Rowan University

# Rowan Digital Works

3-25-2002

# Bibliometric Analysis of Core Papers Fundamental to Tissue Engineering

Diana Hicks
*CHI Research*

Mike Albert
*CHI Research*

Anthony Breitzman
*Rowan University*, breitzman@rowan.edu

Peggy Cheney
*CHI Research*

Back to The Emergence of Tissue Engineering as a Research Field

# Bibliometric Analysis of Core Papers Fundamental to Tissue Engineering

March 25, 2002

*Prepared by*
Diana Hicks, Mike Albert, Tony Breitzman, and Peggy Cheney
CHI Research, Inc., 10 White Horse Pike, Haddon Heights, NJ 08035, Tel.: 856.546.0600 Fax: 856.546.9633
www.chiresearch.com

## CONTENTS

# I. Executive Summary

This bibliometric study of core papers fundamental to tissue engineering produced results in four areas: an overview of the growth of the field, an analysis of NSF's role in the field, a mapping of co-authorship patterns, and an analysis of international patenting

The foundation of the paper side of the study is a database of information on core papers fundamental to tissue engineering. This database was carefully constructed in a process developed to meet the challenge of identifying the boundaries of such an interdisciplinary area. The study focuses on research that synthesized many areas of biomedicine with the aim of seeding autologous cells and growth factors onto three-dimensional biodegradable scaffolds with the aim of forming new functional tissue. Papers and patents in this area were identified using search strategies or "filters" described in the appendices. The set of papers found using the filters was augmented by papers highly cited in the patents and in review papers. Of the papers analyzed in the study, 66% were cited in review articles or patents, and 33% were found using the search strategies described by the filter.

The analytical results revealed that the number of core papers fundamental to tissue engineering has been growing strongly since about the mid 1980's. The paper most cited in reviews of the field is: Langer & Vacanti, "Tissue Engineering," <u>Science</u> 1993 May 14;260(5110):920-6. This paper was cited 39 times in the reviews and 11 times in patents. This paper acknowledges funding from NSF as well as funding from other sources.

Analysis of the use of the term "tissue engineering" in titles and abstracts of papers indexed in PubMed suggests that there were three phases in the spread of the concept of tissue engineering. In the first phase, researchers imagined the possibility of designing replacement tissue. This is exemplified by papers in 1984/85 by Wolter and Meyer examining a prosthesis removed from an eye after 20 years. Wolter and Meyer discussed: "the significance of the successful adaptation of the plastic materials of the prosthesis to the tissues of the cornea and the fluids of the inner eye for the future of tissue engineering in the region of the eye." In the second phase, 1989 through 1997, the term "tissue engineering" began to be used regularly in abstracts and titles. During this period, the term was applied to work concerning all the main organs closely connected to tissue engineering: bone, cartilage, blood vessels, liver, skin, neurons and also to biomedical materials. The third phase of dramatic growth began in 1998 and continues. In this phase we also see a few papers concerning other organs, and in fact the return of papers concerning eyes. Overall, the growth in the use of the term "tissue engineering" in titles and abstracts seems not unlike the growth in number of core papers fundamental to tissue engineering.

We find that NSF supported about 12% of the papers in the field overall. However, NSF focused its support on basic research and biomaterials. Therefore, when clinical research is excluded from consideration, NSF's share rises to 20%. 86% of NSF-supported work is published in the most basic journals or in the two leading biomaterials journals: *Biomaterials* and the *Journal of Biomedical Materials Research*. In contrast, 52% of research supported by other funders is basic or in those two journals. NSF's research is also focused on the core participants in the field. 17% of the papers from leading institutions acknowledge NSF support compared to 2% of papers

from institutions that appeared only once on a core paper fundamental to tissue engineering. More peripheral, and one-off participants are much less likely to acknowledge NSF research support. Thus it is no surprise to find that NSF played a larger than expected role in supporting the work of leading researchers such as R Langer, JP Vacanti, and DJ Mooney.

The patterns of co-authorship in the field are portrayed in an innovative series of figures, tables and maps developed for this study. These reveal the highly collaborative nature of the work undertaken by R Langer and JP Vacanti, with whom most lead authors in the area have worked at least once. Papers by Langer and Vacanti list over 250 coauthors. Several leading authors appear to have started as students of Langer or Vacanti, and several more appear only as their co-authors. Six multi-dimensional maps of the paper-by-paper development of lead authors' work in the area were developed for authors supported by NSF. These reveal the interweaving of public and private knowledge and the public and private sectors in the development of tissue engineering research, and precisely position NSF support in relation to this.

In parallel with the analysis of tissue engineering literature, CHI was engaged to do a patent analysis to study the international patenting trends in tissue engineering. We found:

1. Patenting in the area is increasing steadily and has not yet peaked.

2. Most of the patents are coming from US inventors and assignees.

3. Most of the key inventions are coming from US assignees, especially MIT, Advanced Tissue Sciences, and Regen Biologics Inc.

## II. Introduction

CHI Research, Inc. was engaged by the National Science Foundation through a subcontract to Abt Associates to undertake a bibliometric analysis of the emerging area of tissue engineering with the intent of describing quantitatively NSF's role in the area and examining the co-authorship structure of the field.

The project consisted of five parts:

1. Identifying core papers fundamental to tissue engineering

2. Constructing a database of information on the papers

3. Analyzing the nature and extent of NSF's overall role in the field as revealed through funding acknowledgements on papers

4. Developing representations of coauthorship information for leading authors in the field, with indications of NSF's presence.

5. An analysis of international patenting in tissue engineering

This report describes each of these steps in turn. The first section describes how the foundation for the analysis was carefully laid through development of a sophisticated methodology developed specifically to identify core papers fundamental to tissue engineering. After this, a basic description is offered of the growth of tissue engineering, as revealed in the full paper set and in a special set of papers that use the term "tissue engineering" in their abstract or title. There follows a quantitative analysis of NSF's role as revealed through acknowledgments of funding reported on papers. Then maps and tables are presented that together reveal the patterns of coauthorship in the field and NSF's presence within the oeuvre of leading authors. Finally an analysis of international patenting in tissue engineering is reported.

## III. Methodology

### A. Finding core papers fundamental to tissue engineering

The fundamental methodological work in this project was to devise a way of identifying core papers fundamental to tissue engineering. This was very challenging. CHI needed to identify the papers in a rapidly evolving area that brings together a heterogeneous set of technologies and research approaches, and in which no two researchers seem to agree on a definition. At some level, all biomedical knowledge not directly concerning disease probably will contribute to tissue engineering. However, time was limited, so every biomedical paper could not be assessed for relevance to tissue engineering.

## II. Introduction

CHI Research, Inc. was engaged by the National Science Foundation through a subcontract to Abt Associates to undertake a bibliometric analysis of the emerging area of tissue engineering with the intent of describing quantitatively NSF's role in the area and examining the co-authorship structure of the field.

The project consisted of five parts:

1. Identifying core papers fundamental to tissue engineering

2. Constructing a database of information on the papers

3. Analyzing the nature and extent of NSF's overall role in the field as revealed through funding acknowledgements on papers

4. Developing representations of coauthorship information for leading authors in the field, with indications of NSF's presence.

5. An analysis of international patenting in tissue engineering

This report describes each of these steps in turn. The first section describes how the foundation for the analysis was carefully laid through development of a sophisticated methodology developed specifically to identify core papers fundamental to tissue engineering. After this, a basic description is offered of the growth of tissue engineering, as revealed in the full paper set and in a special set of papers that use the term "tissue engineering" in their abstract or title. There follows a quantitative analysis of NSF's role as revealed through acknowledgments of funding reported on papers. Then maps and tables are presented that together reveal the patterns of coauthorship in the field and NSF's presence within the oeuvre of leading authors. Finally an analysis of international patenting in tissue engineering is reported.

## III. Methodology

### A. Finding core papers fundamental to tissue engineering

The fundamental methodological work in this project was to devise a way of identifying core papers fundamental to tissue engineering. This was very challenging. CHI needed to identify the papers in a rapidly evolving area that brings together a heterogeneous set of technologies and research approaches, and in which no two researchers seem to agree on a definition. At some level, all biomedical knowledge not directly concerning disease probably will contribute to tissue engineering. However, time was limited, so every biomedical paper could not be assessed for relevance to tissue engineering.

The approach we adopted was to develop a "gold standard" method to find papers. The method had two stages. In the first stage, we identified manually papers and patents in a narrowly defined core area, which could be nothing else, but tissue engineering and that all would agree were tissue engineering. We defined the core of tissue engineering to be seeding autologous cells and growth factors onto three-dimensional biodegradable scaffolds with the aim of forming new functional tissue. We found core papers by developing filters (combinations of keywords and classifications used to search PubMed or the USPTO databases, see Appendices 1 & 2) to identify papers and patents that met the definition, then reading abstracts and titles to screen documents found by the filters.

In the second stage, bibliometric links were used to find papers seen by at least two researchers as relevant to the core. This was implemented by finding papers cited in the core patents by at least two inventors or in the core papers that were reviews of tissue engineering by two authors. Complications were added to the citation element of the method by the need to consider coauthorship. For if one group habitually cites a paper, should that count as a paper that two tissue engineering authors agree is tissue engineering? We implemented a strict version of the criterion in which at least two groups had to cite a paper. We did this by choosing papers whose number of citations exceeded the number of citations from the most citing inventor/author. This is not perfect, and one could imagine situations in which it fails. However, a search for the perfect criterion quickly gets extremely complex and expensive. Note that our criterion works to give a lot of power to those who wrote just one review of the field. Their "votes", as expressed in papers they cited in their review, carry as much weight as 5 or 10 "votes" from papers of prolific review writers.

Using this method, 1,824 core papers fundamental to tissue engineering were identified. Table 1 describes how these 1,824 papers were obtained.

**Table 1 – The construction of the base set of core papers fundamental to tissue engineering**

| Number of candidate papers | How they were found | Number of TE papers | How they were chosen |
|---|---|---|---|
| 1,814 | filtered from PubMed[1] → | 872 | found to be TE upon reading abstracts and titles |
| | 165 of these are review papers | | |
| 5,051 | cited in review papers → | 783 | of these are cited by at least 2 authors[2] |
| 2,009 | cited in TE patents (266) | 221 | of these are cited by more than 2 inventors[3] |
| | | 330 | additional papers were cited in both a patent and paper |
| | | 1,824 | after duplicates are removed. |

We designed the filter and associated paper gathering strategy to address the challenges inherent in defining tissue engineering. In an area where no two scientists completely agree on the boundaries, CHI's methods require that we begin work with an explicit definition, which we make public. No doubt, scientists in the area who do not agree with each other on a definition can all agree with each other that they disagree with the CHI definition. Nevertheless, as we read the abstracts of papers, we were pleased to find that our definition was in line with definitions found in abstracts whose authors made statements of the kind: "tissue engineering is . . .".

Note also the importance of the citation component. Citations from review papers and from filtered patents were used to find papers. This element makes the judgments of the scientific community central to the decision to include a paper or not. 66% of the papers included in the study entered because of citation links. Only 33% entered solely through the paper filter.

In some sense, most of biomedical knowledge except disease diagnosis and treatment can be related to tissue engineering. Tissue engineering builds most directly on: cryopreservation,

---

[1] Review and research papers only

[2] Excluding coauthorship, i.e. the number of citations to the papers overall exceeded the number from the most citing author.

[3] Excluding coinvention, i.e. the number of citations to the papers overall exceeded the number from the most citing inventor.

development of bioreactors, cell culture techniques, understanding of growth factors, peptides, collagen, fibrin, polymers, development of biomaterials, understanding of cell growth and differentiation, knowledge of how nerves, blood vessels, bone, heart, bladder, liver and skin all work - and no doubt more besides. All of this should really be included to capture all the knowledge that goes into TE. However, an unfocused study of all of biomedicine except disease diagnosis and treatment would not be practical or useful.

So we focus. At its heart, the filter focuses on those who brought things together, combined elements, in the ways they needed to be combined to do tissue engineering. It highlights synthesis work. Thus, those who may have had the vision of such a synthesis earlier and may have pushed it harder might appear more prominently.

Synthesizing elements means bringing together disparate high-level expertise. So perhaps the emphasis on synthesis is related to the highly collaborative nature of the work included. We might also expect that the most ardent synthesizers would be the most highly collaborative.

The emphasis on synthesis will create the appearance of incompleteness from an individual scientist's perspective. This is because to participate an individual has to have a highly relevant skill and knowledge set, for example, cardiovascular fluid dynamics. Understanding cardiovascular fluid dynamics is crucial to building blood vessels. But it is really the point at which expertise in cardiovascular fluid dynamics is applied to building new vessels that we are trying to capture. To build new blood vessels will require more than even being the world expert on cardiovascular fluid dynamics - hence the idea that synthesis of this expertise with something else is crucial to the work that got pulled into the paper set here.

Synthesis work is clearly much harder to identify than say, all work on liver or on growth hormone X. So although CHI always goes to great lengths to search properly and go for 95% of what is out there, here it may well not have been possible to achieve that high a percentage. Because citations were used to find many of the papers, we expect that more cited papers are more likely to be included and uncited papers less likely.

## B. Constructing the analysis paper set

There are 1,824 papers in the tissue engineering set, and 1,056 in the analysis set. The construction of the analysis set and the reason for the difference in size are described in this section.

The first reason that the analysis set is smaller is that we are analyzing only US-authored papers and the full 1,824 tissue engineering set contains both foreign and domestic papers. The second reason the analysis set is smaller is that it contains only papers for which we obtained full information. We had bibliographic references only for each paper in the tissue engineering set. To conduct our analysis we needed to obtain for each US-authored paper a complete set of information including: all authors, all institutions, and all funding sources acknowledged on the paper.

CHI combined several sources to construct this information. For most papers, complete author and institution information was bought from ISI.[4] However, NSF was concerned not to limit the study to papers on which ISI could provide information, therefore it was necessary to look up institutional information for some papers in the library. Funding information was obtained from CHI's database of funding acknowledgements on US-authored papers cited in patents. However, library work was needed to obtain funding information on quite a few papers that were not already in this database.

Inevitably, all three pieces of information could not be obtained for every paper and the size of the set was reduced further. Papers were only looked up if there were at least two papers in the same journal. This necessary economy eliminated most papers in obscure journals that were not in libraries. Nevertheless, some papers could not be found because the journal was not available, or because the volume was missing or because the reference was so incorrect that the research assistants had no luck searching for the paper. After the lookup was completed, papers that lacked one or more pieces of information (authors, institutions, funding) were eliminated. Note that if a paper was examined and lacked funding acknowledgments, the paper was not eliminated, rather it was kept and marked as "no funding acknowledged".

The analysis set contains US-authored papers for which we have looked up funding acknowledgments, for which we know who all the authors were, and for which we know all their associated institutions. There are 1,056 papers in the analysis set.

---

[4] Note that PubMed does not provide complete institutional information, which is why ISI was used.

C·H·I

## IV. A few characteristics of the paper set

Figures 1 illustrates the composition of the 1,056 analysis paper set by year of publication. The 2001 numbers are lower because the set was constructed before the year was finished.

Figure 2 also shows the number of papers by year. This time the papers are split up by source. The cited papers tend to be older because of lags in citing and publication. The filtered papers tend not to be so old because PubMed only goes back so far.

The paper most cited in the reviews is: Langer & Vacanti, "Tissue Engineering," *Science* 1993 May 14;260(5110):920-6. This paper was cited 39 times in the reviews and 11 times in patents. This paper acknowledges funding from NSF along with funding from NIH; Advanced Tissue Sciences, Inc; Thomas Anthony Pappas Charitable Fdn. Inc. and the Holly Ann Soulard Research Fund.

The paper most cited in the patents is: Thuroff JW, Bazeed MA, Schmidt RA, Luu DJ, Tanagho EA. "Cultured rabbit vesical smooth muscle cells for lining of dissolvable synthetic prosthesis." Urology. 1983 Feb;21(2):155-8. This paper was cited 29 times in the patents and was not cited in the reviews. Nor did it enter into the core set of papers. This paper did not acknowledge any US funding agency.



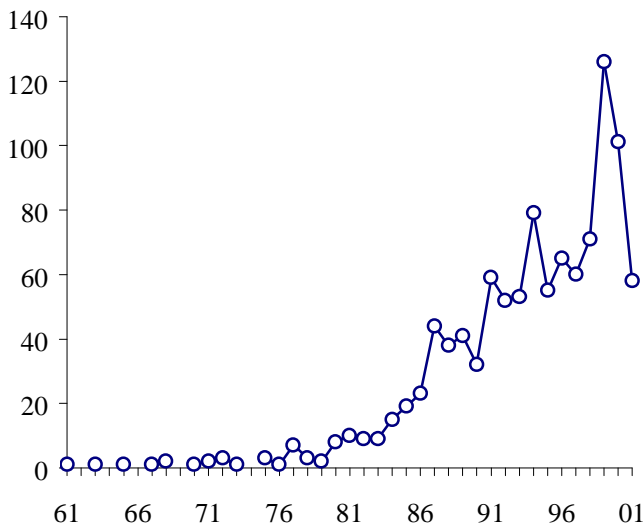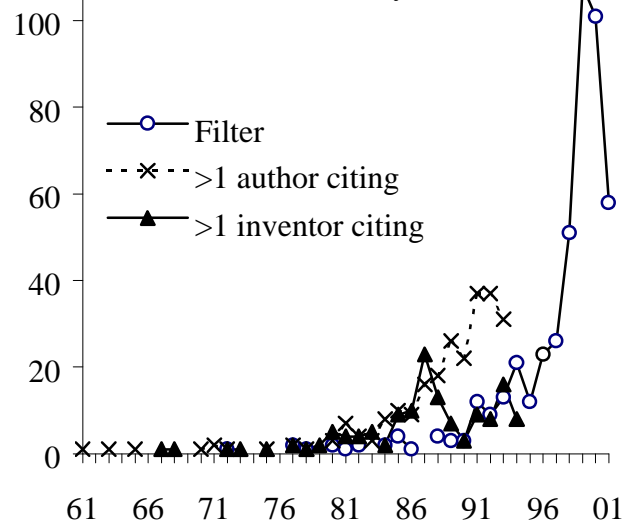Figure 1 - Number of papers by year



Figure 2 - Number of papers by source and year

Note: categories are not mutually exclusive

# V. Use of the term "tissue engineering"

CHI has conducted an analysis of the use of the term: "tissue engineering" in the research literature. This work was undertaken using a set of papers downloaded from PubMed . The papers were found by searching for the term "tissue eng*" in titles or abstracts.[5] Table 2 reports the results of this work. The table reports the number of papers by year overall, for research and review papers, and by subject matter. The subject matter section is ordered by year of first appearance, which is reported in the "1st year" column.

At the time the search was conducted, in mid-2001, 685 papers were identified that used the term tissue engineering, or a variant, in their titles or abstracts. 68% of the papers were research papers and 29% were review papers.[6] The abstracts and titles were read, and the papers were classified by contents. Thus we can see that bone & cartilage and more basic research, not associated with any particular body part, are the two dominant categories, each accounting for about 20% of the papers. Only 6% of the papers concerned skin, which might seem low since skin is a rather well developed application. The skin papers also begin rather late, in 1995. We hypothesize that work on skin was an independent stream, going much farther back in time, and only in 1995 did someone draw the connection to work on other tissues by using the term "tissue engineering." 7% of the papers were found to be outside the field. This frequently occurred in review articles which described the available, not very satisfactory, options for treating a medical condition and then held out the hope that tissue engineering would provide better solutions in future.

There seem to be three phases to the use of the term "tissue engineering." In 1984/85 JR Wolter and RF Meyer imagined the possibility of tissue engineering after removing from an eye a prosthesis that had been in place 20 years. Their abstract reads as follows:

> *Clinical observation and cytological study of a reasonably successful keratoprosthesis removed along with a corneal button about 20 years after its implantation in an aphakic eye revealed an acellular epithelium-like film on its outer surface, firm anchoring of its supporting skirt by stable fibrous connections to the corneal stroma, and a continuous separating membrane composed of a homogeneous proteinaceous film and fibroblast-like cells of macrophage origin on its inner surface. The significance of the successful adaptation of the plastic materials of the prosthesis to the tissues of the cornea and the fluids of the inner eye for the future of tissue engineering in the region of the eye is discussed.*

---

[5] This paper set was one input to the filtering process described above, but is really a different set of papers. Some of these papers are in the final analysis set and some are not.

[6] The other 3% were classified as "other." Examples include: a discussion of recent patents in tissue engineering, or a discussion of recent regulatory changes relevant to tissue engineering.

C·H·I

After a gap of a few years, a second phase began in 1989 and lasted through 1997, during which time the term "tissue engineering" began to be used regularly in abstracts and titles. During this period, the term was applied to work concerning all the main organs closely connected to tissue engineering: bone, cartilage, blood vessels, liver, skin, neurons and also to biomedical materials.

The third phase began in 1998 and continues. Recent years have seen dramatic growth in the use of the term "tissue engineering". 1998 saw more than a doubling of papers using the term as compared to 1997, and the number almost doubled again in 1999. In this phase we also see a few papers concerning other organs, and in fact the return of papers concerning eyes.

Overall, the growth in the use of the term "tissue engineering" in titles and abstracts seems not unlike the growth in number of core papers fundamental to tissue engineering that is reported in Figure 1.

**Table 2 – Papers using the term "tissue engineering" in their titles or abstracts**

| Category | 1st year | Papers | % Share | 1984 | 1985 | … | 1989 | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| All papers | 1984 | 685 | 100% | 1 | 1 | | 1 | 1 | 8 | 9 | 7 | 11 | 14 | 30 | 30 | 79 | 153 | 214 | 126 |
| | | | | | | | | | | | | | | | | | | | |
| Research | 1984 | 466 | 68% | 1 | 1 | | 1 | 1 | 3 | 3 | 4 | 2 | 8 | 18 | 18 | 55 | 103 | 137 | 111 |
| Review | 1991 | 199 | 29% | | | | | | 4 | 5 | 3 | 8 | 6 | 11 | 11 | 23 | 46 | 71 | 11 |
| Other | 1991 | 20 | 3% | | | | | | 1 | 1 | | 1 | | 1 | 1 | 1 | 4 | 6 | 4 |
| | | | | | | | | | | | | | | | | | | | |
| Ophthalmology | 1984 | 6 | 1% | 1 | 1 | | | | | | | | | | | | 3 | 1 | |
| Cardiovascular | 1989 | 77 | 11% | | | | 1 | | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 11 | 15 | 28 | 11 |
| General | 1990 | 83 | 12% | | | | | 1 | 2 | 4 | 2 | 3 | 2 | 3 | 6 | 9 | 13 | 27 | 11 |
| Bone & Cartilage | 1991 | 149 | 22% | | | | | | 2 | | | 4 | 3 | 5 | 5 | 18 | 38 | 49 | 25 |
| Basic | 1991 | 147 | 21% | | | | | | 1 | 2 | 3 | 1 | 3 | 11 | 7 | 19 | 24 | 42 | 34 |
| Outside field | 1991 | 48 | 7% | | | | | | 1 | | | 1 | 1 | 2 | 1 | 5 | 10 | 13 | 14 |
| Liver | 1991 | 15 | 2% | | | | | | 1 | 1 | | 1 | 1 | 1 | | | 2 | 5 | 3 |
| Skin | 1995 | 38 | 6% | | | | | | | | | | 2 | 2 | 3 | 8 | 8 | 10 | 5 |
| Pancreas | 1995 | 4 | 1% | | | | | | | | | | 1 | | | 1 | 1 | | 1 |
| Neural | 1996 | 16 | 2% | | | | | | | | | | | 1 | | 2 | 2 | 7 | 4 |
| Dentistry | 1996 | 14 | 2% | | | | | | | | | | | 1 | 1 | 1 | 3 | 6 | 2 |
| Tendon & Ligament | 1996 | 10 | 1% | | | | | | | | | | | 1 | | | | 7 | 2 |
| Kidney | 1996 | 7 | 1% | | | | | | | | | | | 2 | 2 | 2 | 1 | | |
| Muscle | 1997 | 9 | 1% | | | | | | | | | | | | 2 | 1 | 4 | 2 | |
| Genitourinary | 1998 | 27 | 4% | | | | | | | | | | | | | 2 | 5 | 13 | 7 |
| Gene Therapy | 1999 | 9 | 1% | | | | | | | | | | | | | | 7 | 2 | |
| Other tissue | 1999 | 9 | 1% | | | | | | | | | | | | | | 3 | 4 | 2 |
| Meniscus | 1999 | 6 | 1% | | | | | | | | | | | | | | 4 | | 2 |
| Stem Cells | 1999 | 4 | 1% | | | | | | | | | | | | | | 1 | 3 | |
| Digestive | 1999 | 4 | 1% | | | | | | | | | | | | | | 2 | | 2 |
| Lung | 2001 | 3 | 0% | | | | | | | | | | | | | | | | 3 |

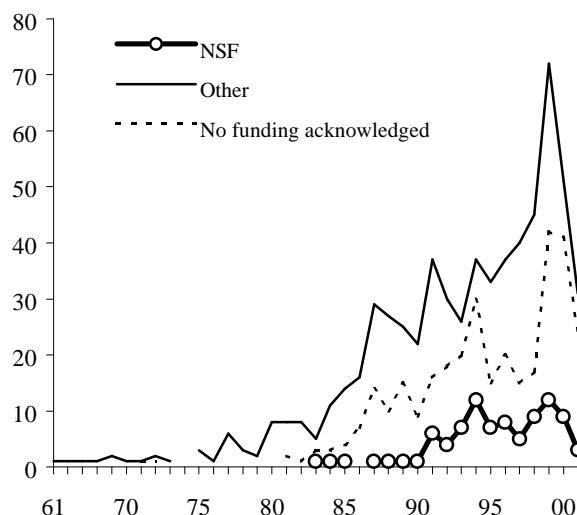# VI. NSF funding of core papers fundamental to tissue engineering

In this section, we begin discussion of the 1,056 analysis paper set with an examination of NSF's role in supporting core papers fundamental to tissue engineering.

In the analysis set, 31% of papers did not explicitly acknowledge a source of funding. Of the 727 that did, 89 or 12% acknowledged NSF support. Figure 3 displays the number of NSF funded papers in each year compared with the number of papers acknowledging other funders and the number acknowledging no support sources. Since 1990, NSF has had a fairly steady presence in supporting tissue engineering related work.

However, NSF funding is not evenly distributed across tissue engineering. NSF tends to fund scientific as opposed to clinical research. Of the papers that acknowledge a support source, 20% of non-clinical



Figure 3 - Number of NSF funded papers by year

papers acknowledge NSF support whereas only 3% of clinical papers acknowledge NSF support. Appendix 4 Table A illustrates this, comparing the field distributions of papers acknowledging NSF support with papers acknowledging other funders and papers that do not acknowledge research support. Non-clinical fields are in bold. Almost 90% of NSF-supported papers are in non-clinical fields, whereas half the papers supported by others are non-clinical. The lists of fine fields by support type clearly demonstrates NSF's emphasis on basic research. The papers not acknowledging funding are rather similar in distribution to the papers supported by other funders.[7,8]

We might expect that if NSF focuses support on non-clinical fields that its research tends to be more basic. That this is so is indicated in Table 3 which is based on CHI's classification of Science Citation Index journals into four levels of "basicness." Each level contains journals reporting roughly the same type of research, from level 4 basic research to level 1 clinical observation. The table indicates that compared to other funders, NSF funds a higher share of the most basic papers, level 4, and a lower share of the most applied, level 1. NSF also funds a higher share of papers in the two leading journals in the field – Biomaterials and Journal of

---

[7] Excluded from this analysis are 116 papers not classified into fields. These are papers in journals not covered in the *Science Citation Index*. See the bottom of the table.

[8] The field analysis and the level analysis below are based on CHI's classification of *Science Citation Indexed* journals into fields and level of basicness.

<u>Biomedical Materials Research</u> (both classified as level 2).  The share of papers in these two journals has been removed from level 2 and is reported on a separate line in the table.  NSF funds one-quarter of the core papers fundamental to tissue engineering that acknowledge funding and are published in these two journals.

Table 3 – How basic is NSF-funded research?

| | Level | NSF | Other | None |
|---|---|---|---|---|
| | 4 | 42% | 34% | 27% |
| | 3 | 11% | 14% | 9% |
| | 2 | 1% | 14% | 11% |
| | 1 | 1% | 19% | 34% |
| Biomaterials & Journal of Biomedical Materials Research (2) | | 44% | 18% | 18% |
| Number of papers | | 81 | 576 | 276 |

A reasonable interpretation of all this is that NSF support is targeted to basic research and biomedical materials.  NSF has supported 15% of the basic work in tissue engineering and up to one-quarter of the biomedical materials work.  Others support the clinical work which is such an important part of tissue engineering, and so NSF's overall presence is somewhat less, about 12%, judging by papers that acknowledge funding agency support.

## *A. Institutions*

Another way of examining NSF's role in the field is to examine papers and funding by institution.  This is the purpose of Appendix 4 Table B.  Table B lists institutions and the number of papers that list their address.  The institutions are ordered descending on number of papers.  The table also reports the share of papers that acknowledge NSF support as a fraction of those acknowledging any support.  The final three columns tally the number of papers that list NSF support, the number that list support sources but do not mention NSF and the number that acknowledge no support source.

Institutional name variants have been unified to produce this table, but a problem remains.  Not infrequently, authors in this area have a dual university/hospital affiliation.  Such authors list their addresses on papers in several ways, and this has consequences for the counting of papers by institutions.  If authors list one address only, then the other institution gets no credit for the paper.  If the author lists two separate addresses on the paper, then both institutions get credit for the paper and it is indistinguishable from a collaboration between researchers at two institutions.  If the author combines the institutions in one address (as one might list both a department and a university name) then the first address only is counted here.  If time were available to straighten

all this out,[9] it would affect Table B because MIT, Harvard, and the Children's Hospital and Medical Center in Boston employ lead authors in the field who have dual affiliations.

The table reveals that the leading institutions in the area are Harvard, MIT, University of Michigan, Children's Hospital Boston, and the University of Texas. The names of over 350 US institutions appeared on core papers fundamental to tissue engineering; 21 of these institutions produced at least 25 papers. A glance at the table suggests that NSF has had a greater than expected role in supporting work at the leading institutions, that is those producing 25 or more papers. Further analysis reveals that NSF supported 17% of the papers (that acknowledge research support) that were produced by authors working at leading institutions. In contrast, only 8% of the papers from the rest of the institutions acknowledged NSF support. In fact, only 2% of the 186 papers from institutions appearing only once acknowledge NSF support. The institutional analysis elaborates the picture that the NSF role in tissue engineering focuses on basic research and biomaterials research by suggesting that its research is also focused on the core participants in the field. More peripheral, and one-off participants are much less likely to acknowledge NSF research support.

## B. Authors

In analyzing the role of NSF funding in tissue engineering, we need to look also at NSF's role in supporting particular authors. Appendix 4 Table C does this for authors with more than 10 papers. The table's seven columns detail:
1. The number of papers that list the author's name. Only authors with more than 5 papers are shown. There are 2,553 author names in all; 135 are listed here.
2. The number of funding agencies listed on the author's papers. That is, the number of agencies from which the author has received funding. This count is not exact because minor funders were recorded in categories such as "non-profit" or "other Federal government."
3. The number of NIH agencies. Researchers acknowledging NIH funding usually list the NIH Institute concerned, such as the National Cancer Institute or National Eye Institute. CHI records these and they are counted here. Note that in the count of agencies, NIH was counted as one agency and multiple Institutes did not add more agencies to the total.
4. The share of papers acknowledging funding that acknowledge NSF funding.
5. The number of papers by funding type where there are three types:
   - Acknowledges NSF funding
   - Acknowledges funding, but does not mention NSF
   - Does not acknowledge funding.

The list reveals that NSF has had a substantial role in supporting the lead researchers in the field. Although acknowledged on only 12% of papers (that acknowledge research support) overall, the

---

[9] That is, if institutional addresses combined on one line and institutions listed separately were counted the same way.

three most prolific researchers – Vacanti, Langer & Mooney - acknowledge NSF funding on 19%-37% of their papers (that acknowledge research support). BS Kim, LG Cima, JA Hubbell, PM Kaufmann, CT Laurencin and WM Saltzman also acknowledge NSF on one-third or more of their papers. In contrast, NSF has had no role in supporting, amongst others, AI Caplan, LE Freed, VM Goldberg or G Vunjaknovakovic. And A Atala keeps his funding sources a secret.

### C. A Note on Government Interest Patents

Among the tissue engineering patents were 19 which contained a statement of government interest. That is, the work underlying the invention had been declared by the inventors to have resulted from a government grant. Of these, NIH had 8, NASA 6, NSF 3, and DHEW 2.

## VII. Co-authorship maps and tables

The depiction of co-authorship patterns undertaken in the final stages of the project does not lend itself to easy summary. In this type of work, the intellectual exercise is not aimed at compact verbal descriptions of salient features. Rather, novel graphics were developed to provide intelligible representations of extremely complex patterns, representations that do not distort the phenomenon nor so remove features in an effort at simplification that any deep understanding is precluded.

In this project, the lead authors' webs of coauthorship were portrayed in an innovative, multi-level system of tables and maps. Lead authors were defined as those with 10 or more core papers fundamental to tissue engineering. Three types of maps and tables are presented:

1. An overview map/table portraying links between lead authors

2. For each lead author (not included in a map), a table listing all coauthors, the number of papers collaborated on and the years in which joint work was published. Any NSF-supported work is noted. Finally, information useful for identifying PhD students of the lead author is included.

3. For authors who acknowledge NSF funding, detailed, paper-by-paper maps were produced that depict in some detail the development of the author's work in core papers and patents fundamental to tissue engineering. These maps are multi-dimensional and include: coauthorship, funding, topics, citations, and institutional affiliation. Exceptions to the rule that maps were drawn for lead authors who acknowledge NSF funding are that maps were not drawn for Langer, Vacanti and Mooney whose vast oeuvre and exceptionally interlinked coauthorship patterns precluded mapping using this technique which is best suited to in-depth portraits of smaller oeuvres.

## A. Overview of lead author coauthorship patterns

Appendix 4 Tables D and E together display a high level overview of the publication pattern of lead authors. Lead authors are those with 10 or more papers who have produced some papers independently of Vacanti or Langer. Appendix 4 Tables F.1–F.22 display details on each lead author's coauthorships. Table E summarizes the interrelationships between the lead authors themselves. For each author and the author's papers in the analysis set, the figure displays:

- the first year in which a paper by the author appeared (1st year)

- the author's total number of papers (papers)

- the number of papers published before 1990 (pre-1990)

- the number of papers published every year between 1990 and 2001

- the number of papers acknowledging NSF support The number "2/1" means that of two papers in that year, one acknowledged NSF support.

- whether two authors worked in a permanent collaboration author ({)

- collaborative links with other lead authors ($\chi$)

- collaborative links with Vacanti or Langer ($\Rightarrow$)

Table D provides a legend that explains how each of these elements is portrayed in Table E.

Table E successfully depicts the interrelationships between lead authors. The figure reveals that JP Vacanti and R Langer are prominent not just because of their highly cited *Science* paper, referred to above; not just because compared to any other lead author they have double or triple the number of papers in the set; but also because of the highly collaborative nature of their work. Nine of the other lead authors in this figure co-authored papers with Vacanti and/or Langer. Many of these might be PhD students who became established in their own right, including Mooney, Atala, Mikos and Ma. Mooney appears to have little independent work, but in fact in 1999 and 2000 most of his papers were not collaborative with either Langer or Vacanti and he should be considered independent. In a possibly 2nd generation relationship, Atala perhaps has established a PhD student – Yoo, whose substantial line of work so far is all collaborative with Atala. Caplan & Goldberg worked closely together during the 1990s, linking up with Bruder on occasion and working once with Langer in 1990. Boyan & Schwartz also form a permanent collaborative team. Others collaborated over shorter periods, for example, Yannas & Spector or Aebischer & Winn. Finally there is a set of authors not linked to any other lead authors, namely: Reddi, Green, Bell and Hansbrough.

## B. Patterns of co-authorship

Appendix 4 Tables F.1-F.22 depict the full coauthorship pattern for lead authors. Again, lead authors are those with 10 or more papers who have produced some papers independently of Vacanti or Langer. The figures are ordered descending by total number of papers, so for example DJ Mooney with 53 papers is second (Table F.2), while PM Galletti with 10 papers is last (Table F.22).

For a lead author, each figure provides the following information:

- the first year in which a paper appeared (1st year)

- the total number of papers (collaborative papers)

- the number of papers by year

For each co-author and the co-author's papers in the analysis set, the figure displays:

- whether a co-author is also a lead author. If a co-author is also a lead author (i.e. with their own map or figure) *their name is in italics* and is right justified.

- the first year in which a paper by the author appeared (1st year)

- the number of papers the author produced in collaboration with the lead author (collaborative papers)

- the number of papers produced that were **not** collaborative with the lead author (other papers)

- for authors with more than one paper in the analysis set, an answer to the question: Was the author's first paper produced in collaboration with this lead author? (1st paper)

- the number of papers published before 1990 – individual years are displayed

- the number of papers published every year between 1990 and 2001

- the number of papers acknowledging NSF support. The number "2/1" means that of two papers in that year, one acknowledged NSF support.

Tables F.1 through F.22 again illustrate the dominance of R. Langer and JP Vacanti within the set of core papers fundamental to tissue engineering. Their eight page table lists over 250 coauthors. It subsumes substantial authors whose entire oeuvres, in this set of papers, are collaborative with either Langer or Vacanti including: CA Vacanti, B Schloo, LG Cima, J Upton, JE Mayer. BS Kim is another substantial work almost all of whose work is collaborative with DJ Mooney and/or JP Vacanti. LE Freed and G Vunjaknovakovic are on the borderline of this

category. The vast majority of their work is collaborative with R Langer, but they were treated as lead authors and a separate figure produced.

DJ Mooney is the subject of the second figure which lists 93 co-authors. Here we can see how his work from 1990 to about 1997 was closely associated with Vacanti & Langer, but after that he develops largely independently with another circle of coauthors developing including most prominently, BS Kim. Mikos (57 co-authors) and Ma (22 co-authors) seem to follow a similar pattern of early work closely linked to Langer & Vacanti, followed by independent work within a separate circle of coauthors.

As discussed above, other authors are less highly interlinked. Other authors with many co-authors are Wozney with 53 and Caplan & Goldberg with 45. Ingber worked for a few years in the early 1990s with Langer & Vacanti, but had produced papers in the area previously and continued publishing in the area afterwards. The large numbers of authors appearing on only one paper is a characteristic of science in general, and not specific to this set of papers.

## C. Maps

Appendix 5 Figures A.1-A.6 are detailed maps of co-authorship and patenting for authors with a substantial component of NSF funding. Vacanti, Langer and Mooney are not treated in this way because the technique works only for smaller oeuvres. These paper-by-paper maps depict in some detail the development of the author's work in core papers and patents fundamental to tissue engineering. There are maps for: JA Hubbell, BD Boyan & Z Schwartz, CT Laurencin & HR Allcock, WM Saltzman, P Ducheyne, and RM Nerem.

These maps are multi-dimensional and include information on: coauthorship, funding, topics, citations, and institutional affiliation. The maps are essentially a matrix with authors/inventors in the rows and documents (papers or patents) in the columns. For each author, the documents co-authored/co-invented are identified. For each document, the authors/inventors are identified. Authors/inventors who appear on one document only are not individually displayed. Documents that acknowledge NSF funding are highlighted, and highly cited documents are noted. To the right of the maps are notes on institutional affiliations that focus on the leading authors on the map. The legend on each map explains the symbols and colors used. The maps are meant to be viewed in color. The maps are not meant to be read at a glance, rather they repay a little study and contemplation.

The first map concerns JA Hubbell who combines biomaterials with peptides to enhance cell adhesion and development. He has worked on both vascular and neural systems. Many of Hubbell's papers in the early 1990s at the University of Texas acknowledge NSF support, and two of these papers are highly cited by tissue engineering patents. This high citation rate may be largely due to Hubbell's own patenting with inventors at Focal, Inc. Seven patents were produced in this work, some of which are quite highly cited. Hubbell moved on to Caltech and now to ETH Zurich. His map illustrates the intermingling of public and private sector work in this area.

The same theme is seen on the map of BD Boyan & Z Schwartz. Boyan & Schwartz examine osteoblasts and chondrocytes regulating events in their extracellular matrix. The theme of private and public intermingling is continued here with co-patenting between the University of Texas and Osteobiologics. There is also patenting by the University of Texas alone. Here we see a lesser role for NSF funding, and less highly cited work as well.

On the map of CT Laurencin and HR Allcock, public and private knowledge are mingled, but only the public sector participates. Here we see both papers and patents acknowledging NSF support (that is, patents declaring that NSF has an interest in the work derived from its support of the research). Two of the patents are highly cited. There are three streams of Laurencin work in this map. The first is work in collaboration with HR Allcock that resulted in one patent. Allcock is a chemist who works on polyphosphazenes. Laurencin & Allcock worked on using polyphosphazenes in skeletal tissue replacement and this is the subject of their patent. Laurencin's second stream of work was with Attawia and Devin examining osteoblast growth on various scaffolds and this resulted in the two highly cited patents. The third stream brings in some NASA money and rotating bioreactors in the collaboration with Pollack and Levine.

# VIII. Analysis of international patenting

## *A. Methodology*

To compile the database of international patenting in tissue engineering, patents from more than 60 countries were searched using CHI's internal US, EP, and PCT databases as well as Derwent's World Patent Index. The search used the filter described in Appendix 2. Although the same filter was used, the patent set analyzed here differs from the set of 266 patents used to find core papers fundamental to tissue engineering. In this analysis the filter was used in a looser way; every patent abstract was not read. Some obviously irrelevant patents were excluded on a quick pass through, but for the most part, patents that met the filter were included. Thus, the 266 US patents are included in this analysis of international patenting, but there are more US patents here in addition.

The equivalent patent documents for multiple countries were assembled into patent families, standardized and put into a database for analysis. Note that a patent family is a set of equivalent patent documents from different countries. For example, when a scientist invents something, he/she will typically file the patent in his/her home country, and then file equivalent patents in every country for which he/she wishes to have patent protection. Note that the equivalent patent documents are not different inventions, so when analyzing global technology it is best to consolidate the various patent documents into families in order to get an idea of the actual number of innovations.

Because of the stringent copyright issues related to Derwent patents, the patent search was first done using CHI's databases, and then a supplementary search was done for any patents filed worldwide, but not filed in the US (US Patent Office), EP (European Patent Office), or PCT (Patent Cooperation Treaty A.K.A. World Patents, or World Intellectual Property Office Patents) systems. This was done for completeness, but as is often the case, it was found that the majority of patents could be found in the US, EP, and PCT systems.

Specifically, some 851 patent documents were found, and assembled into 567 individual patent families. Ninety-two percent (523) of the patent families have at least one patent equivalent in the US/EP/PCT systems and there is strong evidence that the other 8% are more than likely of little value. We can make this latter claim because we see that the 44 patent families that are outside of the US/EP/PCT set mainly come from countries that are well represented in the US and EP systems. In particular 19 of the 44 are from Japan, and 10 of the 44 are from Germany. In the first case, because of the peculiarities of the Japanese patent system, patents filed only in Japan tend to be worth little so that only patents filed in Japan and at least one other patent system are studied by patent analysts. The additional patent systems in which Japanese inventors file their patents are usually patent systems where Japanese companies export, that is the US and Europe. Similarly, German patents that are only filed in Germany and not through the PCT, EP, or US systems tend to be patents from individual inventors and very small companies rather than major biotech and pharmaceutical companies.

Note that a database of the 567 patent families accompany this report, but for the 44 Derwent patents we were only allowed to include the patent number, publication date, and our standardized assignee name; titles and other information were removed so as not to violate Derwent's copyright.

## *B. Results*

We see in Figure 4 that patenting in tissue engineering has been trending up since 1980 and has not yet peaked. In particular, in the last 5 years patenting has increased 226% over the previous 5 years, which in turn was an increase of 138% over the prior 5 years.

The bulk of this innovation is coming from the US as we see in Figure 5. This figure shows the patents by priority country (or country of inventor) for the 567 worldwide patent families. We see that 71% of the global tissue engineering patents are invented in the US, followed by 18% in Europe (led by Germany and Great Britain) and 6% in Japan. The remaining 5% come from some 20 other countries including China with 4, Canada with 3, and 1 or 2 each from the remainder.

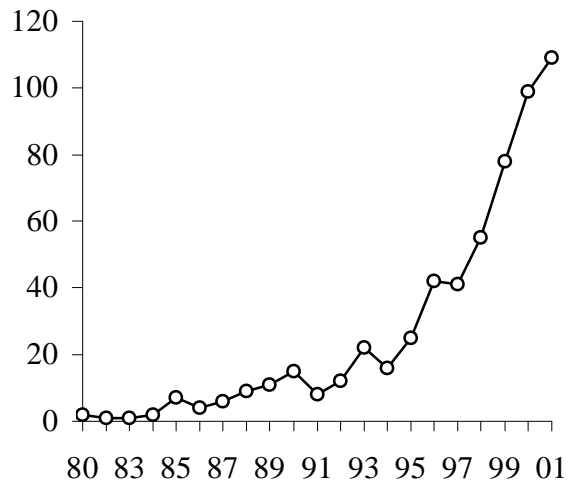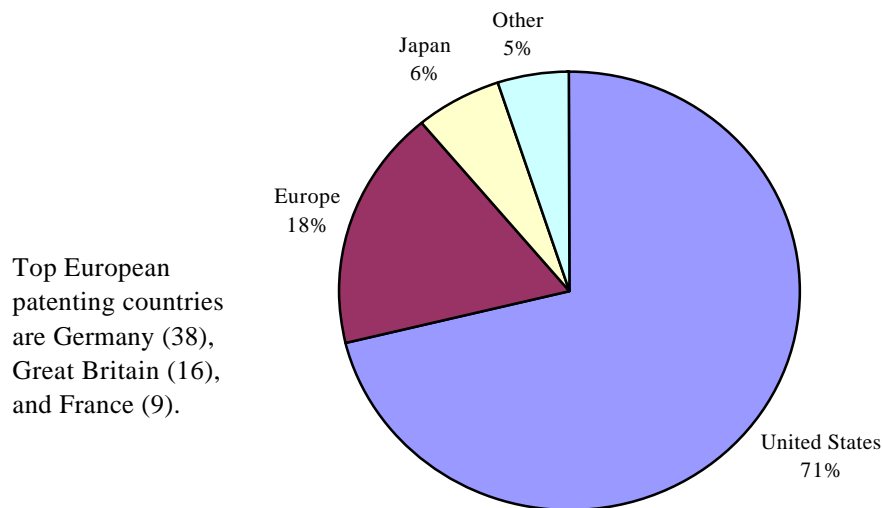Figure 4 - Tissue Engineering Patent Families by Year



Figure 5 - Priority (Inventor) Country of Worldwide Tissue Engineering Patents (1980-2001)

Top European patenting countries are Germany (38), Great Britain (16), and France (9).

Given that most of the invention is coming from the US, it is not surprising to see that most of the patent assignees are US institutions. Figure 6 shows all assignees with 4 or more global patent families. Note that only 2 of the top 25 are foreign (assignees in black are US; assignees in gray are foreign). Top assignees include companies as well as universities. Prominent assignees include Advanced Tissue Sciences, MIT, Procter & Gamble, Regen Biologics and others.
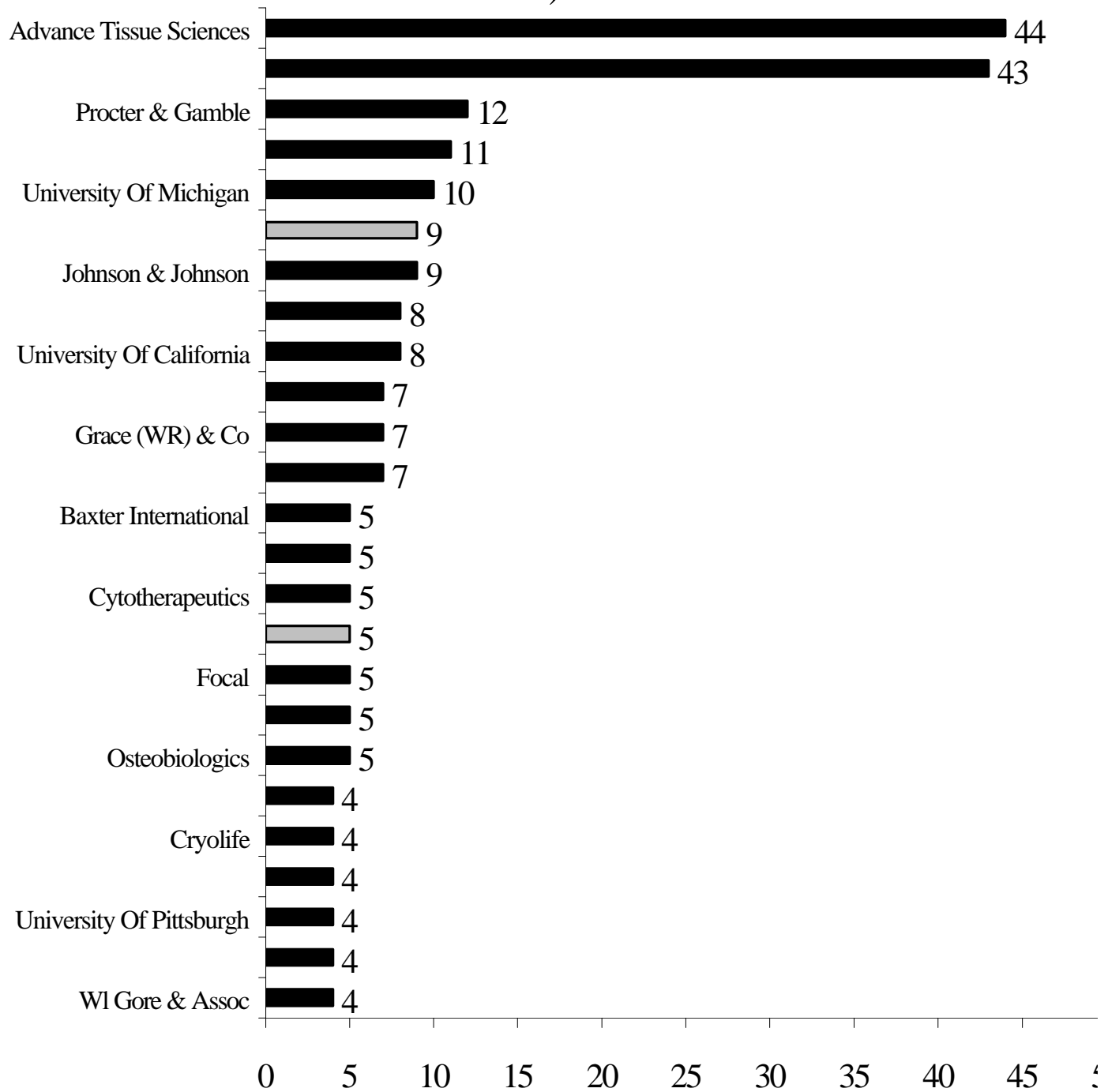
When trying to identify specific key patents within a technology such as this, one of the most accepted methods is using patent citation analysis. Numerous validation studies have shown associations between citations from later patents and various measures of success, such as increases in sales, profits, and stock prices, inventor awards, high expert opinion, and increased licensing opportunities.

Since citations accumulate over time, analysts must take care to normalize the citations by age and technology. In this case, we normalized the patents by technology by computing the average citations received for all families within the tissue engineering set in each year. Since some years had few patents and were dominated by a few very highly cited patents, the citation norms were computed by fitting a curve to the actual yearly averages. Once the normalization values were established, we defined a highly cited patent family as one with at least 3 citations that has received 1.5 or more citations than expected, or a patent family that has received at least 20 citations total. Note that citing patents are not double counted, that is if 2 or more patent equivalents from a family each receive a citation from patent X, that citation is counted only once.

A list of the 100 most highly cited tissue engineering patent families is given in Appendix 4 Table G. Note that the highest relative cited patent family is a 1999 Isotis patent that has received 11 citations already. Since a typical 1999 patent family has just over 1 citation, this patent is cited 7.5 times as often as expected. The US patent equivalent was chosen as the representative patent for the family. This patent is entitled: "Device for tissue engineering bone." The highest overall cited patent family is an Advanced Tissue Science invention "Three-dimensional cell and tissue culture system." This 1990 patent has received 162 citations from later patents, which is almost 6 times the expected number (28.3) for a 1990 tissue engineering patent family.

Rather than detail each of the 100 patents, we will let the reader read through to identify patents of interest. We do note however that many of the highly cited patents are coming from the patenting leaders (in other analyses we've done, this has not always been the case). This is further illustrated in Table 4, where we see that MIT and Advanced Tissue Sciences have the most highly cited patents by far. Among the most effective patenting companies is Regen Biologics Inc., which has 8 of its 11 patents among the highly cited set.

# Figure 6 - Assignees with 4+ TE Global Patent Families (1980-2001)



Advance Tissue Sciences — 44
43
Procter & Gamble — 12
11
University Of Michigan — 10
9
Johnson & Johnson — 9
8
University Of California — 8
7
Grace (WR) & Co — 7
7
Baxter International — 5
5
Cytotherapeutics — 5
5
Focal — 5
5
Osteobiologics — 5
4
Cryolife — 4
4
University Of Pittsburgh — 4
4
Wl Gore & Assoc — 4

Axis: 0  5  10  15  20  25  30  35  40  45  5

# Patent Families

US assignees in black; foreign assignees in gray.

C·H·I

**Table 4 – Share of patents that are highly cited by assignee**

| Standardized Assignee | Families | Highly Cited | % Highly Cited |
|---|---|---|---|
| Advanced Tissue Sciences Inc | 44 | 15 | 34% |
| MIT | 43 | 20 | 47% |
| Procter & Gamble Co The | 12 | 0 | 0% |
| Regen Biologics Inc | 11 | 8 | 73% |
| University Of Michigan | 10 | 1 | 10% |
| Isotis BV | 9 | 1 | 11% |
| Johnson & Johnson | 9 | 0 | 0% |
| NASA | 8 | 2 | 25% |
| University Of California | 8 | 0 | 0% |
| Childrens Medical Center Corp | 7 | 3 | 43% |
| Grace (Wr) & Co | 7 | 1 | 14% |
| Organogenesis Inc | 7 | 2 | 29% |
| Baxter International Inc | 5 | 1 | 20% |
| Case Western Reserve University | 5 | 2 | 40% |
| Cytotherapeutics Inc | 5 | 1 | 20% |
| Fidia Advanced Biopolymers Srl | 5 | 2 | 40% |
| Focal Inc | 5 | 3 | 60% |
| Keraplast Technologies Ltd | 5 | 2 | 40% |
| Osteobiologics Inc | 5 | 1 | 20% |
| Collagen Corp | 4 | 1 | 25% |
| Cryolife Inc | 4 | 2 | 50% |
| Tissue Engineering Inc | 4 | 0 | 0% |
| University Of Pittsburgh | 4 | 0 | 0% |
| University Of Texas | 4 | 2 | 50% |
| Wl Gore & Assoc Inc | 4 | 0 | 0% |

# IX. Conclusion

This bibliometric study of core papers fundamental to tissue engineering provided an overview of the growth of the field, an analysis of NSF's role in the field, a mapping of co-authorship patterns, and an analysis of international patenting. All three analyses of the growth of the field (papers, papers using the term "tissue engineering" and patents) suggest that interest in the area began to emerge in the mid-1980s. The three analyses also agree that growth accelerated dramatically in recent years. Patent analysis of trends in international patenting found in addition that most patents are invented in the US and assigned to US companies. Leading institutions include: MIT, Advanced Tissue Sciences, and Regen Biologics Inc.

We find that NSF supported about 12% of the papers in the field overall. However, NSF focused its support on basic research and biomaterials and on the leading institutions and authors in the field, where it played a larger role.

The patterns of co-authorship in the field were portrayed in an innovative series of figures, tables and maps developed for this study. These reveal the highly collaborative nature of the work undertaken by R Langer and JP Vacanti, with whom most lead authors in the area have worked at least once. Six multi-dimensional maps of the paper-by-paper development of lead authors' work in the area reveal the interweaving of public and private knowledge and the public and private sectors in the development of tissue engineering research, and precisely position NSF support in relation to this.

## Appendix 1 - Paper filter used in PubMed (9-10, 2001)

tissue engineer*  (papers from the most prolific authors found in this search that were missed were examined and relevant papers were added)

biodegradable polymer scaffolds
regeneration scaffold
vascularization AND scaffold

=============OR==============
"seeded" OR "seeding"                (quotes used to prevent PubMed search term expansion)
AND
scaffold
regeneration
Schwann
vascularization
=============OR==============
the following terms in the journals Biomaterials AND J Biomed Mater Res
(these were top 2 biomedical engineering journals as identified in the
tissue engineer* search).

extracellular matrix
growth factor
Schwann
intestinal submucosa
engineer* AND cartilage

=============OR==============

about 50 papers identified by Abt in interviews

## *Appendix 2 - Patent filter used in USPTO system  (09/26/01)*

International patent subclasses used as a broad screen:

A61F or A61L or C12M or C12N or C12P

====== AND any of the following title/abstract/claim words (* is a wildcard) ======

(all tissue types)

| | | |
|---|---|---|
| bone* | cardiac | cartilage |
| cell* | connective | epiderm* |
| epithel* | fibro* | heart |
| keratin* | kidney* | ligament* |
| liver | musc* | nerve |
| neuro* | osteo* | pancrea* |
| skin | spleen | tendon* |
| tissue* | | |

====== AND any of the following title/abstract/claim words ======

(core technology is to grow 3D tissue)

scaffold*

three adj dimens*                      (adj means adjacent words same order)

3D

(grow* or cultur*) near5 (matri* or foam)(near5 means within 5 words either dir)

====== AND NOT any of the following title/abstract/claim words ======

(to kick out drug delivery, etc.)

artific*

controlled

delivery

drug*

release

sustained

=============OR==============

IPCs listed above ANDED with

tissue near2 engineer*

## *Appendix 3 – Patent Database*

Submitted with this report is a patent database assembled from the patents obtained from CHI and Derwent Databases. The database is in MS Access 2000 format and includes 4 main tables, several queries that were used for Figures 8-10, and a report used for the highly cited patent list in Appendix 4 Table D.

The main tables consist of the "Main Family Table" that contains a CHI patent family number, a representative patent number and title, a standardized assignee, priority country, and earliest publication date. The reader will recall that the patents have come from multiple databases, so that value added in this database is mainly the assembling of patent families (outlined above) and the standardization of assignee names. Note that there are two levels of assignee standardization. First, differences between standard name reporting across databases is accounted for (e.g Grace (W.R.) in some databases versus W.R. Grace in others). The second standardization involves grouping subsidiary patents with their parents (e.g. Marrow-Tech. Inc. is mapped to Advanced Tissue Sciences Inc.).

The second table "Identified Family Members" consists of each of the identified patent equivalents for each patent family. For example a patent family might consist of equivalents from the US, EP and elsewhere. Someone wishing to further analyze these individual patent documents can do so by using this table.

The third table "Citing Table" shows each of the citing patent documents from the US, EP, and PCT databases. Someone wishing to extend the analysis to look further into the patents that build upon tissue engineering can use this table.

Finally the "Citation Norms" table contains the average citation counts for tissue engineering patents of each year as explained above.

## Appendix 4 – Tables

# Appendix 5 – Figures