% Australia	292 U London Imp Col
1222 Immunology	257 J Biomat Sci - polymer ed.	2.0% Spain	289 Osaka U
1186 Pharmacology & Pharmacy	219 PNAS	1.9% Sweden	276 UCLA
1107 Materials Science, Multidisciplinary	219 J cellular Biochem	1.6% Taiwan	272 UCSF
1089 Peripheral Vascular Disease	218 J Orthopaedic Res	1.5% Brazil	264 Chinese Ac Sci
1054 Biophysics	206 Circulation	1.5% Israel	259 U Penn
1034 Orthopedics	205 Bone	1.4% Singapore	248 Johns Hopkins U
1029 Endocrinology & Metabolism	193 J Appl Polymer sci	1.2% Belgium	247 Seoul Nat U
985 Transplantation	175 Acta Biomaterialia	1.0% Austria	247 Stanford U
931 Neurosciences	160 J cellular Physiology	0.9% India	239 Rice U
	159 Exp Hematology	0.9% Denmark	226 INSERM
	157 Cardiovascular Research		213Duke U
	155 Biotech Bioeng		205 Case Western U
	153 J Clin Periodontology		201 UCSD
	Selection of other journals		200 U Minnesota
	148 Cell Transplantation		
	138 Cytotherapy		
	92 Regenerative Medicine		
	90 J Tissue Eng & Regen Med		
	79 Tissue Eng & Regen Med		
	70 Bone Marrow transpl		

* Articles, letters, notes and reviews. ** Journals in which the documents have appeared. # Integer counting.

Medicine (2007) with their low position in the lists reflecting their age. Finally, a variety of chemistry journals are on the list, such as *Abstracts papers ACS*, *Journal of Biological Chemistry*, *Biophysics and Biochemistry Research Communications*, and also the multidisciplinary journal *PNAS*.

The USA dominates the research field with a share of about 38% of the papers. The USA is followed by Japan, Germany, the UK, France and Canada. The Netherlands places 10th with 3% of publications, above Switzerland, Australia and Sweden. The share of the Netherlands is higher than the Netherlands overall average in all fields (about 2%)[8] and in biomedical research (about 2.3%).[9]

At the level of research institutes the US is again dominant with Canadian and Japanese universities also placing in the top 15. Lower on the list, we see several UK, and Asian based institutes.

8 *Science and technology indicators 2008*, p22. Ministry of Education, Culture and Science; Den Haag, 2008.

9 In the Netherlands, 38% of output is in biomedical research whereas the average of a set of relevant other countries is about 33% (NOWT 2008, p28). This indicates that in the Netherlands the biomedical output is about 15% more than the world average. The Netherlands share in world biomedical research therefore is about 2.3%.

4 Regenerative Medicine: structure and knowledge relations

In the previous section we indicated in which journals the retrieved papers were published and to which subject areas these journals belong. In this chapter, we analyze the structure of the RM field using the dominant journals in the most recent period 2005-2008[10]. The resulting journal set is used to create a map of regenerative medicine and the related research fields.

4.1 Dominant journals

What are the dominant journals in RM? We use two criteria: (1) the absolute number of papers of a journal in the RM document set and (2) the percentage of papers of a journal that is included in the set. The journal *Blood*, for example, scores high on the list, at 10th place with 161 papers with a share of 0.7% in the RM document set. However, *Blood* is a large journal with a total of 5224 papers in the period 2005-2008. In other words, only 3% of the papers in *Blood* count as Regenerative Medicine. So *Blood* is not a RM journal in a strict sense.

In table 7 we show those journals in which more than 100 papers from the document set have appeared (column 4) and/or that have at least 5% of their papers in RM (column 1). The journals are ordered in terms of the share of papers of a journal that is included in the document set. For example, 1205 of the retrieved documents appeared in the journal *Biomaterials*, which is 50.7% of all papers in the journal and 5.5% of all documents in the set.

Table 7, column 1 shows for all the journals how strongly they count as regenerative medicine: which share of the papers they publish belong to the retrieved document set - and therefore count as regenerative medicine. At the top of this list we find the *Journal of Tissue Engineering and Regenerative Medicine*. Almost 90% of the papers in this journal belong to our document set.[11] Some other new (and small) journals on regenerative medicine are high on the list, as are *Tissue Engineering*, and several biomaterials journals. Next we have the stem cells journals, of which between 30% and 40% papers are in the document set.

The share of the journals in the document set changes over the years, possibly indicating changes in research emphasis in the field of RM - and the maturation of the field: an increasing role of focused specialist journals. Figures 2 and 3 show the journals with respectively increasing and decreasing shares within the set of papers over time. The higher the peak, the larger the share of journal is within the field (in terms of the percentage of papers in the document set). On the left side of figures 2 and 3 the journals shown there have the *largest growth* or *decline* between the period 2000-2004 and the period 2005-2008. At the right side one finds the journals with the smallest growth or decline.

As is clear from figure 2, quite a few journals in the field were established recently, and these are visible on the left side of the figure: *Acta Biomaterialia* (established in 2005), the *Journal of Tissue Engineering and Regenerative Medicine* (est. 2007), *Tissue Engineering and Regenerative Medicine* (est. 2007), *Stem Cells and Development* (est. 2006) and *Regenerative Medicine* (est. 2006). Of the journals that already existed in the first period (2000-2004), *Stem*

10 Some relevant journals such as *Tissue Engineering* have a large proportion of 'proceedings papers', a relatively new category in the WoS, Including them makes no difference for the overall picture.

11 This suggests that the keywords used are accurate, but not perfect - if one would expect that 100% of the dedicated journals should belong to the document set.

Cells, Biomacromolecules and *Tissue Engineering* have become more important. The same holds for *Cytotherapy*, the *Journal of Applied Polymer Science and Cell Transplantation*. The latter journal added in 2003 "*regenerative medicine*" as a subtitle. The other 'growers' are also mainly in materials research, cell research, and biochemistry.

Table 7 Regenerative Medicine journals 2005-2008 (>1% papers in RM (column 1) or >100 papers (column 4))

Journal	Papers in the document set			Share in the document set		
	%	of a total of		%	number	Place
	1	2		3	4	5
J Tissue Engineering & Regenerative Medicine	87,4	(103)		0,4	(90)	27
Tissue Engineering (1)	75,1	(837)		2,9	(629)	3
Tissue Engineering & Regenerative Medicine	69,3	(114)		0,4	(79)	30
Regenerative Medicine (2)	62,6	(147)		0,4	(92)	26
J Bioactive & compatible polymers	58,6	(70)		0,2	(41)	44
Biomaterials (3)	50,7	(2376)		5,5	(1205)	1
Journal Of Biomedical Materials Research Part A (4)	47,3	(1560)		3,3	(738)	2
Biomedical Materials	46,0	(161)		0,3	(74)	31
Acta Biomaterialia (5)	45,1	(388)		0,8	(175)	9
J of Biomaterials Applications	41,6	(101)		0,2	(42)	42
Cytotherapy (6)	40,1	(277)		0,5	(111)	21
Stem Cells And Development (7)	39,0	(344)		0,6	(134)	16
Journal Of Biomaterials Science-Polymer Edition (8)	38,2	(364)		0,6	(139)	14
Stem Cells (9)	35,9	(1132)		1,8	(406)	4
Matrix biology	31,9	(119)		0,2	(38)	46
Stem Cell Reviews	29,3	(147)		0,2	(43)	41
Cell Transplantation (10)	29,0	(321)		0,4	(93)	24
Journal Of Materials Science-Materials In Medicine (11)	27,9	(835)		1,1	(233)	7
Cells Tissues Organs	25,1	(183)		0.2	(46)	5
J Biomedical Materials Research Part B-Applied Biomater (12)	25,1	(991)		1,1	(249)	40
Macromolecular Bioscience	24,1	(435)		0,5	(105)	22
Annals Of Biomedical Engineering	22,7	(370)		0,4	(84)	28
Mater Sci & Engin C-Biomimetic and Supramolecular Systems	19,5	(210)		0,2	(41)	44
Int J Periodontology & Restorative Dentistry	18,9	(222)		0,2	(42)	42
Clinical Oral Implants Research	18,1	(459)		0,4	(83)	29
Wound Repair And Regeneration	17,6	(386)		0,3	(68)	35
Artificial Organs	17,3	(358)		0,3	(62)	36
Expert Review Of Medical Devices	16,7	(282)		0,2	(47)	39
Journal Of Orthopaedic Research	16,0	(842)		0,6	(135)	15
Journal Of Cellular And Molecular Medicine	15,6	(449)		0,3	(70)	33
Journal Of Periodontology	13,7	(1142)		0,7	(156)	11
Biomacromolecules	13,2	(1880)		1,1	(249)	5
Advanced Drug Delivery Reviews	13,2	(408)		0,2	(54)	33
Expert Opinion On Biological Therapy	13,2	(532)		0,3	(70)	38
International Journal Of Artificial Organs	12,8	(431)		0,2	(55)	37
Experimental Hematology	12,5	(746)		0,4	(93)	24

▶

Journal	Papers in the document set			Share in the document set		
	%	of a total of		%	number	Place
	1	2		3	4	5
Journal Of Clinical Periodontology	12,0	(593)		0,3	(71)	32
Bone	10,7	(1117)		0,5	(120)	18
Journal Of Cellular Biochemistry	8,1	(1587)		0,6	(128)	17
Journal Of Cellular Physiology	8,0	(1396)		0,5	(112)	20
Biotechnology And Bioengineering	6,6	(1510)		0,5	(100)	23
Blood	3,1	(5224)		0,7	(161)	10
Biochemical And Biophysical Research Communications	2,6	(8790)		1,0	(227)	8
Proceedings of the National Academy of Sciences of the USA	2,3	(6671)		0,7	(151)	12
Journal Of Applied Polymer Science	1,9	(7681)		0,7	(144)	13
Journal Of Biological Chemistry	0,7	(17156)		0,5	(113)	19

In red are shown those journals of which more than 25% of their papers belong to the regenerative medicine document set AND in which at least 75 papers of the document set are published.
2: number of papers in journal
1: % of 2 included in the RM document set
3: % of documents in the RM set published in this journal
4: number of documents in the RM set published in this journal
5: rank order based on column 4

Figure 2 Most used journals within the document set (2005-2008): the 'growers'

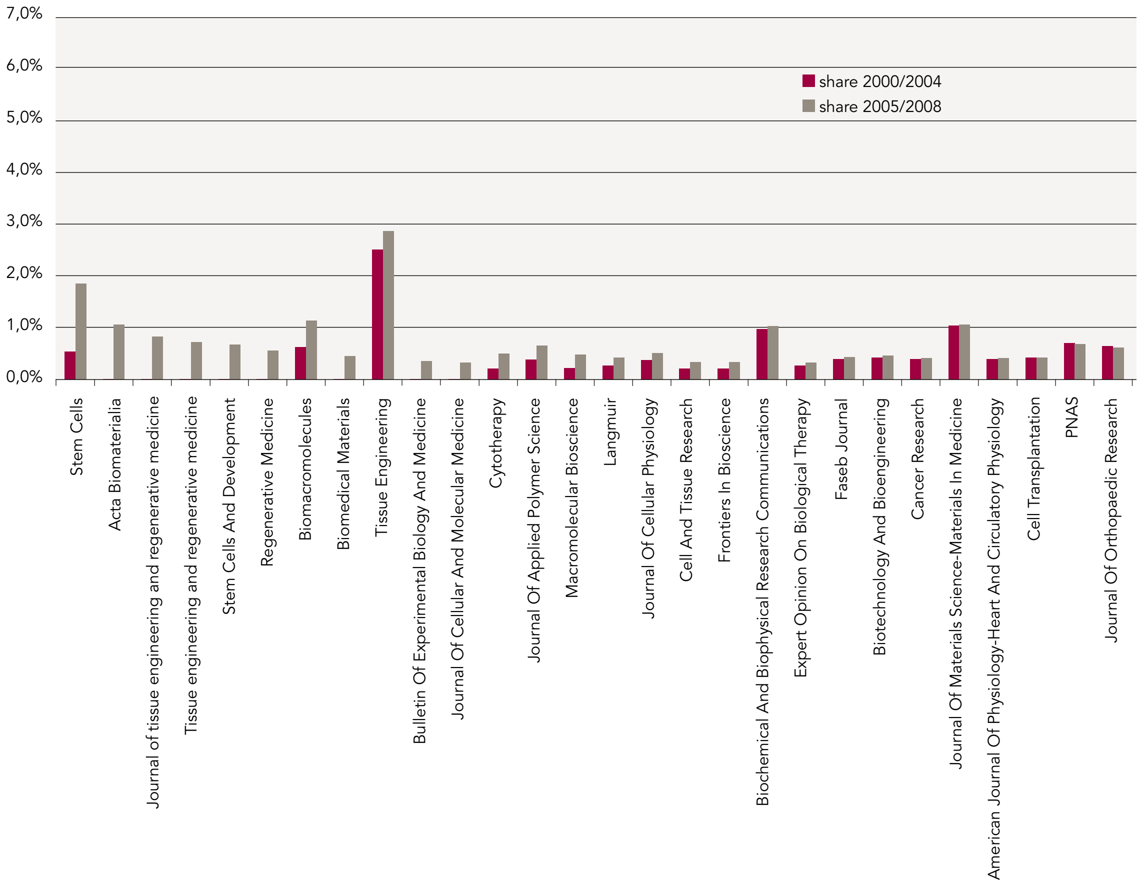
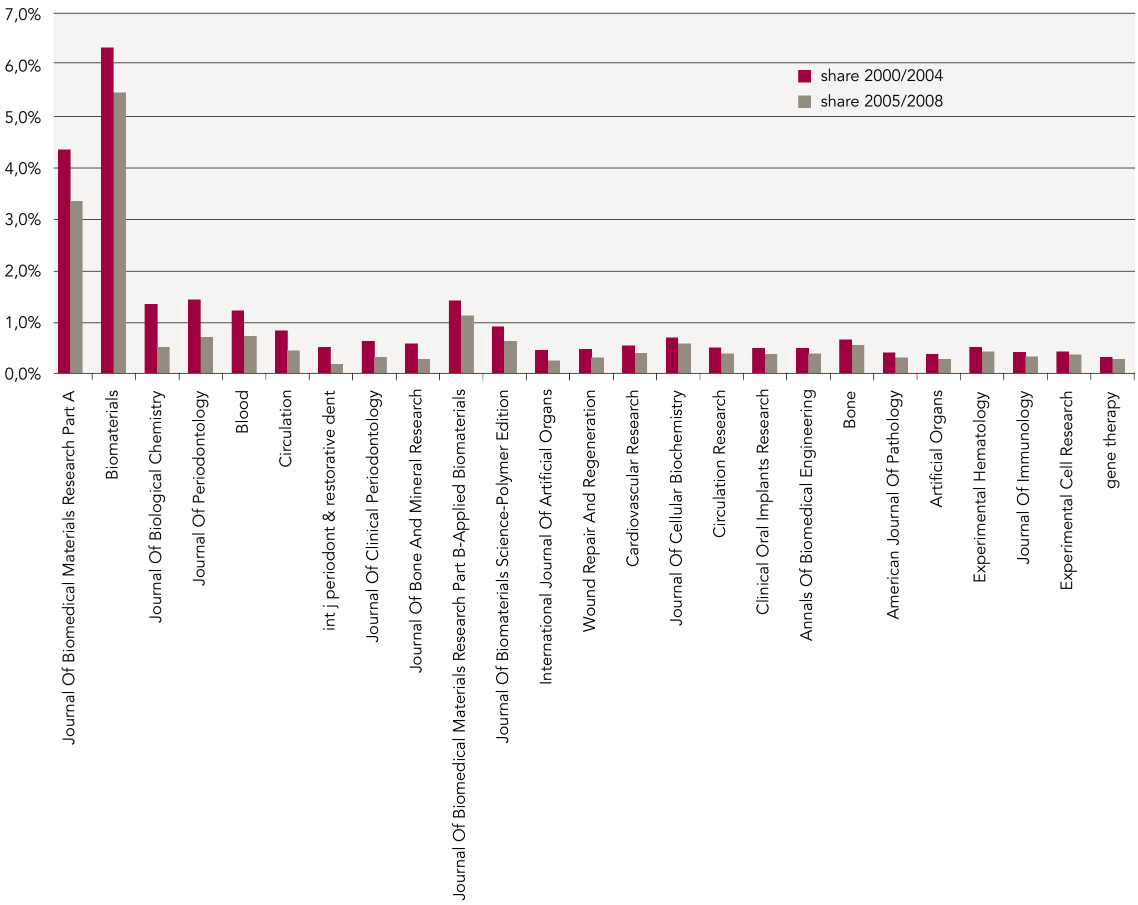


Figure 3 Most used journals within the document set (2005-2008): the 'decliners'



The growth of these tissue and biomaterials related journals in the document set is balanced by the relative decline of the two largest journals in both periods: *Biomaterials* and the *Journal of Biomedical Materials Research A* (figure 3). Both show a declining share over the years. This suggests that the tissue and biomaterials related papers gradually move to newer and more specialized journals. Other relative decliners are the journals focusing on specific tissues and organs, and general journals like the *Journal of Biological Chemistry*.

In summary, new specialized RM journals, tissue engineering journals and (stem) cell research journals find their share increasing, whereas biomaterials journals decrease - but still dominate the field. Also journals on specific tissues and organs see their share going down. The emergence of a variety of new specific regenerative medicine journals indicates also a growing identity (and possibly convergence) of the research field.

4.2 Structure of the regenerative medicine field

Journal maps, based on the citation relations between the journals, can provide a wider perspective on the development of regenerative medicine: can we identify a set of journals that represents the emerging field of RM? And, how are these journals situated in the larger journal space? In order to show this, the matrix of journal-journal citations is factor-analyzed. Each of

Table 8 Factors in the journal space in 2007 (in red: the entrance journals)

1: mol cell biol
j cell physiol
j cell biochem
exp cell res
bioch bioph res co
j biol chem
cell biol int
faseb j
embo j
j cell sci
mol cell biol
j cell mol med
j cell biol
oncogene
ann ny acad sci
j clin invest
cancer res
circ res
method cell biol
proteomics
am j physiol-lung c
nat med
j biosci bioeng
diabetes
biol reprod
biophys j
mol ther
oral dis
diabetologia
hepatology
biotechnol bioeng
invest ophth vis sci
b exp biol med+

2: Hematology
haematol-hematol j
ann hematol
brit j haematol
Int j hematol
curr opin hematol
leukemia lymphoma
biol blood marrow tr
leukemia
exp hematol
bone marrow transpl
blood
cytotherapy
cytom part b-clin cy
transfus med hemoth
hum gene ther
transfusion
j clin oncol

4: neuroscience
eur j neurosci
neuroscience
brain res
exp neurol
dev neurobiol
brain res bull
j neurosci
j neurosci res
j neurosci meth
j comp neurol
mol cell neurosci
neuron
eur arch psy clin n
j neurotraum
neurotox res
cell transplantation

13 Transplantation
curr opin organ trans
transplantation
am j transplantation
transplant p
xenotransplantation

7: stem cells & RM
stem cell rev
cell stem cell
nat biotechnol
development
dev boil
dev dynamo
regen medicine
j r soc interface
curr opin biotech
cloning stem cells
cell res
semin cell dev boil
gene dev
differentiation
p natl acad sci usa
bmc genomics
cell
aging cell
drug discov today
bmc dev boil
curr pharm biotech
nat genet
trends biotechnol
stem cells dev
stem cells

10: immunology
eur j immunol
j immunol
cancer immunol im
j immunother
j exp med
j transl med
j biomed biotechnol
expert opin biol th
arth rheum/ar c res

11: cardio
circulation
clin sci
j am coll cardiol
j mol cell cardiol
trend cardiovas med
new engl j med
clin pharmacol ther

15: neurology
curr opin neurol
neurology
ann neurol
lancet
stroke
mrs bull

12: pharma
pharm res
int j pharm
j control release
j pharm sci-us
adv drug deliver rev
int j nanomed
bioconjugate chem

3: biomaterials
biomed mater
j biomed mater res a
acta biomater
biomaterials
j biomat sci-polym e
j mater sci-mater m
j biomed mater res b
mat sci eng c-bio s
tissue eng
j bioact compat pol
macromol biosci
eur cells mater
expert rev med devic
nanomedicine-uk
int j artif organs

6: nano, adv mater
j membrane sci
nanotechnology
j nanosci nanotechno
adv mater
aip conf p
appl phys lett
nat nanotechnol
mater lett
appl surf sci
j mater chem.
microelectron eng
j optoelectron adv m
j am chem soc
lab chip

9: dental materials
j dent
am j dent
dent mater j
dent mater
j adhes dent
oper dent
j oral rehabil
j prosthet dent
j dent res
j endodont

5: polymers
macromol symp
polym int
polymer
prog polym sci
eur polym j
macromolecules
react funct polym
j polym sci pol chem.
polym rev
j appl polym sci
biomacromolecules
soft matter
langmuir
colloid surface b
colloid surface a
carbohyd polym
j adhes sci technol

8: material sci
mater sci forum
scripta mater
mat sci eng a-struct
acta mater
adv eng mater
j mater sci
key eng mater
j mater res
j eur ceram soc
j am ceram soc
surf coat tech

14: ortho, bone
j orthop res
j biomech
clin orthop relat r
j bone joint surg am
j biomech eng-t asm
ann biomed eng
osteoarthr cartilage
bone
j bone miner res
spine
ieee t bio-med eng
plast reconstr surg

the resulting factors consists of journals with *similar citing behavior*. Similar citing behavior indicates that journals have a similar relation to the relevant literature, and therefore can be considered as belonging to the same research field. In other words, the factor analysis results in a number of factors, of which each of them represents a research field in the vicinity of RM.
A visual representation of the results of the factor analysis can be used for further analysis of the dynamics of the field.

The maps are based on so-called 'entrance journals'. We used as 'entrance journals' the journals mentioned in table 7 that satisfy the following conditions:

- more than 25% of their papers belong to the regenerative medicine document set *AND*
- they have at least 75 papers in the set.

This resulted in 14 journals (see table 7 outlined in red). The two new specialized RM journals, the *Journal of Tissue Engineering and Regenerative Medicine* and *Tissue Engineering and Regenerative Medicine* are new and were not as of yet included in the Journal Citation Report of 2007. The remaining 12 journals were used in the factor analysis of the 2007 data.

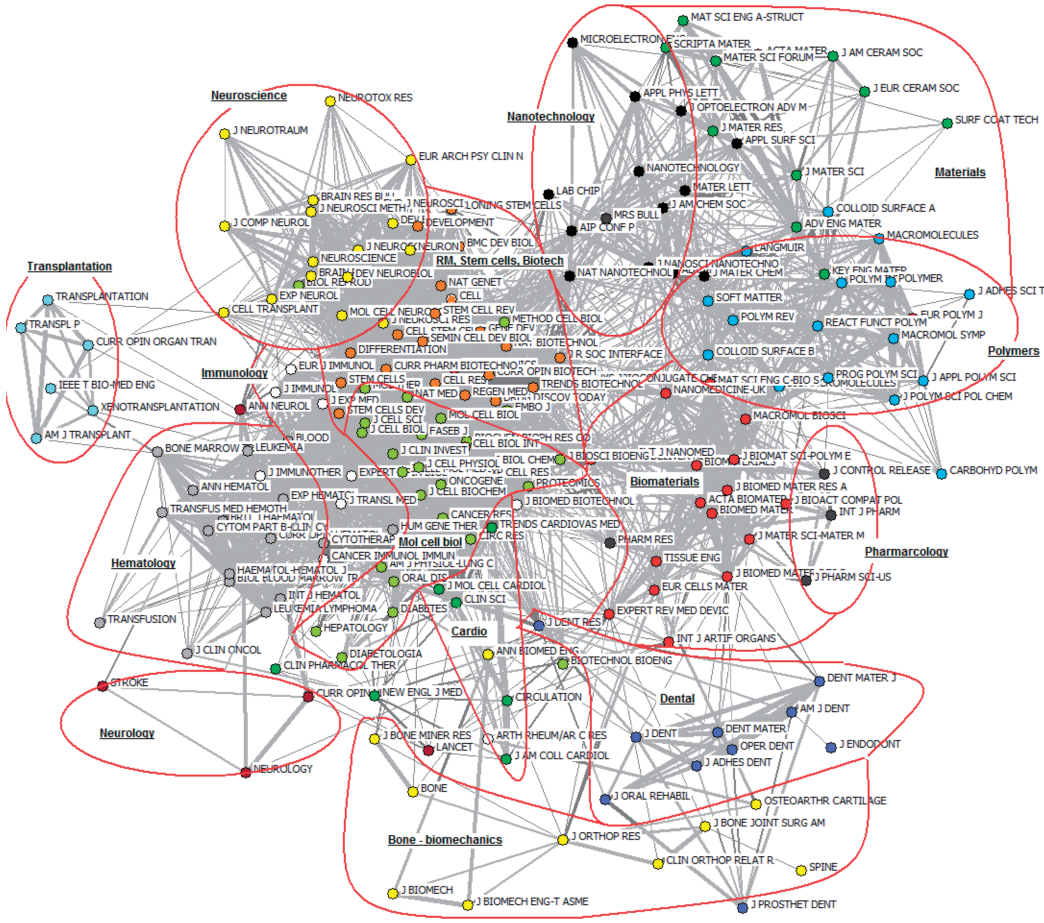
The citation environment of the twelve journals consists of 205 journals. A factor analysis resulted in a 15 factors solution. Table 8 shows the factors found, and the journals are subsumed under the factors they have the *highest* loading on. In general, journals load on one factor, and have only very low (negligible) loading on other factors. Only in case of interdisciplinary or multidisciplinary journals, the journal loads equally (but not very strongly) on different factors.

This is exactly the case here. Factor 7 consists of stem cell research journals, developmental biology research journals, and the journal *Regenerative Medicine*. Of the twelve entrance journals, three load on this 'hybrid' factor. Factor 7 is in the vicinity of molecular cell biology (factor 1) and hematology (factor 2). All journals listed under factor 7 load almost equally as high on either factor 1 (molecular cell biology) or factor 2 (hematology) as on 7. One may conclude that stem cell research is an interdisciplinary field between molecular cell biology and hematology.

To obtain an overall view, we produced a summary map (fig. 4).The map shows an interesting geography. In the left part of the map we find medical research specialties: neuroscience (factor 4), immunology (factor 10), cardio and circulation research (factor 11), transplantation (factor 13) and neurology (factor 15). The right side of the map consists of materials research related factors.

In the core of the right side we see biomedical materials (factor 3), with seven of the twelve entrance journals. Interestingly, the biomaterial and tissue engineering journals do not exhibit multidisciplinarity. Summarizing, the analysis results in a number of factors, each representing a research field in the vicinity of RM. A visual representation of the results of the factor analysis can be used for further analysis of the dynamics of the field.

Figure 4 Regenerative Medicine journals: the 2007 journal network



4.3 The development of the regenerative medicine field

To investigate the *development* of the field, we repeated the factor analysis for the years 2003 and 2000. In 2003, *Acta Biomaterialia*, *Regenerative Medicine*, and *Stem Cell and Development* were not in the database, or did not yet exist. Nevertheless, the structure of the journal environment of the nine remaining journals is rather similar to the 2007 map, and contains most of the large factors that were visible in 2007. The main difference with 2007 is that in 2003 we did not yet have a factor representing regenerative medicine, stem cells and developmental biology. The stem cell journals were in the cell biology factor and/or the hematology factor. Furthermore, the biomaterials factor was less prominent in 2003, and the advanced materials factor did not contain nanoscience journals in 2003.

In 2000, the *Journal of Biomedical Materials Research* was not yet divided in "A" and "B". Consequently, we have eight journals left. Using these eight as entrance journals gives a map of RM in its very early stage. Although the main structure resembles the later maps, the position of the entrance journals is different from the later phase. *Tissue Engineering* was a multidisciplinary journal in 2000, in between biomaterials, cell biology, and bone and biomechanics research.

In 2003 and 2007, *Tissue Engineering* functioned as a pure biomedical materials journal. *Stem*

Cells and *Cytotherapy* show an opposite development. Whereas these journals were fully in the hematology factor in 2000, in 2003 they are in between cell biology and hematology and in 2007 they have become part of an interdisciplinary factor with other journals on stem cell, on developmental biology, and on regenerative medicine. Another main difference is that the factor of biomaterials has become more dominant, and nanotechnology and advanced materials factor was not visible in the 2000 map. On the other hand, important separate factors in 2000 on orthopedics, urology, oncology and plastic surgery have disappeared from the environment of the RM journals. A few journals from these fields have remained in the map, and now belong to other factors.

Obviously, there is not a single factor representing the whole field. The regenerative medicine (entrance) journals are distributed over a few factors (in 2007: biomedical materials (F3), and stem cells & developmental biology (F7), and hematology (F2)). Regenerative medicine seems to consist of two clearly separated parts: a rather disciplinary biomedical materials & tissue engineering part (F3), and an interdisciplinary part focusing on stem cell research & therapy (factor 7), at the boundary of molecular cell biology (F1) and hematology (F2).

4.4 Knowledge streams: relations between the relevant research fields
It is also interesting to determine the knowledge flows between the different relevant research fields (as represented by the factors). We calculated the citation relations between the factors, and use these as an indicator for knowledge flows. This has been done for two years, 2000 and 2007, respectively table 9 and 10. The table gives the percentage of references from a factor (column) to a specific factor (row). E.g., of all references in the journals in the cell biology factor, 83,5% are to other journals in the same factor, and 5% is to journals in the neurology factor.
It is clear that in 2000 all fields substantially cite the molecular and cell biology factor - whereas the molecular and cell biology journals hardly cite the other specialties. Cell biology is clearly a source of knowledge for regenerative medicine; advances in cells research are a crucial input. Furthermore, a few clusters of fields can be discerned with mutual knowledge flows. This holds for a variety of medical specialties, such as hematology, molecular therapy, cancer research, immunology, and heart and circulation research. The same holds for a few other pairs of journals, especially biomaterials and chemical materials. Finally, some specialties do cite other fields but are not cited themselves in this network: transplantation, urology, bone research, and reconstructive surgery. This suggests that these fields are not a *source* for regenerative medicine, but are users of RM related knowledge.

In 2007 the pattern has changed. We observe knowledge exchange between molecular cell biology, stem cell research and neuroscience. Again, all fields draw upon molecular cell biology. Factor 7 has a somewhat hybrid composition, and is strongly overlapping with factor 1. Studying the overlap more in detail, we found that it consists of mainly stem cell research. The majority of references from F7 to F1 go to the stem cell research part of factor 1.

We also find here the knowledge network of the medical specialties, however somewhat more differentiated: 1) neuroscience and neurology; 2) cardiology and neurology; and 3) hematology, immunology and cardiology. Finally, the knowledge network of materials research has become larger and more pronounced.

Overall, the analysis shows cell biology as a main source of knowledge for both parts of regenerative medicine (biomaterials and cell therapy). The biomaterials part of the field increasingly also draws from other advanced materials fields, such as nanoscience and polymers. The stem cell related part of RM heavily depends on basic molecular science and on basic (stem) cell research.

Table 9 Knowledge streams in 2000 (citations between the research fields)

Citing 2000	molc	neu	mol t	onc	hem	imm	car	tran	urol	phar	rec	orth	bone	biom	che
molecular cell biology	83,5	34,0	45,2	40,9	28,8	46,9	25,7	20,4	10,5	19,4	6,1	7,2	37,8	11,7	7,2
neurology	5,0	62,8					2,7	4,1				4,1			
molecular therapy			35,4	2,3		2,2				2,5					
oncology	2,5		3,2	38,2	6,6		4,1		8,9	2,7					
hematology			2,9	5,7	47,1	5,0	3,0	3,6							
immunology	3,0		6,5	4,2	7,9	39,5	2,2	9,6							
cardiology / general			2,1	5,2	6,3		55,6	9,8	4,7		3,0	3,5	4,7	2,6	
transplantation							2,3	44,6							
urology									67,5						
pharmacology										60,3				2,5	
reconstruction surgery											74,8				
orthopedics											7,5	75,8	7,7	10,2	
bone tissue												2,8	44,3		
biomaterials										4,5		2,3		57,2	2,2
chemical materials										5,3				5,3	88,6

The values in the cell indicate the percentage of all references from a research field (column) to a research field (rows). E.g., 34% of the references in the neurology journals refer to molecular biology journals, and 62.8% to the journals within the neurology factor. Values below 2% are not shown.

Table 10 Knowledge streams in 2007 (citations between the research fields)

	s/n/p	cel	sc/ rm	neu	neur	car	hem	imm	tra	pha	orth	dent	biom	polym	nano	mat
science/ nature/pnas	36,0	12,9	20,9	16,0	6,0	5,5	8,0	13,9	4,5	7,5	3,8		6,0	6,1	17,8	4,8
cell biology	19,2	34,4	10,7	12,0	6,3	16,0	13,8	17,2	11,2	13,2	9,9	4,0	10,8	2,7	3,0	
stemcell/ regenerat. med.	30,4	41,9	55,0	17,2	8,7	18,5	17,5	20,9	12,5	16,4	12,3	4,7	13,8	3,2	4,0	
neuroscience	5,2	2,2	5,0	49,6	5,9											
neurology				3,1	54,5	7,0			2,5							
cardiology					12,8	47,6	5,1	2,1	6,9	2,5	2,6					
hematology		2,1	3,2		3,0	2,4	45,7	6,1	5,5							
immunology	3,0	2,6			2,0		6,7	36,0	9,0		2,5					
transplantation									46,9							
pharmacology										39,8			5,8	3,3		
orthopedics / bone											61,8		8,5			
dental materials												77,7	3,6			
biomatererials										6,1	2,2	5,7	30,6	3,7		4,5
polymers										5,5			8,1	63,6	9,4	5,4
nanoscience	2,3									3,3			3,5	15,4	57,0	15,6
material science													2,8		5,4	67,0

5 The position of the Netherlands in the document set

5.1 The position of the Netherland over the years

In table 6, the share of the Netherlands in total RM output proved to be 3% over a longer period. In figure 5, the development of the Dutch share over time is visible (3 year moving averages) with the Netherlands share fluctuating around 3%. So the Netherlands RM research is not losing ground, but is also not improving its share.

Figure 5 Percentage of publications of Dutch researchers as percentage of the whole document set

5.2 Position of the Netherlands by subject area

How are the Netherlands' papers distributed over the various subject areas? And does this differ from the global patterns? To answer this question, we used the *journal classification* of the WoS, which assigns research field classes to all journals. Journals can belong to more than one class. For example, the journal *Biomaterials* belongs to two classes: biomedical engineering, and biomaterials; *Tissue Engineering* is classified as biotechnology & applied microbiology, and as cell biology. We use the classification here as a first approximation of the emphasis of RM research activity.[12]

Some subject areas are stronger represented in the Netherlands regenerative medicine field than internationally (Table 11). These are 'dentistry, oral surgery & medicine', 'cardiac & cardiovascular systems', 'biomedical engineering', 'peripheral vascular diseases', 'othopedics', 'biophysics', 'biomaterials', and 'biotechnology and applied microbiology'. Weaker than average in the Netherlands are subject areas such as 'biochemistry & molecular biology', 'research & experimental medicine', and 'polymer science'. The last column of table 11 shows the share of the subject area in the total set of papers: large numbers represent large fields and vice versa.

12 The accuracy of the WoS subject area classification of journals is disputed, but on an aggregate level, it can be used.

Table 11 The position of the Netherlands by subject area (2005-2008)

Category	Share of papers with NL author	Nr publications NL/world*
Dentistry, Oral Surgery & Medicine	5,8	47 / 810
Cardiac & Cardiovascular Systems	5.4	51 / 951
Engineering, Biomedical	4.4	149 / 3353
Peripheral Vascular Disease	4,3	26 / 601
Orthopedics	4.1	25 / 615
Biophysics	3.9	27 / 689
Materials Science, Biomaterials	3.9	118 / 3036
Biotechnology & Applied Microbiology	3.9	85 / 2191
Hematology	3.2	52 / 1615
Immunology	3.2	23 / 727
Cell Biology	2.9	101 / 3848
Oncology	2.8	32 / 1151
Endocrinology & Metabolism	2.7	16 / 593
Transplantation	2.5	15 / 621
Pharmacology & Pharmacy	2.4	19 / 795
Surgery	2.0	22 / 1088
Biochemistry & Molecular Biology	1.9	41 / 2148
Medicine, Research & Experimental	1.9	26 / 1373
Polymer Science	1.8	19 / 1063
Physiology	1.6	8 / 501
Chemistry, Multidisciplinary	1.5	7 / 460
Neurosciences	1.3	8 / 594
Materials Science, Multidisciplinary	1.2	9 / 732

* Similar data are in table 6, but there it covers a longer period.

A more precise indicator, showing the position of the Netherlands within the international scene, can be derived from the 14 core journals. Table 12 shows the total number of papers in these journals, as well as the share of papers with an address in the Netherlands.[13]
The Netherlands is strong in the biomaterials and tissue engineering parts of the field, and less so in the cell therapy and cell transplantation part.

13 Table 12 refers to all publications in the core journals, so not only those identified using the search terms.

Table 12 The position of the Netherlands by subject area (2005-2008)

Journal	Share NL		Papers total		Papers NL	
	2000-2004	2005-2008	2000-2004	2005-2008	2000-2004	2005-2008
Regenerative Medicine J Tissue Engineering & Regenerative Medicine Tissue Engineering & Regenerative Medicine		3.1		229		7
Tissue Engineering	7,5	6,2	320	761	24	47
Biomaterials	7,4	5,5	797	1171	59	64
J Biomedical Materials Research A	5,6	5,6	286	730	16	41
J Biomedical Materials Research B	8,8	4,1	57	270	5	11
J Biomedical Materials Research	6,8		352		24	
J Materials Science - Materials in Medicine	8.2	2.4	133	208	11	5
Acta Biomaterialia		0,6		175		1
Stem Cells	1,4	1,6	70	383	1	6
Stem Cells and Development		1.6	74	253		4
Cytotherapy		3,6	26	111		4
Cell Transplantation	2,0	2,3	51	87	1	2
TOTAL	6,4	4,5	2033	4170	130	187

5.3 Visibility of the Dutch universities and research institutes

Table 6 contains a list of dominant research institutes worldwide in RM but no Dutch institution feature at the top of the list. What is the position of Dutch universities and research institutes within RM? A large problem of the WoS is that many different *name forms* of institutes are present in the database. Consequently, for a correct counting of an institute's number of publications, a normalization of the names of institutes is required. This was done manually for the 2000-2008 data. Table 13 shows the result, but the numbers cannot be compared with table 6.[14]

Table 13 The Netherlands' research institutes in the document set[15]

Universities		Universities	
Radboud U. Nijmegen	212	U of Technology Eindhoven	73
U of Groningen	134	Wageningen U	13
Leiden U	134	Delft U of Technology	10
Utrecht U	133		
U of Twente	132		
Erasmus U. Rotterdam	94	Public Research Institutes	
U of Amsterdam	83	KNAW (NICI, Hubrecht, NIN)	34
Maastricht U	75	TNO	22
VU U Amsterdam	74	NKI-ALZ	11

14 To illustrate this point, all 134 Leiden University publications use "Leiden University" as institutional name. For Radboud University Nijmegen we found 8 different names: "Radboud Univ Nijmegen" (83 times), "Univ Nijmegen" (74), "Radboud Univ Nijmegen Medical CTR" (16), "Univ Med CTR Nijmegen" (12), "Radboud Univ" (8), "Univ Nijmegen Hosp" (7), "Radboud Univ Med CTR" (6), "UMC" (5) "Univ Nijmegen St Radboud Hosp" (4), adding up to 212 publications in total.

15 We also found Dutch companies: Isotis (52 papers), Organon (7), Progentix (5) and Cellcotex (3). They are not included in the rest of the analysis. In table 14, only institutes with ten or more publications are included.

5.4 Collaboration

We also investigated collaboration between Dutch research institutions in the field of regenerative medicine research. We compared collaboration within the Netherlands in two periods: 2000-2004 and 2005-2008. In the first period, 35% of the papers with an address in the Netherlands have more than one Dutch corporate author. Apart from the universities and the university medical centers, quite a few other research organizations are in the collaboration network, such as general hospitals with a research task, public research institutes and a few companies

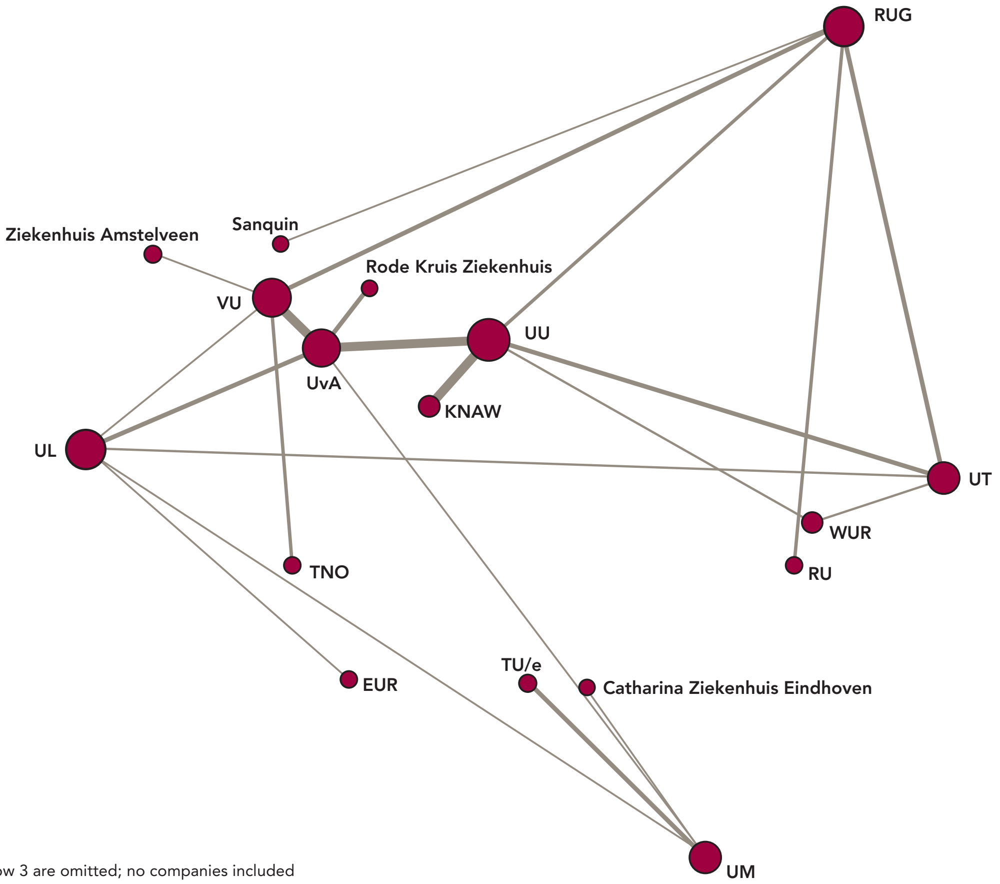
Table 14 RM co-authorships between the Netherlands' research institutes

	change	2000/2004	2005/2008	Share 2000/2004	Share 2005/2008
UU	(↓)	69	96	11,2	9,5
UT	(↓)	64	95	10,4	9,4
UvA	(↓)	57	64	9,3	6,3
RUG	(↓)	52	75	8,4	7,4
UL		41	63	6,7	6,2
VU		38	69	6,2	6,8
UM		30	51	4,9	5,0
RU	(↑)	28	60	4,5	5,9
KNAW (ICIN, Hubrecht, NIN)		23	31	3.7	3,1
WUR	(↓)	18	8	2,9	0,8
Red Cross Hosp	(↓)	14	2	2,3	0,2
TU/e	(↑)	13	67	2,1	6,6
EUR	(↑)	12	77	1,9	7,6
TNO	(↑)	10	33	1,6	3,3
CLB Sanquin	(↓)	10	6	1,6	0,6
Catharina Hosp Eindhoven		5	11	0,8	1,1
NKI		5	4	0,8	0,4
Amstelveen Hospital		4		0.6	
Twente Hospital	(↑)	2	13	0,3	1,3
TUD	(↑)		17		1,7
RIVM			7		0,7
HAGA Hospital			4		0.4
Other	(↓)	109*	132**	19,7	16,0

In the period 2005-2008, the number of co-authored papers increased to 65%. Some new players have emerged, notably the Technical University Eindhoven that was barely present in the collaboration network in the first period but tripled its presence in the second period. Also Erasmus University and Radboud University became more visible in the collaboration network.

Figures 6 and 7 show the co-author networks for the periods 2000-2004 and 2005-2008. Nodes are the public research institutes and the universities; the Dutch companies active in RM research are not included. Links represent the number of co-authorships between organizations. A thin line in the graph represents three co-authored papers. The thicker the link is, the larger the number of co-authored papers. The university is the unit of analysis. The authors can be based in different research groups. And, if a paper has two University of Utrecht authors, it is not counted as 'co-authored'. The University Medical Centers are treated as part of the university they are affiliated with. The large nodes are those with the higher degree centrality i.e. they have the most co-author links in proportion to the rest of the network. In both figures we have removed all weak links(<3).[16]

Figure 6 The collaboration network 2000-2004



links below 3 are omitted; no companies included

In the period 2000-2004, the strongest link was between Utrecht University (UU) and the University of Amsterdam (UvA). However, the map (fig 6) seems to be regionally divided: at the right side we find the research institutions in the center and north-east of the country, and the left side is for the research institutes in the west. The southern universities in Eindhoven (Tu/e) and Maastricht (UM) link primarily through the main western nodes of UvA and University of Leiden (UL).

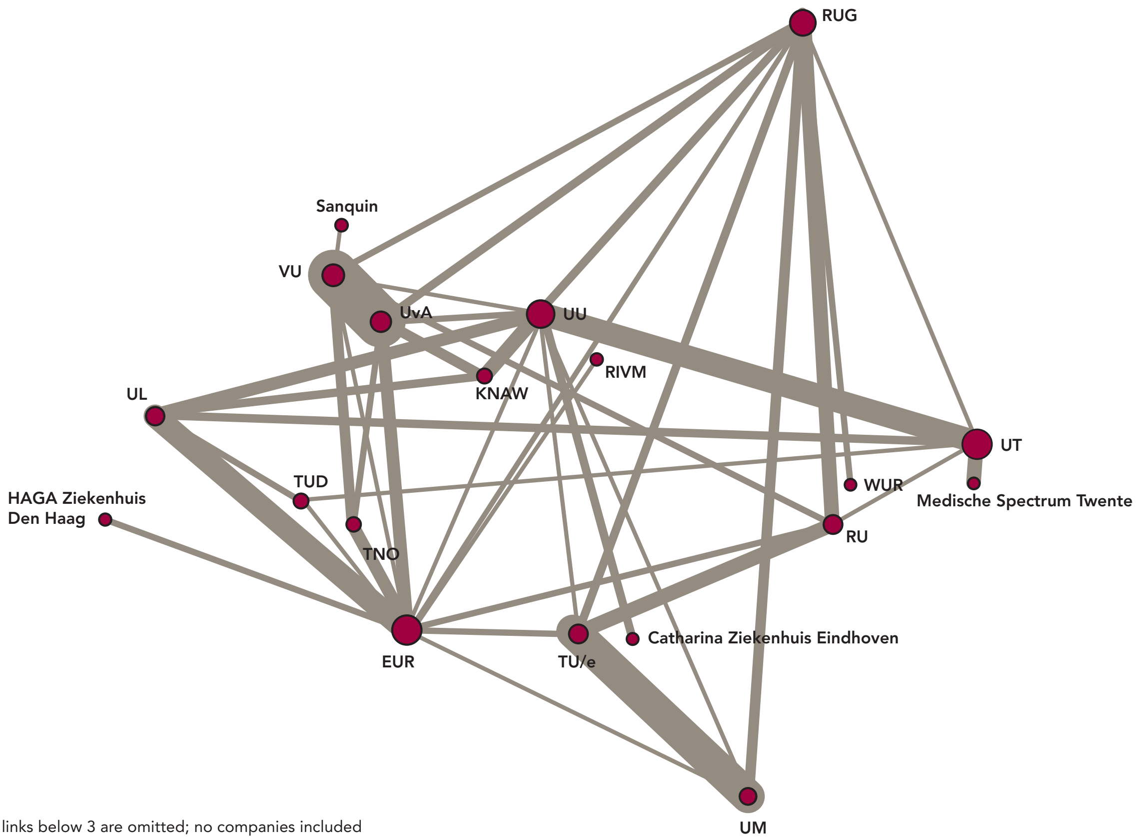
Things have slightly changed in the later period 2005-2008, as shown clearly in table 14. Figure 7 shows strong collaborations between universities in the east: University Maastricht (UM) and Technical University Eindhoven (TU/e) (28 co-authorships); Technical University Eindhoven (TU/e)

16 Note that this implies that some nodes with high degree centrality actually have hardly links in this figure, as these were removed through this threshold

and Nijmegen (13); Groningen and Nijmegen (12); between Twente University and the Enschede hospital (11); and finally between Twente University and Utrecht University (18). The other 'sub-network' is in Amsterdam, between the two Amsterdam Universities, UvA and Free University (VU) (22 co-authorships) and between the Free University (VU) and ACTA (15). Finally, Leiden University (UL) and Erasmus University Rotterdam (EUR) cooperate with 19 co-authorships. Obviously, the University Medical Centres are not the only players in regenerative medicine. The technical universities are prominently visible too, and they do collaborate actively with the medical centers. This collaboration intensified over the years. Within the network of university hospitals and technical universities, the share of the hospital-technical universities links increased from 29% in 2000-2004 to 38% in the more recent period.

Quite a number of regional and local hospitals are in the network, but the number of co-authored papers is generally low, so they are not included in the maps of the network. Furthermore, nodes are often locally connected. E.g., the Utrecht based KNAW institutes mainly co-author with Utrecht University (UU).

Figure 7 The collaboration network 2005-2008



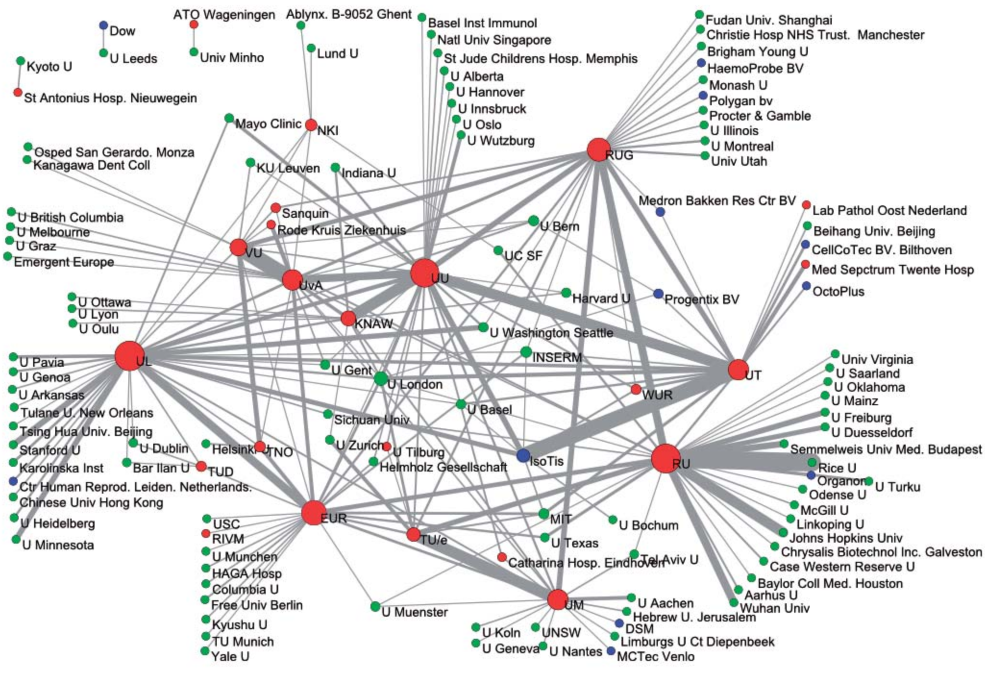
links below 3 are omitted; no companies included

Finally, we analyze the international collaboration network. In the period 2005-2008, 43% of the papers with an author with a Dutch address are co-authored by an author with a non-Dutch address. More than half of these papers have authors from more than two other countries. In total, the number of nodes is 431. By introducing a threshold (lower than in figures 6 and 7) of at least 2 co-authored papers over the period, this was reduced to 238 nodes. The resulting network is in figure 8. The size of the node indicates the degree of the node (the number of co-authorship links in proportion to the rest of the network). Lines represent the co-authored papers with the thickness of the lines representing the count of papers.

To aid viewing, we present the network configuration at a set threshold of at least 3 co-authored papers. The number of nodes goes down by more than 50% to 113, resulting in figure 8. Size of node again represents degree centrality, and thickness of line represents count of co-authored papers.

The strongest internationally linked Dutch research institutions are the Radboud University, Leiden University, and Utrecht University. The three universities seem to have quite separated networks, although Utrecht and Leiden also cooperate together. Erasmus University, the two Amsterdam Universities, and Groningen University have somewhat smaller networks.

Figure 8 The international collaboration network 2005-2008: (links below 2 are omitted)



Red node = NL university or NL public research institute
Blue node = NL Company
Green node = international organization (mainly universities)

6. Summary and conclusions

1. Regenerative Medicine is an emerging field, with a fast growth: 18% per year over more than 15 years now

2. RM is not stabilized as a journal based communication system. RM seems to exist of two rather loosely coupled parts:
   a. an emerging interdisciplinary part, with stem cell & cell therapy oriented RM research
   b. biomedical materials and tissue engineering research in RM

3. The two parts have different positions on the knowledge map, and the knowledge flows between the two parts are weak.

4. The stem cell part of RM is situated at the boundary between molecular and cell biology and hematology. With the increasing number of specialized RM journals, this interdisciplinary cluster may converge to a stronger disciplinary identity.

5. The Netherlands is strongly visible (3% of the output); the output is stronger in the biomedical materials & tissue engineering part of RM research than in the stem cell part of RM.

6. The Netherlands research groups increasingly collaborate, which is visible in growing numbers of co-author relations between the various universities, UMCs and public research institutes.

7. The international networks are concentrated around the universities - in which three are dominant.

Annex 1. Ethical issues in Regenerative Medicine

Within the set of retrieved papers (2000-2008), we searched for the keyword *ethic**. This resulted in 245 papers (about 2%). The set consists of 84 reviews and 161 journal articles. They were published in a large number (177) of journals. The most important journals are *Stem Cells* (13 papers), the *Journal of Medical Ethics* (5) and *Expert Opinion on Biological Therapy* (5). The other main journals in RM were represented too: *Tissue Engineering* (4), *Biomaterials* (3), *Cytotherapy* (3), *Cell Transplantation* (2). The authors are from 33 countries and we list the countries with more than 1% of the papers.

Table 1 Ethics papers by country

Country	Papers	Share	Country	Papers	Share	Country	Papers	Share
Usa	70	25.3	Netherlands	8	2.9	Switzerland	6	2.2
Uk	32	11.6	Pr China	8	2.9	Belgium	5	1.8
Germany	24	8.7	Singapore	7	2.5	Taiwan	5	1.8
Japan	19	6.9	Spain	7	2.5	Turkey	4	1.4
France	17	6.1	Australia	6	2.2	Austria	3	1.1
Italy	15	5.4	Korea	6	2.2			
Canada	8	2.9	Sweden	6	2.2			

These 240 papers under consideration include *ethic** in the title, abstract or as keyword. Inspection of the retrieved papers suggests that those papers with ethic* in the abstract often only refer to the existence of ethical issues, without in depth discussing them. Secondly, other keywords may also point at ethical discussions. We therefore conducted a somewhat different search within the set papers: we selected the subset of papers with a query on the *title* field and the *keywords* field only - so omitting the abstract.

Extended query: Like "*ethic*" Or Like "*regula*" Or Like "*polic*" Or Like "*future*" Or Like "*prospect*" Or Like "*politi*" Or Like "*norm*"

These keywords all refer to ethical, normative, regulatory and policy issues. The selection resulted in a subset of 64 papers[17]. The abbreviated keywords also included some 'wrong' title/keywords such as: 'Down-*Regula*tion', 'Developmental *Regula*tors', '*Regula*tory T-Cells', and '*Prospective* Identification'. Removing these resulted in a core list of 57 papers. We checked whether the papers were retrieved trough title words or through author keywords. The title words proved dominant in this selection.

From a content point of view, the social, regulatory, legal, policy and ethical issues are debated in the literature. But as the journal titles suggest, most papers were not published in the core journals of the RM field on in the medical top journals. Only the journal *Stem Cells* is four times on the list. The papers were not retrieved using ethics related keywords, but are a subset of the papers retrieved using RM keywords. So most probably we have missed much of the ethical and philosophical discussions about RM and stem cell research. And, ethical, political, legal and social discussion about RM also takes place in other journals than the RM scholarly journals. Therefore, a search was done in the whole of the WoS, using the following broad query.

17 This shows that omitting the abstracts reduces the set considerable.

(TS=ethic* Or TS=legal* OR TS=polic* Or TS=politi*)[18] AND
(TS=("regener* medic*") OR TS=("tissue engin*") OR TS=(biomaterial*) OR TS=("stem cell*"))

This resulted in some 1180 published between 2000 and 2008. We deleted all papers with the ethics keywords only in the abstracts, and this left us with 673 papers. The 673 papers are published in the following journals - we list only those with 4 or more papers (table 2). Now several important multidisciplinary journals are included, as well as several core RM journals.

Table 2 Journals with ethical papers on RM and stem cell research: journal name and number of papers

Journal	No. of papers	Journal	No. of papers
Reproductive Biomedicine Online	28	Stem Cell Reviews	6
Nature	27	Embo Reports	5
Science	21	Chemical & Engineering News	5
Journal Of Medical Ethics	18	Internal Medicine Journal	5
New England Journal Of Medicine	17	Zygon	5
Bone Marrow Transplantation	16	Chemistry & Industry	5
Human Reproduction	13	New Genetics And Society	5
Bioethics	13	Nature Reviews Genetics	5
Regenerative Medicine	12	Womens Health Issues	5
Stem Cells	11	Atla-Alternatives To Laboratory Animals	4
Jama-J American Medical Association	10	Nature Medicine	4
Kennedy Institute Of Ethics Journal	10	New Scientist	4
Journal Of Medicine And Philosophy	9	Current Science	4
Lancet	8	Fertility And Sterility	4
Science And Engineering Ethics	8	Fetal Diagnosis And Therapy	4
American Journal Of Bioethics	8	Comptes Rendus Biologies	4
Nature Biotechnology	8	Gene Therapy	4
Technology Review	7	Pediatric Blood & Cancer	4
Social Science & Medicine	7	Health Care Analysis	4
Metaphilosophy	6	Zeitschrift Fur Evangelische Ethik	4
Hastings Center Report	6	Theological Studies	4

The discussion is highly dominated by the ethical controversies around stem cells, which becomes evident when removing "stem cell" as keyword. This reduces the recall from 1180 to only 124 papers. The paper set was further analyzed using a visualization tool (BibTechMon). The underlying clustering algorithm places those papers together on the map, which share title words and references (so called "word-reference co-occurrence").[19] The method works quite well. In the keyword search we also retrieved papers on *patelet transfusion*. As the map is not only based on keywords, but also on the references used in the papers, the cluster of *patelet transfusion* papers is unrelated to the ethical papers: the papers do share keywords, but they do not share the references to the ethical literature. The map shows a few - partly related - research fronts, mainly about stem cells research and therapy:

18 In this search the keywords "*regula*", "*future*", "*prospect*" en "*norm*" created very much noise in the recall (so: low precision) and were therefore not used.

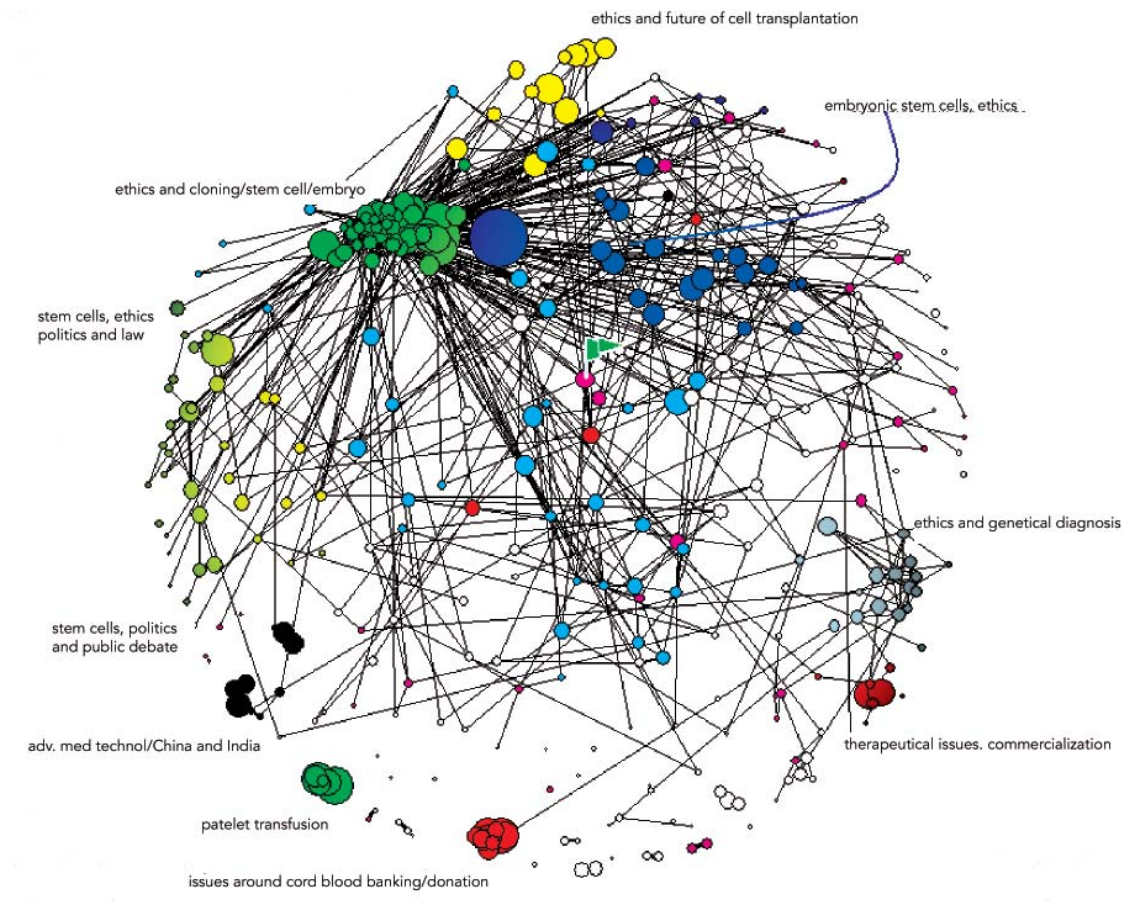
19 Van den Besselaar and Heimeriks, 2006.

- The ethical issues around embryonic stem cells,
- Ethical issues around cloning,
- The ethics of cell transplantation,
- Legal and political aspects of stem cell research and therapy,
- The public debate about stem cells.

Furthermore we see small clusters of papers around other issues:
- Genetic diagnoses,
- Issues around commercialization,
- Medical technology in developing countries such as China and India,
- Cord blood banking.

Concluding, the ethical, legal and political debate on Regenerative Medicine still has to start. Until now, most attention went to stem cell research, but this is only a part - although a core part - of RM.

Figure 1 A topics map of the ethical discussions



Annex 2. Exploration of topics in Regenerative Medicine

Method
Title words may be used as indicators of the topic under discussion whilst cited references provide the context or background from which the topic is approached. By combining the two indicators[21] title words and cited references from articles within the regenerative medicine set are combined to create unique combinations for each publication. For example title word A, B to *n* are combined with cited reference 1, 2 to *x* to form A1, A2, Ax B1, B2, Bx ... *n*. Articles may then be rated as having a similarity to other articles based on the number of shared combinations. Similarity is calculated using the Jaccard Index. Maps of the articles and their similarity values are then created over the periods 1990-1995, 1996-2000, 2001-2002, 2003, 2004, 2005, 2006 and 2007

Two approaches are presented, the first being one in which the articles are compared in terms of and the topics broached by the titles are recorded and presented to indicate the change (if any) of topics related to regenerative medicine. The networks of articles are visualized using a three-dimensional Fruchterman-Reingold layout[22], a force directed layout, in which the nodes are presented as being on the surface of a sphere, where nodes repel each other unless linked. This algorithm allows us to dynamically explore the network through cluster positioning.

The second approach entails highlighting the entrance journals, as selected from Table 7 by which the articles of these journals are assigned specific colour values within the network. Other journals are represented as small, non-colored nodes. The networks are visualized using the Kamada-Kawai force directed layout algorithm[23], and subnetworks are sorted according to size. Thresholds are set in both approaches to aid viewing.

Conclusions from network maps using word-reference combinations:

1. Stem cell research has remained separate in research topics until 2001-2002. Increasing similarity is found between stem cell topics and biomaterials and tissue engineering at later stages, becoming increasingly homogenous from 2005 to 2007.
2. The growth of certain journals is evident from the maps, notably *Tissue Engineering* and *Stem Cells*.
3. Later stem cell journal articles positioned close to *Stem Cells* with only a few occupying areas where *Stem Cells* articles not found.
4. Periodontology has remained an almost separate cluster for most of the periods presented. This is interesting in that one would expect a higher frequency of co-occurrence with biomaterials journals.
5. Cyclic topic divergence and convergence evident at different periods[24], most noticeable in the transition space from period 1 to 4.

---

21 Van den Besselaar and Heimeriks (2006).
22 T.M.J. Fruchterman and E.M Reingold, Graph drawing by force-directed placement, Software Practice and Experience (1991)
23 T. Kamada and S. Kawai, An algorithm for drawing general undirected graphs. Information Processing Letters. (1999)
24 Divergence or convergence refers to the degree of similarity of topics over time. If topics become more similar over time, this is referred to as convergence. If topics become more dissimilar over time, this is referred to as divergence. A measure of divergence or divergence is the structure of the network and the number of articles retained (also known as retention) when links between nodes are removed below a certain value or threshold. If nodes become separate from the network after applying this threshold they are removed from the network, altering the structure and total node count of the network.

   a. In periods 1 and 2, a low threshold (0.01) was applied which resulted in the network fragmenting into multiple unconnected subnetworks with low node retention suggesting a divergence of topics.
   b. Conversely, in period 3 the threshold is higher (0.08) and the node count remained relatively high compared to before the threshold application, with little fragmentation compared to periods 1 and 2. This suggests convergence of topics.
   c. Period 4 has a low applied threshold (0.01) but many subnetworks exist with low node retention suggesting a cyclic return to divergence.
6. *Regenerative Medicine* journal articles are primarily similar to stem cell journal articles, biomaterials journal articles and tissue engineering journal articles, although this is mostly at a low level of similarity.
7. Topics found using article titles suggest that only minor changes occur during the periods under consideration. However, experimenting with threshold differences is useful as it enables us to distinguish weak boundary similarity and strong core similarities.

Period 1: 1990-1995

In figure 1A, we show the map of articles from 1990-1995 with the largest subnetworks highlighted. The topics derived from titles are listed below.

1. Cutaneous wound healing, collagen microstructures.
2. titanium alloy surgical implants; biodegradeable polymer implants; tumour necrosis through gene expression
3. gene and protein expression and inhibition; matrix metalloproteinase
4. collagen scaffolds; bladder cellular matrices
5. biomaterial surface properties; microspheres
6. gene expression; limb regeneration
7. block polymers and hydrogels
8. synthesis and application of hydroxyapatite
9. therapeutic properties and generation of CD4 T cells; autoimmune diseases
10. group chemistry; biodegradeable materials; microfabrication
11. Chitosan; collagen structures

In figure 1B, the entrance journal articles are highlighted and identified by the key table. Various points of interest have been highlighted. A threshold has been set to aid viewing and to highlight overall placement within the map of the journal-articles.

Looking at figure 1B of the period 1990-1995, specific areas are visible immediately. The black nodes in area 1 (*Stem Cells* articles), are generally diffuse on the top left side of the largest subnetwork. *Stem Cells* articles link to journals that primarily cover hematological topics in this period. The green nodes in area 2 (*Cell Transplantation*) link to a wider variety of subject areas such as neurobiology, biotherapy, biomaterials and urology amongst many others. The lavender (*Biomaterials*) and blue nodes in area 3 (*Journal of Biomedical Materials Research*) occupy the same general area, indicating that the cited references and title words utilized are common between them.

The *Journal of Materials Science-Materials in Medicine* articles occupy the same area but are more diffuse across the network. The dense cluster highlighted in 4 is periodontology-based. Considering the two maps together, the subject areas are reflected in both, with a high degree of representation of biomaterials, and to much lesser degrees, cell transplantation topics and stem cell topics.

Figure 1A Map of articles (1990-1995) with the largest subnetworks (n>15) highlighted. (n=1357; r>=0.3)

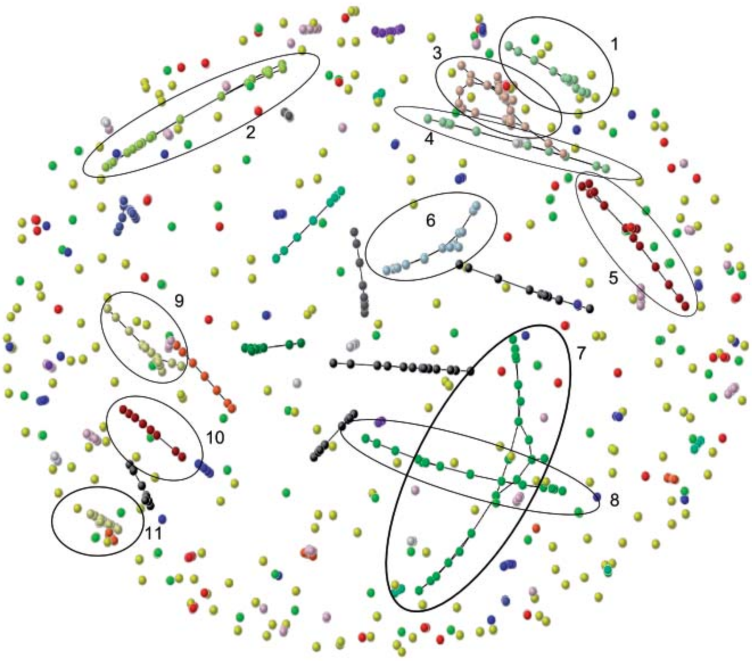
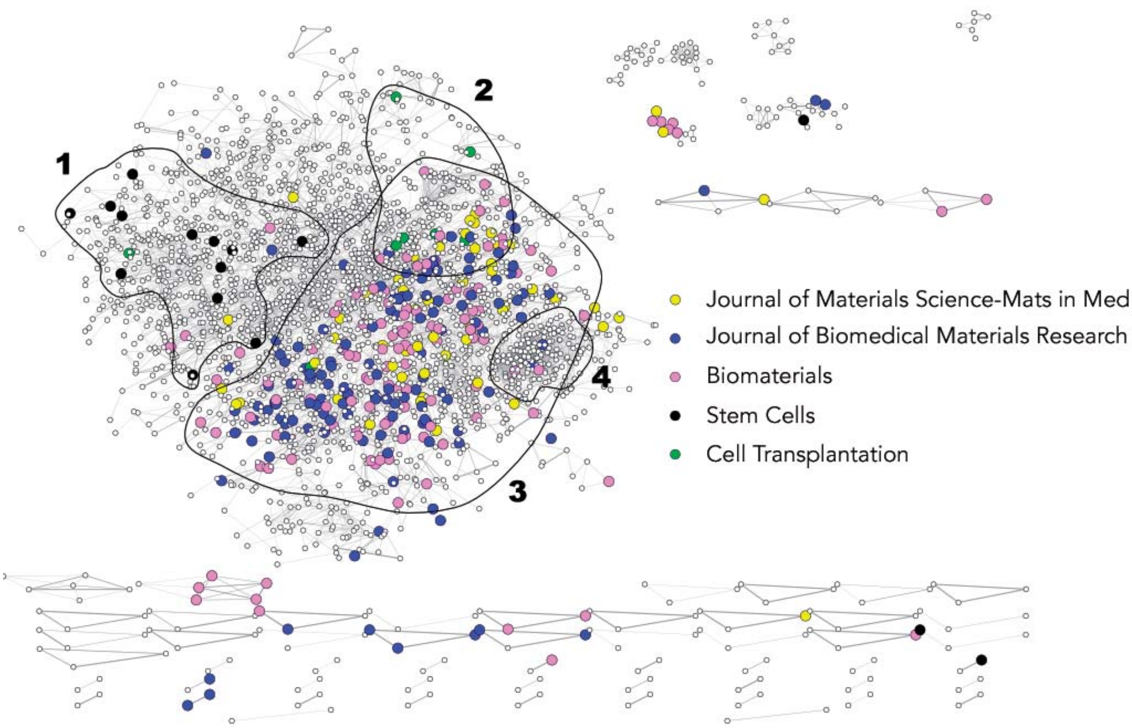


Figure 1B Map of articles within the 1990-1995 period, (n = 2881, r>=0.01)



Period 2: 1996-2000

In figure 2A, we show the map of articles from 1996-2000 with the largest subnetworks highlighted. A threshold has been set to aid viewing and highlight primarily strong links between articles. The topics derived from article titles are listed below.

1. cell encapsulation; cell transplantation; cell therapy
2. integrating biomaterials; analogue designs; liver tissue engineering
3. abdominal wall prostheses; polytetrafluoroethylene micro mesh
4. atomic force microscopy; micropatterned biomolecules; biomaterial surfaces
5. biomaterials; biocompatibility of biomaterials; biomaterials to order
6. angioplasty materials; coronary stent implantations
7. biodegradable polymers; cortical allografts; injectable polymers
8. small intestinal submucosa scaffolds and matrices
9. gene promoters; mRNA; RUSH transcription factors
10. bioartificial nerve grafts; nerve surgery, repair, regeneration
11. intracellular calcium loading; endothelial cell differentiation; endothelial cells in biomaterial research

In figure 2B, the biomaterial journals continue clustering together as shown in the highlighted area 1. The introduction of the journal *Tissue Engineering* is also apparent with small clusters throughout the large subnetwork. These small clusters in area 2 mainly link to other *Tissue Engineering* articles and oncology, thoracic surgery and bioengineering journals; with very few linked to the biomaterials entrance journals. The periodontology articles in area 3 remain tightly clustered with only a few biomaterials articles featuring in the cluster. Area 4 indicates that more entrance journal articles are found within the larger set of articles, whereas in 1990-1995, there are very few coloured nodes found. *Journal of Materials Science-Materials in Medicine* articles are still relatively diffused across the network, with most nodes linking to non-entrance journal articles.

Stem Cells articles are still very diffuse throughout the network, with links to more varied journals such as journals covering hematology, cytokines, immunology, periodontology and inflammation journals, with very few links to biomaterials journals. As with the period 1990-1995 biomaterials dominate the cognitive landscape, along with less the prominent cell therapies and gene therapies.

Figure 2A Map of articles (1996-2000) with the largest subnetworks (n>15) highlighted. (n=2853; r>=0.3)

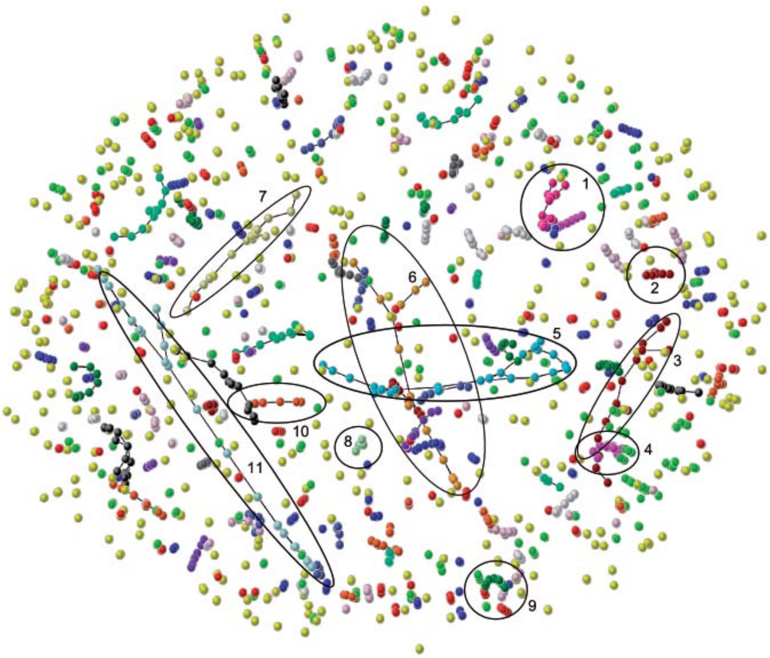
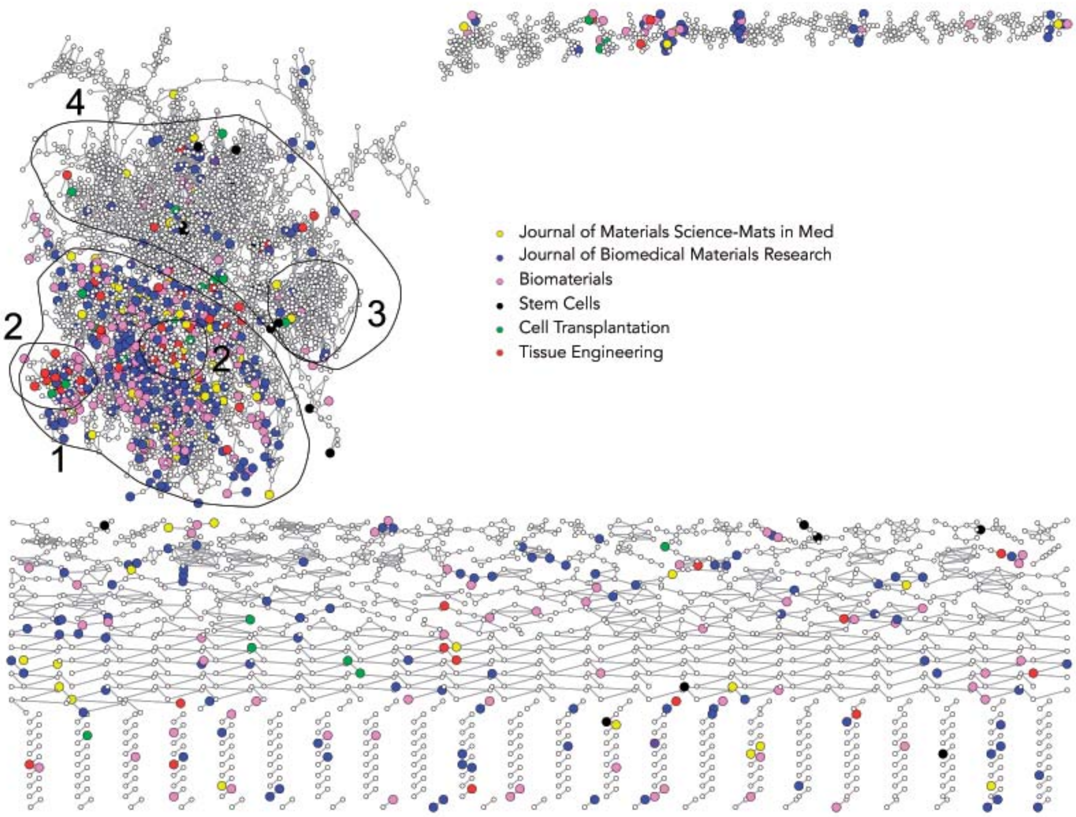


Figure 2B Map of articles within the 1996-2000 period, with entrance journals highlighted (n = 6550, r>=0.01)



Period 3: 2001-2002

In figure 3A, we show the map of articles from 2001-2002 with the largest subnetworks highlighted. A threshold has been set to aid viewing and highlight primarily strong links between articles. The topics derived from article titles are listed below.

1. intrabony defects; enamel matrix proteins
2. bioactive ceramics and glass; sol-gels; fabrication of hydroxyapatite
3. polymer surfaces and adhesion mechanisms
4. skin grafts and substitutes; wound healing; tissue engineered skin
5. polyglycolide and lactide surfaces; high density protein biosurfaces and modifications
6. endothelial and endometrial cells and exposures to chemicals; promoting angiogenesis; mast cells; fibrotic tissues; myofibroblasts; fibronectin
7. myeloma cells; therapeutic affects of multiple myeloma
8. T lymphocites; antiviral and anti-retroviral therapy; HIV
9. Plasminogen activators; vascular smooth muscle cells
10. metalloproteinase; fibroblast growth and factor; vascular endothelial growth;
11. collagen membranes; collagen gels
12. fibrous proteins; silk proteins; structure and stabilisation of collagen; mechanical, electrical and thermal properties of films
13. binding and adhesion to copolymer films (polyeurethanes); metallic and polymeric biomaterials; bacterial and antibiotic effects of biomaterials
14. suicide gene therapy; natural killer cells; T cells; antiretroviral therapy; cell therapy; adoptive tumour therapy
15. bone regeneration, modelling; bone histomorphometrics

In figure 3B the emergence of articles from *Cytotherapy* in the network is visible in area 1 with the few articles mostly linking to biotechnology, stem cell, experimental hematology and neurology journal articles. *Stem Cells* articles are also found within this area, along with *Tissue Engineering* articles and few biomaterials articles. Area 2 covers primarily biology-based journal articles. *Cell Transplantation* articles are generally diffuse across the network as are *Journal of Materials Science- Materials in Medicine*. Periodontology based journal articles have created their own cluster as shown in area 3, with few biomaterials articles within.

Figures 3A and 3B both indicate that the similarities between articles are increasing in terms of topics and cited references. From figure 3A there are more large subnetworks of topics than previous periods, indicating that articles are converging more so in terms if subjects broached. This may also be seen to a lesser degree in figure 3B. Although only the highlighted journals are displayed in figure 3B, the network structure as a whole is more cohesive in general even at a slightly higher similarity threshold. Generally speaking, one would expect the network to differentiate into more subnetworks if the threshold is increased in the case of diverging or static topic coverage, whereas in our case, the network displays greater cohesiveness in the face of an increasing threshold. The topics being introduced are still primarily biomaterials related but the diversification of biomaterials topics is increasing compared to previous periods.

Figure 3A Map of articles (2001-2002) with the largest subnetworks (n>15) highlighted. (n=1572; r>=0.3)

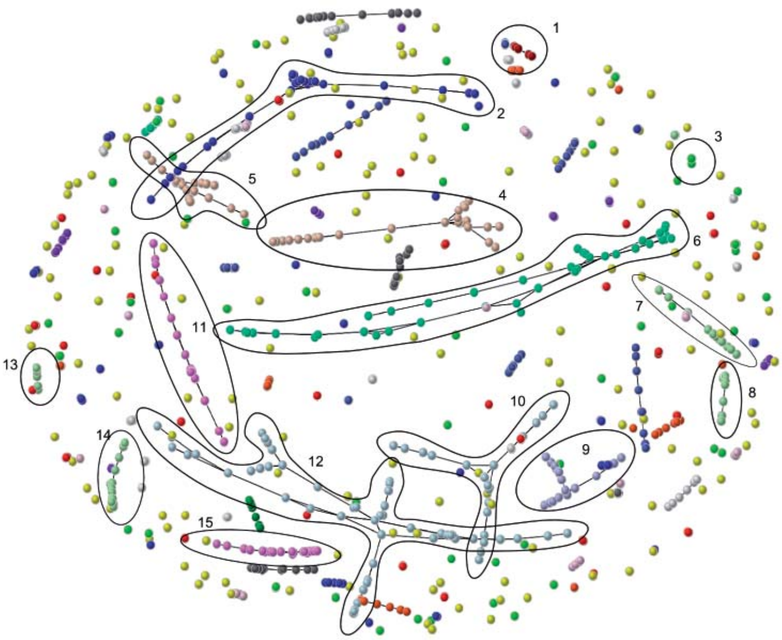
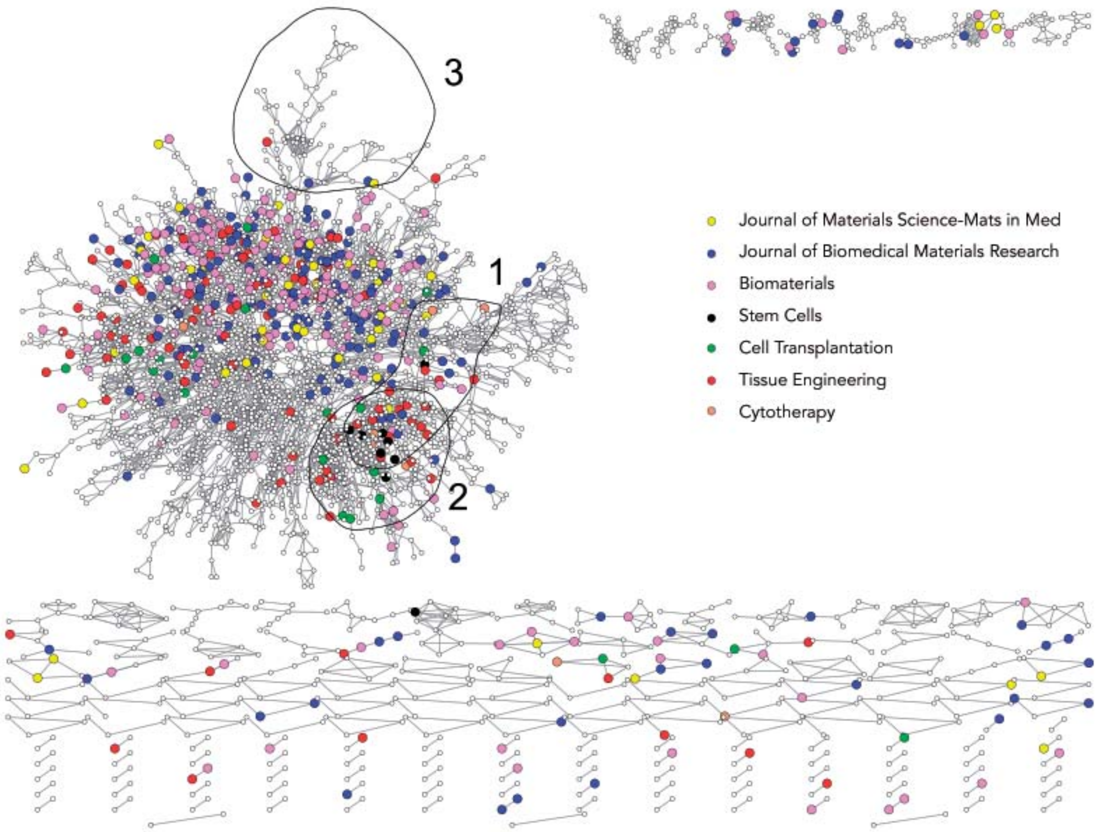


Figure 3B Map of articles within the 2001-2002 period, with entrance journals highlighted (n = 3608, r>=0.08)



Period 4: 2003

In figure 4A, we show the map of articles from 2003 with the largest subnetworks highlighted. A threshold has been set to aid viewing and highlight primarily strong links between articles. The topics derived from article titles are listed below.

1. fracture healing; wound healing; healing mediators and modulators; gene therapy
2. connective tissue growth factor; airway remodelling; asthma; transforming growth factor beta; gene expression patterns, arrays
3. bioactive ceramics, apatites, glass; composition and role of calcium phosphates and carbonates on biomaterials; hydroxyapatites and effects of radiation on; in vitro apatite
4. enamel matrix, intrabony defects, fibroblasts
5. designer blood cells; collagen gels, assembly; fibroblast functions
6. chitosan coatings, prostheses; chitosan biomaterials; peripheral nerve construction; artificial nerve engineering; tissue engineered scaffolds
7. myocardial infarction; metalloproteinase matrices
8. matrix metalloproteinase
9. matrix metalloproteinase; tissue inhibitors
10. metallic biomaterials; growth factors in wound healing; cell sheet engineering; mechanical loading, bone mineralization; artificial skin
11. tumour vaccines, cell therapy; dendritic cells
12. recombinant collagen; angiogenesis; tissue engineered neointestine

In Figure 4B we see the split up of *Journal of Biomedical Materials Research (JBMR)* into parts *A* and *B*. *JBMR A* and *JBMR B* occupy much of the same space as their previous form, but part *A* is much more visible within this network. Area 1 in the network is again occupied primarily by *Stem Cells* articles, along with *Cytotherapy* and *Cell Transplantation* articles. There was very little overlap between the *Cell Transplantation* articles in 2001-2002 whereas the similarity values and links in 2003 have increased to a point where they are locating around *Cytotherapy* and *Stem Cells* articles. Area 2 covers periodontology journals but is less dense in comparison to previous periods. This may suggest that the topics are becoming more similar to other non-periodontology journal subjects. Area 3 is still a large "white space" with very little penetration by our entrance journals.

Figures 4A and 4B are from the first period in which only one year is covered. Accordingly the number of nodes will drop in comparison to the previous maps. Although the split of *Journal of Biomedical Materials Research* into parts *A* and *B* is visible in Figure 4B, the subject matters illustrated in Figure 4A would not illustrate this.

Figure 4A Map of articles (2003) with the largest subnetworks (n>15) highlighted (n=1089; r>=0.3)

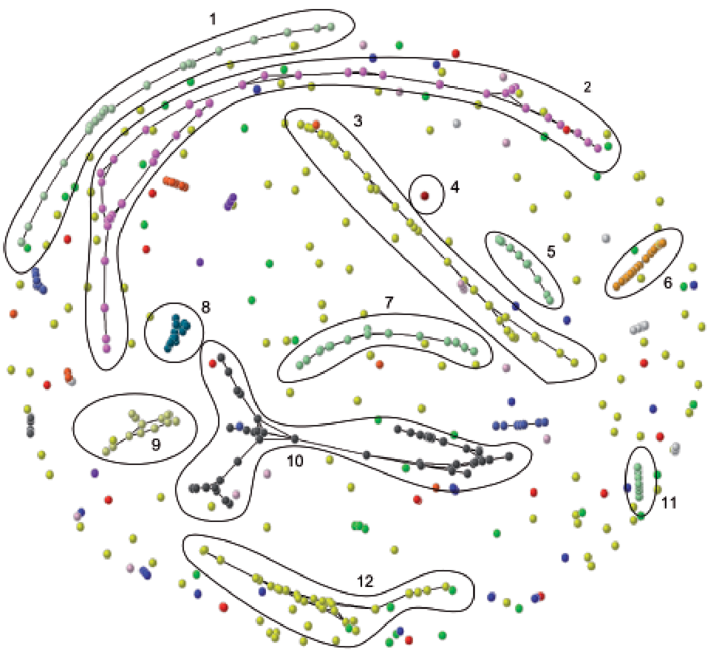
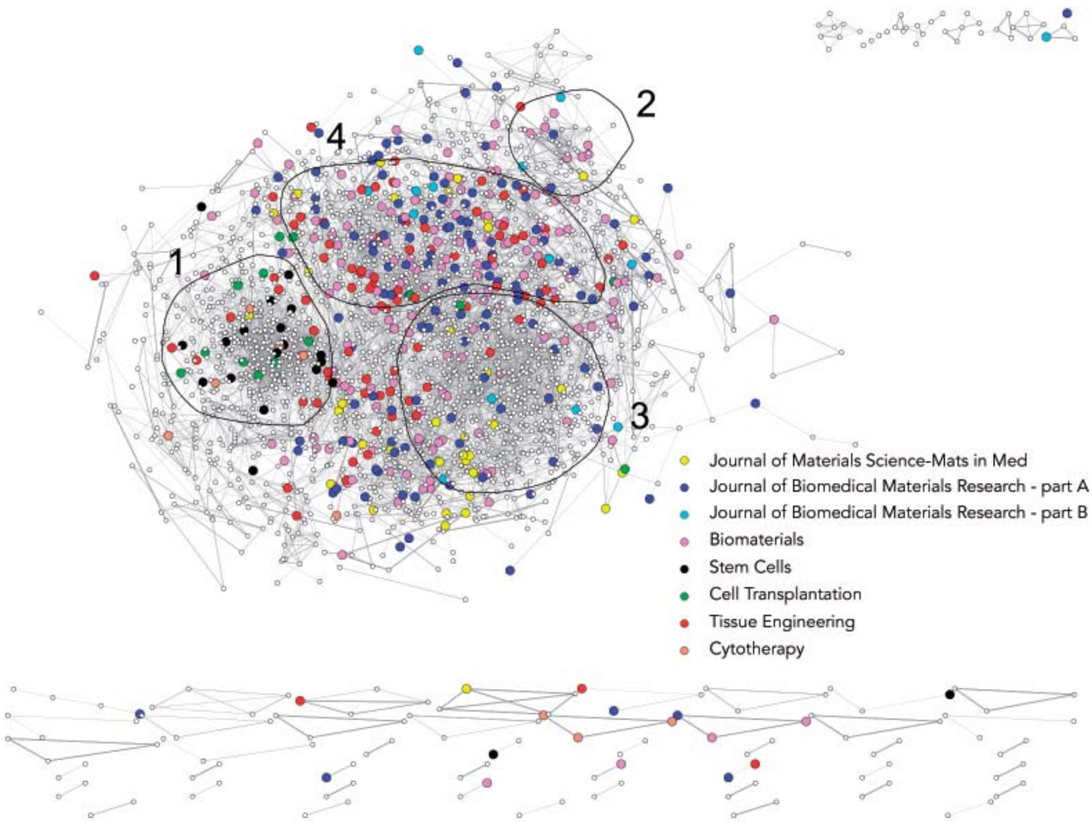


Figure 4B Map of articles in 2003, with entrance journals highlighted (n = 2691, r>=0.01)



Period 5: 2004

In figure 5A, we show the map of articles from 2004 with the largest subnetworks highlighted. A threshold has been set to aid viewing and highlight primarily strong links between articles. The topics derived from article titles are listed below.

1. synthesis and study of hydrogels; microfluidic materials; nanostructure materials; medical implants
2. collagen scaffolds; chitosan thin films;
3. titanium alloys for biomedical applications; biodegradeable polymers
4. hyaluronic acid; cellular colonization; micropatterning
5. CD cells; T cells and applications
6. gene expression; tissue inhibitors; metalloproteinase, matrix
7. wound healing; growth factor beta
8. mechanics of collagen gels; acellular, extracellular matrices
9. limb regeneration; gene expression
10. microfabrication of biodegradeable polymers; bone modelling;
11. hydroxyapatite synthesis and biocompatibility

In figure 5B, Area 1 is interesting as it is the first period in which we see all the entrance journals clustering together, indicating that the articles represented in the map exhibit a high degree of similarity in terms of title word and cited references. Area 1 also contains the first articles from *Stem Cells and Development*. Area 2 still indicates the bulk of biomaterials journals, and less "white space" can be found throughout the map. Area 3 representing the periodontology journals has separated completely from the main sub-network, and still shares little similarity with any biomaterials journals.

Figure 5A and the associated listing of topics are also interesting in that whilst the overall number of articles is higher than in 2003, the number of large subnetworks is less. This would indicate that the topics and cited references of 2004 are more diverse (less similar) than in 2003. This diversification is also visible in figure 5B where the network as a whole contains more prominent gaps between the large branches of the subnetworks. It would seem that only a few of the articles at the core of the large subnetworks provide the links to other branches. In figure 5B this core of articles is seemingly more populated with *Tissue Engineering* articles (between areas 1 and 2) than any of our other entrance journals.

Figure 5A Map of articles from 2004 with the largest subnetworks highlighted (n=1537; r>=0.3; highlighted subnetworks n>15).

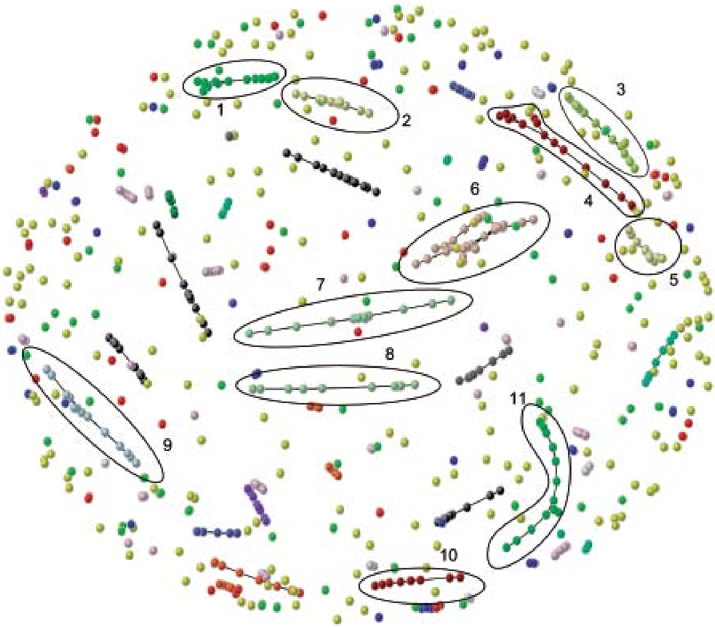
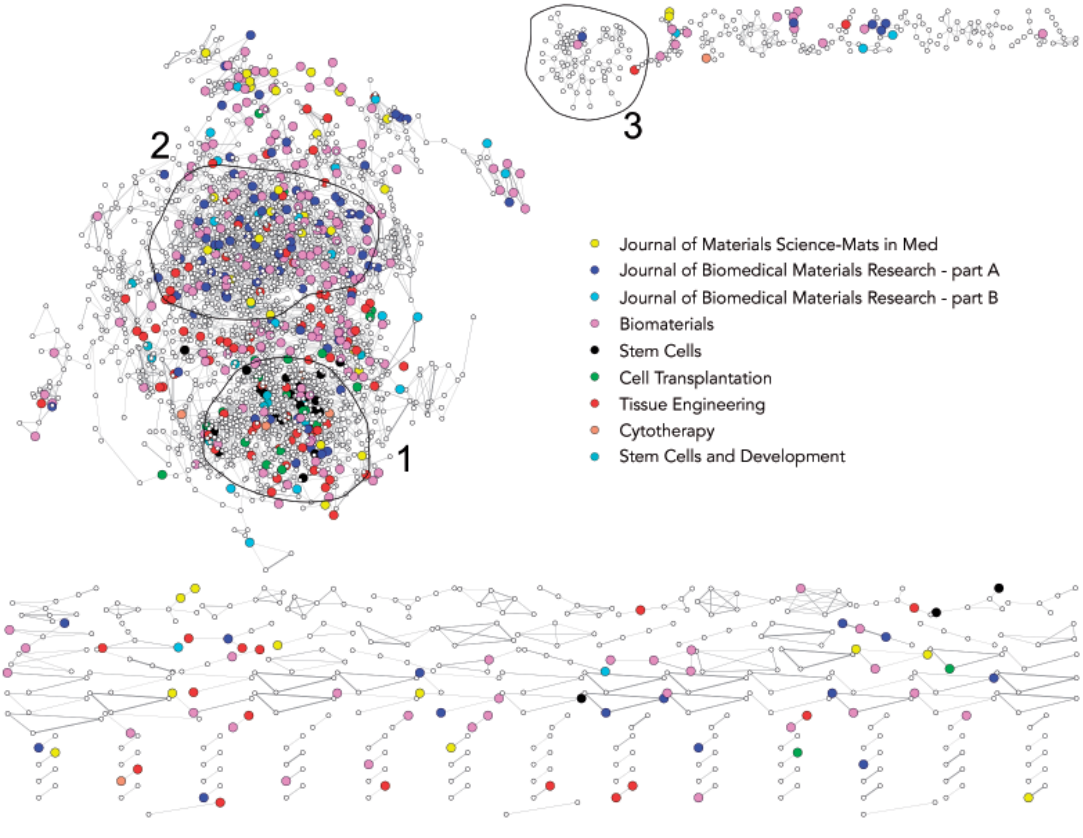


Figure 5B Map of articles in 2004, with entrance journals highlighted (n = 2691, r>=0.01)



Period 6: 2005

In figure 6A, we show the map of articles from 2005 with the largest subnetworks highlighted. A threshold has been set to aid viewing and highlight primarily strong links between articles. The topics derived from article titles are listed below.

1. collagen fibre matrices; fibril scaffolds and assembly
2. soft tissue and wound healing; hyaluronic acid and wound healing; diabetic wound healing
3. composite and polymer nanofibres; electrospun biodegradeable fibres; nano- and micro-fibre meshes
4. chitosan coatings, prostheses; chitosan biomaterials; peripheral nerve construction; artificial nerve engineering; tissue engineered scaffolds
5. inkjet and laserprinting of animal cells; biomaterials surface properties; hydrogels
6. gene therapy; T cells; adoptive immunotherapy; cell therapy
7. hepatic stellate cells; hydrogels
8. endometrial and endothelial cells; angiogenesis; gene expression; allergen induced airway remodelling; asthma
9. hydroxyapatites, preparation; characteristics; nanophase materials; laser irradiation; osteoblast adhesion
10. polypeptide microlayer films; endothelial cells
11. biocomposite fillers; calcium phosphates, wollastonite glass ceramics; silicate ceramics and sol gels
12. nanoscale topography; active cell motion; cell adhesion

The first appearances of *Acta Biomateriala* journal articles are visible in figure 6B, dispersed amongst the bulk of the network map. Area 1 remains stem cell based, with the occasional *Cell Transplantation* article and select biomaterials articles. Area 2 is periodontology based, with the small link coming through materials sciences journals. Area 4 is primarily leukemia based articles. With a high threshold set in figure 6B, the number of nodes retained is high, indicating the similarity between articles is also high. The large subnetworks in figure 6B also indicate that the topics being addressed exhibit higher similarity values than in 2004. From the network maps presented so far, there exists clear trends of convergence and divergence of subjects, which is to be expected in any dynamic representation of a field.

Figure 6A Map of articles (2005) with the largest subnetworks (n>15) highlighted (n=1385; r>=0.3)

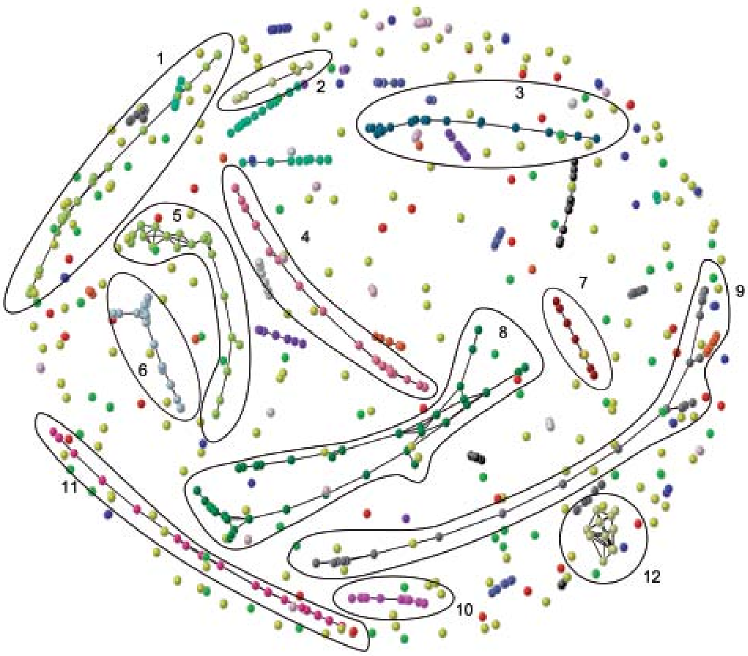
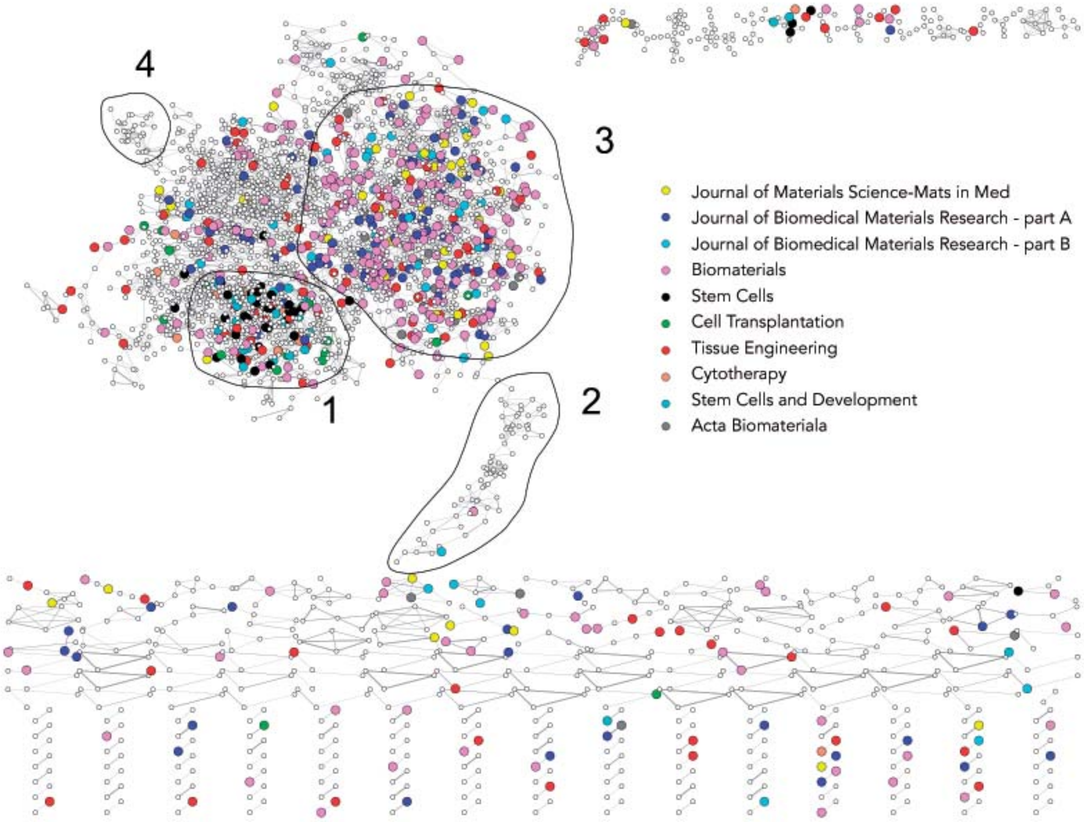


Figure 6B Map of articles in 2005, with entrance journals highlighted (n = 3508, r>=0.01)



Period 7: 2006

In figure 7A, we show the map of articles from 2006 with the largest subnetworks highlighted. A threshold has been set to aid viewing and highlight primarily strong links between articles. The topics derived from article titles are listed below.

1. myocardial wound healing; regulation of angiogenesis
2. fibroblasts; tissue engineered skin
3. growth factor expression; bortezomib; cytotoxicity; multiple myeloma
4. biocompatibility; bone tissues; collagen scaffolds and gels; cell adhesion biomaterial
5. in vitro bioactivity, compatibility; hydroxyapatite biomaterials, nanobioceramics
6. vertical ridge augmentation; bone regeneration; guided tissue regeneration; bone grafting implantation
7. heart valve interstitial cells; tissue engineered heart valves, modelling of and mechanics of
8. fatigue loading, bone mineralization; bone metabolism and bone mass
9. regulatory T cells; allogeneic stell cell transplantation; dendritic cells
10. CD8 T cells; T cell therapy for cancer and immunotherapy

2006 sees the entry of the first articles from *Regenerative Medicine*, and these are positioned primarily within area 1 with a few in area 6. Area 1 in Figure 7B holds primarily stem cell journal articles with a large number of biomaterials and tissue engineering journal articles, as well as the *Regenerative Medicine* articles. The smaller cluster labeled 2 in the map is related to immunology. This would indicate that the target publication area for regenerative medicine articles would be in the region of stem cells and biomaterials and tissue engineering. In areas 3 and 4 are found a few articles from *Stem Cells* and *Stem Cells and Development*. An area of interest is the barrier zone between area 1 and the primary body of the network indicated by area 5. A semi-ring of biomaterials journal articles forms a fuzzy boundary. This boundary first comes to prominence in 2004 but in a lesser form. In Figure 7B this boundary is clearly visible. Prior to 2004, biomaterials journals were scarce and hardly visible within the stem cells cluster. As the subject areas have converged over the following years, a boundary signifying similar topics began to form and in 2005 a much greater number of biomaterials articles are found in the stem cells cluster, with more positioned just outside the boundary. From Figure 7A and associated topic list, this may indicate why there are no “pure” stem cell topics, rather mixed topics encompassing stem cells, tissue engineering and biomaterials.

Figure 7A Map of articles (2006) with the largest subnetworks (n>15) highlighted (n=1428; r>=0.3)

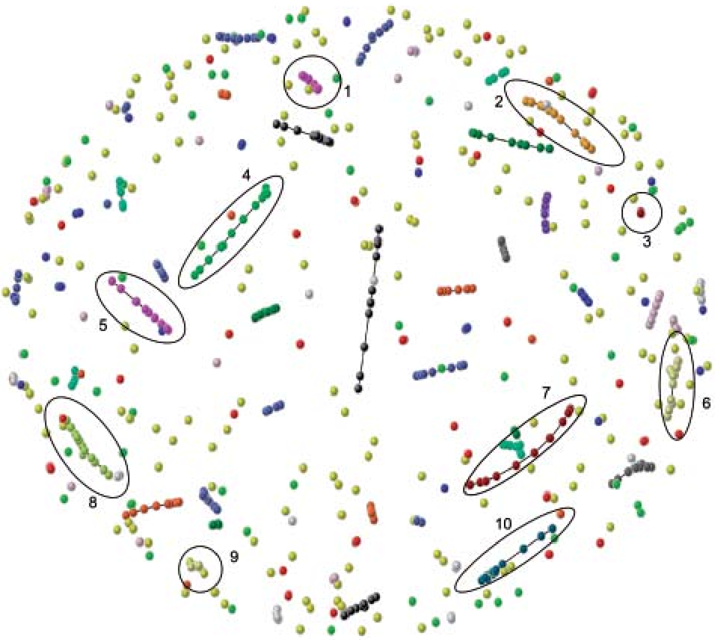
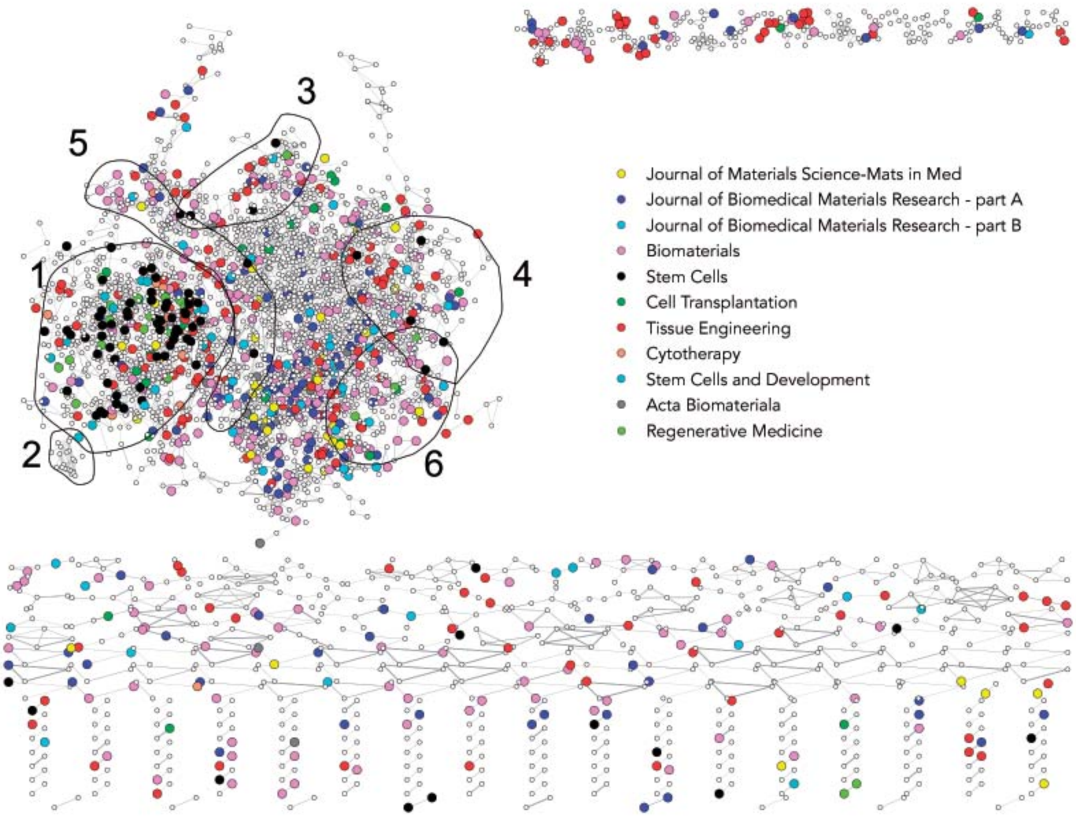


Figure 7B Map of articles in 2006, with entrance journals highlighted (n = 4100, r>=0.01)



Period 8: 2007

In figure 8A, we show the map of articles from 2007 with the largest subnetworks highlighted. A threshold has been set to aid viewing and highlight primarily strong links between articles. The topics derived from article titles are listed below.

1. collagen gels, porcine aortic interstitial cells; cardiac valve interstitial cells; tissue engineered heart valves
2. collagen chemistry, cell therapy; biocompatibility bone cements; cell adhesion biomaterials
3. wound healing, repair; cell therapy
4. bortezomib; multiple myeloma; growth factor expression
5. CD8 T cells; T cell therapy for cancer and immunotherapy
6. vertical ridge augmentation; bone regeneration; guided tissue regeneration; bone grafting implantation
7. tissue engineered skin; fibroblasts; collagen-chitosan bilayers
8. CD cells; T cell regeneration, regulation; dendritic cells
9. hydroxyapatite coatings; in vitro compatibility of glass ceramics
10. fatigue loading, bone mineralization; bone metabolism and bone mass; nanomechanical analysis of bone tissue engineering

From figure 8B, stem cell based articles dominate area 1 (along with large numbers of *Regenerative Medicine* articles). Area 2, slightly hidden is an extremely dense cluster related to stem cells and leukemia, along with tissue engineering articles. Some *Regenerative Medicine* articles are found in area 3, related to materials sciences, more so than in 2006. Area 4 is periodontology based, with one article from *Stem Cells* linking to the cluster. From Figure 8A, it would appear that there are very few large subnetworks, perhaps indicating that some diversification of subject matter has occurred, and most likely starting in 2006.

Figure 8A Map of articles (2007) with the largest subnetworks (n>15) highlighted (n=1428; r>=0.3)

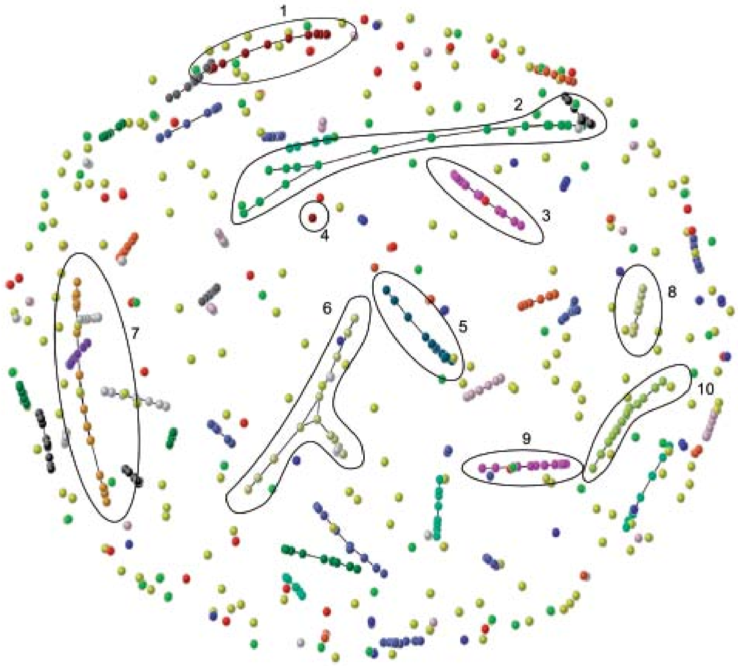
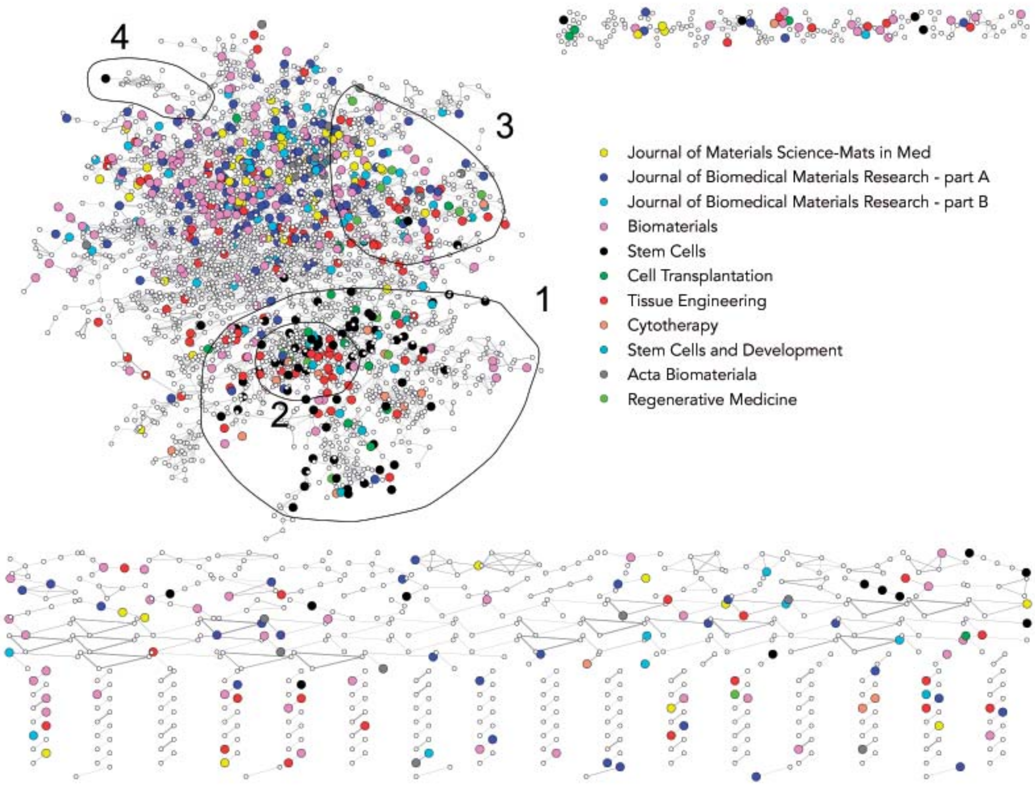


Figure 8B Map of articles in 2007, with entrance journals highlighted (n = 3851, r>=0.08)



Recent Science System Assessment reports:

0701 Anouschka Versleijen, *Nulmeting IOP selfhealing materials*. Den Haag, Rathenau Instituut, maart 2007

0702 Barbara van Balen, Peter van den Besselaar, *Universitaire onderzoeksloopbanen: Een inventarisatie van problemen en oplossingen*. Den Haag, Rathenau Instituut, juli 2007

0703 Anouschka Versleijen, Barend van der Meulen, Jan van Steen, Robert Braam, Penny Kloprogge, Ruth Mampuys, Peter van den Besselaar, *Dertig jaar publieke onderzoeksfinanciering in Nederland (1975-2005): historische trends, actuele discussies*. Den Haag, Rathenau Instituut, juli 2007

0704 Femke Merkx, Anouschka Versleijen, Peter van den Besselaar, *Kustverdediging: wetenschap, beleid, maatschappelijke vraag*. Den Haag, Rathenau Instituut, augustus 2007

0705 Peter van den Besselaar, *Een kaart van communicatie- en media-onderzoek*. Den Haag, Rathenau Instituut, september 2007

0706 Femke Merkx, Inge van der Weijden, Anne-Marie Oostveen, Peter van den Besselaar, Jack Spaapen, *Evaluation of Research in Context; a Quick Scan of an Emerging Field*. Den Haag: COS/EriC, june 2007

0707 Peter van den Besselaar, Loet Leydesdorff, *Past performance as predictor of successful grant applications - a case study*. Den Haag, Rathenau Instituut, december 2007

0808 Jan van Steen, *Informatievoorziening over wetenschappelijk onderzoek*. Den Haag, Rathenau Instituut, juli 2008

0809 Edwin Horlings, Anouschka Versleijen, *Groot in 2008; momentopname van grootschalige onderzoeksfaciliteiten in de Nederlandse wetenschap*. Den Haag, Rathenau Instituut, november 2008

0910 Edwin Horlings, *Investeren in onderzoeksfaciliteiten; prioritering; financiering, consequenties*. Den Haag, Rathenau Instituut, januari 2009

0911 Femke Merkx, Reinoud van Koten, Thomas Gurney, Peter van den Besselaar, *The development of transdisiplinary learning sciences: promise or practice?* Den Haag, Rathenau Instituut, Juni 2009

0912 Peter van den Besselaar & Thomas Gurney, *Regenerative medicine, and emerging field*. Den Haag, Rathenau Instituut, juni 2009

0913 Inge van der Weijden, Maaike Verbree, Robert Braam, Peter van den Besselaar, *Management en prestaties van onderzoeksgroepen*. Den Haag, Rathenau Instituut, augustus 2009

F&F1 Jan van Steen, *Universities in the Netherlands - Facts and Figures 1*. Den Haag, Rathenau Instituut, september 2008

F&F2 Jan van Steen, *Public research institutes in the Netherlands - Facts and Figures 2*. Den Haag, Rathenau Instituut, march 2009

The Rathenau Instituut focuses on the influence of science and technology on our daily lives and maps its dynamics; through independent research and debate.

Anna van Saksenlaan 5
2593 HW Den Haag
Postbus 95366
2509 CJ Den Haag
T 070 342 1542
F 070 363 3488
E info@rathenau.nl
I www.rathenau.nl