5.0 Who Are the Tissue Engineers?

This section examines the people and institutions that are active in tissue engineering or, in a few cases, played a key role in the past. We review some characteristics of the community of tissue engineers viewed in aggregate, introduce specific individuals and six major centers of activity that have played central roles in research or training since the earliest days of the emergence of tissue engineering, and conclude with a few observations on the corporate sector. Our focus here is on those who are actually doing tissue engineering; the role of funding agencies is addressed in a later section.

Our analysis draws heavily on a roster of 231 tissue engineers compiled by the study team, and presented in Appendix 2. These include individuals who have published in the realm of tissue engineering, have trained with notable names in the field, or have otherwise self-proclaimed themselves as tissue engineers. The roster is not intended to be a definitive list of those who should be considered tissue engineers – rather, it should be viewed as a convenience sample intended to shed light in a qualitative sense on the nature of tissue engineering and its participants, and to provide an overall sense of trends affecting the character of the field. With that purpose in mind, however, we believe that the list does contain the great majority of academic, non-physician researchers with faculty appointments in the United States and Canada who have identified tissue engineering explicitly as an important component of their research interests. In addition, the list includes a selection of the most prominent physician-researchers in the field, along with a small sampling of individuals in the corporate sector.

5.1 The Tissue Engineers as a Group

Disciplinary affiliations of tissue engineers are difficult to analyze in a precise quantitative way, because the specific mix of research areas that are included in a department with a given name or are associated with a degree with a given designation, and the number and character of departmental affiliations awarded to faculty, vary from one institution to another in idiosyncratic ways. Nevertheless, overall trends emerge clearly from a rough tally of the available data.

Viewed in terms of both the departments by which their doctoral degrees were awarded and the departments in which those who are in academia now hold faculty appointments, tissue engineers are indeed predominantly *engineers*.

By training, more than half of the individuals for whom we have specific data are engineers. Approximately one fifth of the tissue engineers in our sample hold medical or dental degrees, often in conjunction with an engineering or science doctorate. In view of the critical importance of cells and of physiology in tissue engineering, the fraction of individuals who hold only a doctorate in biological sciences (for example, biology, biochemistry, or non-clinical medical sciences such as physiology or anatomy) is remarkably small – roughly one out of ten. Chemical engineering is by a wide margin the engineering discipline most frequently encountered in this cohort, followed by biomedical or bioengineering, and by mechanical engineering. A more liberal interpretation of which aspects of contemporary orthopedics and biomechanics research should be considered part of tissue engineering would perhaps have yielded somewhat increased weights for biomedical and mechanical engineering in the sample.

Current academic departmental affiliations of these tissue engineers are also strongly weighted toward engineering. However, here bioengineering or biomedical engineering is the leading disciplinary affiliation by a wide margin, followed by chemical engineering and, in a distant third place, mechanical engineering. This pattern may reflect the relatively recent emergence of biomedical engineering as a discipline, and the migration of faculty – especially recent trainees taking their first faculty appointments

– from some of the classical engineering disciplines to newer and often growing departments of biomedical engineering.

Biological science affiliations are few, and are weighted toward basic medical science departments. Clinical and clinical science departmental affiliations are strongly weighted toward surgery and surgical specialties, notably orthopedics. This latter pattern may to some extent be an artifact of selection bias in construction of the sample; for example, it is likely that a more liberal definition of tissue engineering to include a greater part of islet cell transplantation research and a correspondingly more aggressive search for clinicians who have been involved in such work would have resulted in the inclusion of more endocrinologists in the roster. Nevertheless, we would expect surgeons to dominate in any reasonably representative sample of clinician-scientists active in tissue engineering.

More than 70 universities are represented in the list of institutions from which the tissue engineers in our sample received their non-clinical (i.e., PhD and ScD) doctorates. Appendix 2 shows that MIT trained, by a wide margin, the largest number of individuals in this group, followed by the University of Pennsylvania, Rice University, the University of Michigan, the University of Minnesota, Columbia University, Stanford University, and the University of California at Berkeley. Again, a more liberal definition of relevant orthopedics and biomechanics research would perhaps have yielded a slightly stronger representation for Rice, Columbia, the University of California at San Diego (UCSD), and Georgia Tech. When postdoctoral training relationships are traced as well, the relative weight of MIT in this group increases further.

At present, most of the individuals active in this representative sample of tissue engineers entered the field after completing dissertations in other areas. Because of the interdisciplinary character of tissue engineering, the field will likely continue to have a relatively high proportion of post-doctoral-training entrants. However, over time, the fraction of individuals whose thesis research was explicitly in tissue engineering, and the representation of universities other than MIT with broad platforms of research and training activity in tissue engineering, such as Rice, UCSD and Georgia Tech, should increase as a proportion of any roster of researchers active in TE.

One last characteristic of this cohort is noteworthy here. The great majority of individuals are involved in TE on only a part-time basis. That is, academic tissue engineers typically maintain a number of lines of research, some of which meet any reasonable definition of tissue engineering, some of which straddle the ill-defined boundary that delineates the field, and some of which are clearly situated within other intellectual domains. By this measure, tissue engineering could be viewed more as a tactic than as a discipline – as part of an interdisciplinary assault on unsolved therapeutic challenges that draws opportunistically on an ever-wider range of knowledge and tools from science and engineering.

5.2 Notable Participants in Tissue Engineering and Leading Centers in the Field

A bibliometric analysis of papers important to the field of tissue engineering revealed a list of more than 350 US institutions active in research. Our interviews with experts in the field as well as extensive secondary research[92] validated this list and also pointed toward several other institutions as being highly

[92] In compiling these groups of researchers, we examined all major research universities in the country which had bioengineering departments—given the strong link between the field of bioengineering and tissue engineering—and scoured faculty research pages for individuals in those departments to see which of these may participate in TE. The research groups above were selected to appear in this report since, in our judgment, they had made significant research contributions or were comprised of multiple faculty or graduates who are considered major players in the field.

influential in the field—not only in terms of their research contributions, but also in their training of personnel currently active in the field. Below we highlight a sample of the key loci of tissue engineering research.

Boston Area: MIT and Harvard

Perhaps the single most prominent geographical and institutional locus of research in tissue engineering has been in the Boston area, centered on the Massachusetts Institute of Technology (MIT) in Cambridge and the Harvard Medical School (HMS) in Boston, although researchers at other Boston-area institutions have been involved as well.

MIT was the site of three independent, seminal lines of research on substitutes for human skin. During a period from the mid-1970s through the mid-1980s, the laboratory of cell biologist Howard Green, MD (in the biology department at MIT until 1980, subsequently in the cell biology department at Harvard Medical School) achieved a breakthrough in the cultivation of human keratinocytes, developed it into a method for growing epithelial grafts from a small piece of autologous epidermis, and demonstrated the viability of this method in the treatment of burn victims.[93] In 1987, this technique became the basis for a startup company called BioSurface Technology that offered cultured epidermal autografts commercially. The company was acquired by Genzyme in 1994 and became Genzyme Tissue Repair (now Genzyme Biosurgery), and the service is still offered under the name Epicel®.[94] Dr. Green himself has continued his career as a cell biologist at HMS, but has not been prominent in the subsequent development of tissue engineering.

Ioannis Yannas joined the faculty in the mechanical engineering department at MIT in 1966, after completing his PhD at Princeton. From the start, his research focused on the properties of collagen and its role in connective tissues, using approaches from chemistry, physics, and biomechanics. By the 1970s, Yannas was investigating the use of acellular collagen-glycosaminoglycan matrices as wound dressings designed to serve as biodegradable templates for the regeneration of viable skin. In 1977, Yannas, in collaboration with Massachusetts General Hospital and Shriners Burns Institute surgeon John F. Burke, was awarded a patent for a "multilayer membrane useful as synthetic skin".[95] In 1980, they published the first in a series of papers outlining design considerations for what they called an "artificial skin", and shortly thereafter, they reported the successful use of such an artificial skin in the treatment of extensive burn injury.[96] This research resulted in the development of a commercial product, Integra® Dermal Regeneration Template, which is currently licensed to and manufactured by Integra LifeSciences

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93 Rheinwald JG, Green H, "Serial Cultivation of Strains of Human Epidermal Keratinocytes: the Formation of Keratinizing Colonies from Single Cells", *Cell* 1975 Nov;6(3):331-43; Green H, Kehinde O, Thomas J, "Growth of Cultured Human Epidermal Cells into Multiple Epithelia Suitable for Grafting", *Proc Natl Acad Sci USA* 1979 Nov;76(11)5665-8; and Gallico GG 3rd, O'Connor NE, Compton CC *et al.*, "Permanent Coverage of Large Burn Wounds with Autologous Cultured Human Epithelium", *N Engl J Med* 1984 Aug 16;311(7):448-51.

94 Epicel® (cultured epidermal autografts) product information, http://www.genzymebiosurgery.com/opage_print.asp?ogroup=1&olevel=2&opage=96 (URL verified October 26, 2002).

95 Yannas IV, Burke JF, Gordon PL, Huang C, "Multilayer Membrane Useful as Synthetic Skin", US Patent 4,060,081, November 29, 1977.

96 Yannas IV, Burke JF, "Design of an Artificial Skin", *J Biomed Mater Res* 1980 Jan;14(1):65-81; Burke JF, Yannas IV, Quinby WC Jr *et al.*, "Successful Use of a Physiologically Acceptable Artificial Skin in the Treatment of Extensive Burn Injury", *Ann Surg* 1981 Oct;194(4):413-28; and Yannas IV, Burke JF, Orgill JP, Skrabut EM, "Would Tissue Can Utilize a Polymeric Template to Synthesize a Functional Extension of Skin", *Science* 1982 Jan 8;215(4529):174-6.

Corporation.[97] Prof. Yannas has continued to maintain an active research program on the principles and applications of induced tissue regeneration.[98]

Eugene Bell, a long-time faculty member in the biology department at MIT, also pursued in the 1970s a line of research that examined interactions between collagen and skin cells. In 1979, Bell and colleagues published a paper describing the production *in vitro* of a tissue-like structure, obtained via contraction of a collagen lattice seeded with fibroblasts.[99] In 1981 Bell's group reported the successful grafting of a "living skin equivalent" consisting of fibroblasts cast in collagen lattices and seeded with epidermal cells.[100] A patent was obtained for this "tissue-equivalent" in 1984, [101] and Bell left MIT in 1986 to found Organogenesis, Inc. and pursue commercial development of the product. He left Organogenesis in 1991 to return briefly to MIT, but left again in 1992 to found Tissue Engineering Inc. (now TEI Biosciences). Bell has led an active proprietary research program at TEI Biosciences, focusing on the further refinement of collagen fiber-based scaffolds and the enrichment of these scaffolds with signaling molecules that induce stem cell development and tissue regeneration, but has published little in the peer-reviewed biomedical literature in recent years.[102]

Although these three lines of research are widely recognized as milestones in the emergence of tissue engineering, in terms of visibility, and arguably in terms of scientific influence as well, they have long since been eclipsed by the network of TE researchers that grew up around Robert Langer and Joseph (Jay) Vacanti. Langer and Vacanti are widely recognized as coauthors on two seminal papers: the 1993 review article in *Science* that marked the "coming out" of tissue engineering as a field, and, with additional coauthors, the 1988 paper in the *Journal of Pediatric Surgery* that introduced the strategy of using resorbable artificial polymer matrices seeded with cells as a vehicle for cell transplantation.[103] However, their acquaintance and scientific collaboration predated these papers by more than a decade.

Langer's graduate studies were carried out under the supervision of yet another MIT researcher active during the "prehistory" of TE, Clark Colton of the chemical engineering department. Colton's own PhD, completed in the same department in 1969 under the supervision of Kenneth A. Smith, was entitled *Permeability and Transport Studies in Batch and Flow Dialyzers with Applications to Hemodialysis*. Colton's research on filtration technologies relevant to artificial organs continued following the completion of his PhD, and he collaborated with William Chick at Harvard Medical School, Pierre Galletti at Brown University and colleagues on the research which led to a 1975 publication in the

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97 Integra® Dermal Regeneration Template Product Description, http://www.integra-ls.com/bus-skin_product.shtml (URL verified October 26, 2002).

98 Yannas IV, "Synthesis of Organs: *In vitro* or *In vivo*?" *Proc Natl Acad Sci USA* 2000 Aug 15;97(17):9354-6; and Yannas IV, *Tissue and Organ Regeneration in Adults* (New York: Springer, 2001).

99 Bell E, Ivarsson B, Merrill C, "Production of a Tissue-Like Structure by Contraction of Collagen Lattices by Human Fibroblasts of Different Proliferative Potential in Vitro", *Proc Natl Acad Sci USA* 1979 Mar;76(3):1274-8.

100 Bell E, Ehrlich HP, Buttle DJ, Nakatsuji T, "Living Tissue Formed in Vitro and Accepted as Skin-Equivalent Tissue of Full Thickness", *Science* 1981 Mar 6;211(4486):1052-4.

101 Bell E, "Tissue-Equivalent and Method for Preparation Thereof", US Patent 4,485,096, November 27, 1984.

102 Dai J, Kumar J, Feng Y *et al.*, "The Specificity of Phenotypic Induction of Mouse and Human Stem Cells by Signaling Complexes", *In Vitro Cell Dev Biol Anim* 2002 Apr;38(4):198-204; and "Platform Technologies" description, TEI Biosciences web site, http://www.teibio.com (URL verified October 27, 2002).

103 Langer R, Vacanti JP, "Tissue Engineering", *Science* 1993 May 14;260(5110):920-6; and Vacanti JP, Morse MA, Saltzman WM *et al.*, "Selective Cell Transplantation Using Bioabsorbable Artificial Polymers as Matrices", *J Pediatr Surg* 1988 Jan;23(1 Pt 2):3-9.

Transactions of the American Society for Artificial Internal Organs on a "hybrid artificial pancreas" for rats consisting of beta cells cultured on synthetic semipermeable hollow fibers.[104] Colton (with coauthors, graduate student Keith Dionne and postdoctoral fellow Martin Yarmush) was the only senior MIT researcher represented with a paper at the Granlibakken workshop in 1988.

Although contemporaneous with this early work on artificial organ technologies in Colton's lab, the research that formed the basis for Langer's 1974 ScD in chemical engineering was part of a separate line of work being pursued by Colton in the area of enzyme engineering.[105] Langer proceeded to a postdoctoral fellowship in the laboratory of Dr. Judah Folkman at Harvard Medical School and Children's Hospital in Boston. Folkman's pathbreaking work on implantable drug delivery systems and on angiogenesis in cancer addressed a number of fundamental issues that were to be of broader significance for tissue engineering, including identification and analysis of the factors that govern the growth and differentiation of blood vessels, and the design of delivery systems to enable the sustained release of bioactive proteins and other molecules in a desired location in order to influence tissue growth. Langer's first publication in the area of polymeric drug delivery systems, a line of research that was to become the foundation of the work of his own laboratory at MIT, was written in collaboration with Folkman and appeared in *Nature* in 1976.[106]

Langer's entry into tissue engineering was catalyzed by a collaboration with Jay Vacanti. Vacanti earned his MD at the University of Nebraska, and came to Boston in 1974 to begin his postgraduate training in surgery. He completed a residency in general surgery at the Massachusetts General Hospital during 1974-1981, followed by a fellowship in pediatric surgery at Children's Hospital from 1981-1983. During the period of his residency at MGH, he spent two years – from 1977 to 1979 – in the laboratory of Dr. Folkman, where his collaboration with Robert Langer began. Their first joint publication, written in collaboration with Folkman and two other colleagues, reported on experiments in the inhibition of tumor growth in animal models by regional infusion of a cartilage-derived angiogenesis inhibitor.[107]

Returning to MIT following his postdoctoral work with Folkman, Robert Langer built a highly productive research and training program focused primarily on polymer-based drug delivery systems and their applications. Vacanti, following his pediatric surgery fellowship, received two further years of clinical training in the renowned transplantation program at the University of Pittsburgh, then returned to Boston in 1985 to join the staff at Children's Hospital and launch his own clinical and research program.

Vacanti's clinical experience in transplantation in Pittsburgh, and then in launching a pediatric liver transplantation program in Boston, confronted him with the intractable problem of organ supply. Following his return to Children's Hospital in Boston in 1985, he began to explore with Langer the problem of how to extend to three dimensions the early success of Eugene Bell in growing flat sheets of tissue from skin cells. From this emerged the concept of using a porous, resorbable, three-dimensional polymer scaffold as a template for cell growth, and the 1988 paper the *Journal of Pediatric Surgery* reporting its experimental application. This technique was to be enormously influential in shaping the work of other investigators who entered the field – indeed, it could be said that it provided the intellectual

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[104] Chick WL, Like AA, Lauris V *et al.*, "A Hybrid Artificial Pancreas", *Trans Am Soc Artif Intern Organs* 1975;21:8-15.

[105] Langer RS, *Enzymatic Regeneration of ATP*, Thesis (ScD), Massachusetts Institute of Technology Department of Chemical Engineering, 1974.

[106] Langer R, Folkman J, "Polymers for the Sustained Release of Proteins and Other Macromolecules", *Nature* 1976 Oct 28;263(5580):797-800.

[107] Langer R, Conn H, Vacanti J *et al.*, "Control of Tumor Growth in Animals by Infusion of an Angiogenesis Inhibitor", *Proc Natl Acad Sci USA* 1980 Jul;77(7):4331-5.

"scaffolding" for the work of an entire cadre of investigators who shared the long-term vision of creating "replacement" solid organs for therapeutic purposes.

Although Langer himself is not primarily a tissue engineer, TE projects have remained an active line of research in his laboratory. He has mentored an extraordinary number of doctoral and postdoctoral trainees, some of whom focused their work specifically on tissue engineering applications. Many have gone on to establish independent academic careers in which tissue engineering research has played an important part.

Most lead authors in Tissue Engineering have worked at least once with Langer and Jay Vacanti as shown in Table F.1 in Appendix 5. 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. Important alumni of the Langer laboratory who are active in tissue engineering include former graduate students:

- Elazer Edelman (PhD, 1984), currently Professor of Health Sciences and Technology at MIT and director of the Harvard-MIT Biomedical Engineering Center)
- Cato Laurencin (PhD, 1987), currently Professor of Chemical Engineering at Drexel University)
- W. Mark Saltzman (PhD, 1987), currently Goizueta Foundation Professor of Chemical and Biomedical Engineering at Yale University)
- Lisa Freed (PhD, 1988), currently Principal Research Scientist in Langer's laboratory)
- David Mooney (PhD, 1992), currently Professor of Dentistry at the University of Michigan)
- Michael Yaszemski (PhD, 1995), currently Associate Professor of Bioengineering at Mayo Medical School)
- Jennifer Elisseeff (PhD, 1999), currently Assistant Professor of Biomedical Engineering at Johns Hopkins University)
- Guillermo Ameer (ScD, 1999), currently Assistant Professor of Biomedical Engineering at Northwestern University

Former Langer postdoctoral or research fellows include:

- Kam W. Leong (currently Professor of Biomedical Engineering at Johns Hopkins University)
- Linda Griffith (currently Associate Professor of Chemical Engineering at MIT)
- Peter Ma (currently Associate Professor of Biologic and Materials Sciences at the University of Michigan School of Dentistry)
- Antonios Mikos (currently Professor in Bioengineering and Chemical Engineering at Rice University)
- Laura Niklason (currently Assistant Professor of Biomedical Engineering at Duke University)
- Kristi Anseth (currently Associate Professor of Chemical Engineering at the University of Colorado)
- Christine Schmidt (currently Associate Professor of Biomedical Engineering at the University of Texas at Austin)
- Gordana Vunjak-Novakovic (currently Principal Research Scientist in Langer's laboratory and Adjunct Professor of Chemical and Biological Engineering at Tufts University).
- Michael Pishko (currently Associate Professor of Chemical Engineering at Penn State University)
- Venkatram Prasad Shastri (currently Research Assistant Professor at the University of Pennsylvania School of Medicine)
- David Lynn (currently Assistant Professor of Chemical Engineering at the University of Wisconsin, Madison)

Jay Vacanti continues an active research program in his Tissue Engineering and Organ Fabrication Laboratory at the Massachusetts General Hospital. Together with junior colleagues including brother

Charles Vacanti and Anthony Atala, he has helped define a branch of tissue engineering that has earned substantial public visibility with a fairly aggressive approach to early demonstration of potential new clinical applications. He has also played an important role in developing the infrastructure of the field through his active involvement in the creation and early leadership of the journal *Tissue Engineering* and the Tissue Engineering Society.

Another prolific source of researchers who have gone on to be active in tissue engineering is the laboratory of Douglas Lauffenburger, Professor of Chemical Engineering and Director of the Biotechnology Process Engineering Center, an NSF-funded Engineering Research Center at MIT, and formerly a faculty member at the University of Pennsylvania and the University of Illinois. As with Langer, Lauffenburger's own research has been centered away from the core of tissue engineering, focusing primarily at the molecular level on quantitative physicochemical principles governing ligand- and architecture-controlled cell behavior.

Graduates from Lauffenburger's tenure at the University of Pennsylvania who are active in tissue engineering include:

- Robert Tranquillo (PhD in Chemical Engineering, 1986), currently Distinguished McKnight University Professor of Bioengineering at the University of Minnesota

- Helen Buettner (PhD in Chemical Engineering, 1987), currently Associate Professor of Biomedical Engineering at Rutgers University

- Paul DiMilla (PhD in Chemical Engineering, 1991), who served as a postdoctoral fellow in the laboratory of George Whitesides at Harvard, was Assistant Professor of Chemical Engineering at Carnegie Mellon University and most recently served on the staff of Organogenesis, Inc.

From Lauffenburger's tenure at the University of Illinois:

- Christine Schmidt (PhD in Chemical Engineering, 1995) completed a postdoctoral fellowship with Robert Langer and is now Associate Professor of Biomedical Engineering at the University of Texas at Austin.

From Lauffenburger's tenure at MIT:

- Sean Palecek (PhD in Chemical Engineering, 1998) is now Assistant Professor of Chemical Engineering at the University of Wisconsin, Madison

- David Schaffer (PhD in Chemical Engineering, 1998) is now Assistant Professor of Chemical Engineering at the University of California, Berkeley

- Anand Asthagiri (PhD in Chemical Engineering, 2000) is now Assistant Professor of Chemical Engineering at the California Institute of Technology

Former Lauffenburger postdoctoral fellows include:

- Peter Zandstra, now Assistant Professor in the Department of Chemical Engineering and Applied Chemistry at the University of Toronto

- Fred Allen, now Assistant Professor of Biomedical Engineering at Drexel University

Another important laboratory active in tissue engineering, with links to both Harvard and MIT, is the Center for Engineering in Medicine / Laboratory of Surgical Science and Engineering at the Massachusetts General Hospital, led by Ronald G. Tompkins, who also serves as Chief of Staff and Director of Research at the Shriners Burns Hospital in Boston. Dr. Tompkins earned his MD at Tulane University in 1976, and his ScD in chemical engineering at MIT in 1983, under the supervision of Clark Colton and Kenneth A. Smith. Another long-serving senior member of the lab and Colton postdoctoral alumnus, Martin Yarmush, MD, PhD, has recently assumed the leadership of the Department of Biomedical Engineering at Rutgers University. A third lab member, Mehmet Toner, earned his PhD in 1989 from the Medical Engineering and Medical Physics Program in the Harvard-MIT Division of Health Sciences and Technology, under the supervision of Ernest Cravalho. Tompkins, Toner, Yarmush and other colleagues have been collaborating on fundamental research intended to lay the foundations for rational design of a bioartificial liver. Yarmush/Tompkins postdoctoral fellow Howard Matthew has established a research group at Wayne State University focusing on biomaterials for tissue engineering. Toner alumna Sangeeta Bhatia (PhD in the HST Program, 1997) is now Associate Professor of Bioengineering and head of the Microscale Tissue Engineering Laboratory at the University of California, San Diego, and Toner/Cravalho alumnus Jens Karlsson (PhD in Mechanical Engineering, 1994) is now Associate Professor of Mechanical Engineering at Georgia Institute of Technology and a member of the Georgia Tech/Emory Center for the Engineering of Living Tissues.

Alan Grodzinsky, who earned his ScD in electrical engineering at MIT in 1974, under the supervision of James Melcher, with a thesis on membrane electromechanics, is now Professor of Electrical, Mechanical, Bioengineering and Biological Engineering and Director of the Center for Biomedical Engineering at MIT. Grodzinsky leads a wide-ranging research program on the mechanical, chemical and electrical properties of connective tissue, including studies on cartilage tissue engineering. Grodzinsky lab alumnus Robert Sah (ScD in the HST Medical Engineering and Medical Physics Program, 1990) is now Associate Professor of Bioengineering and leads the Cartilage Tissue Engineering Laboratory at the University of California, San Diego.

Donald Ingber, another physician-researcher who served as a postdoctoral fellow in Judah Folkman's laboratory during the mid-1980's, now maintains his own laboratory as a Professor of Pathology at Harvard Medical School and Children's Hospital. Ingber's work has been distinctive for its focus on mathematical and mechanical engineering approaches to molecular and cellular structures. Collaborators in recent years have included George Whitesides of the chemistry department at Harvard, and Whitesides' postdoctoral fellow from 1994-96, Milan Mrksich, who is now associate professor in the chemistry department at the University of Chicago.

Other Boston-area alumni prominent in tissue engineering through their own work and/or through those they have trained include:

- Nicholas Peppas completed his ScD in Chemical Engineering at MIT in 1974, under the supervision of Edward Merrill, and did postdoctoral work at the MIT Arterisclerosis Center under HST faculty member Robert Lees. Peppas has been on the faculty at Purdue University since 1976 and is presently the Showalter Distinguished Professor in the School of Chemical Engineering; he will be moving to the University of Texas at Austin in December, 2002. Peppas's work has focused primarily on polymers and drug delivery technology. He supervised Antonios Mikos's master's and doctoral theses at Purdue.

- Michael Sefton completed an ScD in Chemical Engineering at MIT in 1974, under the supervision of Edward Merrill, and is now director of the Institute of Biomaterials and Biomedical Engineering at the University of Toronto

- Barry Solomon, PhD served as a postdoctoral fellow at MIT from 1975-77 and published in collaboration with Clark Colton, and has pursued research on biohybrid artificial organ systems at Amicon, WR Grace, and most recently at Circe Biomedical

- Rena Bizios completed her PhD in Chemical Engineering at MIT in 1979 under the supervision of Robert Lees. She is presently Professor of Biomedical Engineering and leads an active TE research program at Rensselaer Polytechnic Institute.

- Elliot Chaikof, MD, PhD completed a residency in general surgery at Massachusetts General Hospital and a PhD in Chemical Engineering at MIT in 1989, under the supervision of Edward Merrill; he is now Chief of the Division of Vascular Surgery at Emory University and a member of the Georgia Tech / Emory Center for the Engineering of Living Tissues

There is no single institutional or programmatic locus for tissue engineering in the Boston area. "Regenerative biological technologies", defined as encompassing tissue engineering, micro- and nano-scale biomedical engineering, and hybrid systems, has become one of three major research thrust areas of the Harvard-MIT Division of Health Sciences and Technology (HST). The Department of Chemical Engineering, the Division of Biological Engineering and the Center for Biomedical Engineering at MIT are also central to the network of tissue engineering researchers at Harvard and MIT, and most of the more prominent researchers have multiple appointments in these and other units while maintaining numerous collaborations that cross formal departmental or program boundaries.

University of California, San Diego

Tissue engineering at the University of California, San Diego (UCSD) is centered on the Department of Bioengineering, the latest incarnation of one of the oldest bioengineering programs in the United States. The program's origins can be traced to 1964-65, when Benjamin Zweifach, a physiologist with a lifelong interest in the study of blood microcirculation, took a sabbatical from his professorship at New York University to serve as a visiting professor at the California Institute of Technology. While at Caltech, Zweifach had the opportunity to share ideas with Harold Wayland, a pioneer in the engineering study of microcirculation, and his colleagues Y.C. Fung, Professor of Aeronautics and Applied Mathematics at Caltech, and research fellow Marcos Intaglietta, who had completed his PhD in Applied Mechanics at Caltech in 1963. In 1966, Zweifach, Fung and Intaglietta moved to the then-new UCSD to launch a new bioengineering program in its Department of Applied Mechanics and Engineering Sciences.

In addition to his pioneering activities in biomechanics and bioengineering, Fung was to play a central role in the creation of the concept of tissue engineering as we know it today. As noted previously in Chapter 3, in 1985, Fung submitted a proposal to NSF for an Engineering Research Center to be entitled "Center for the Engineering of Living Tissues".[108] Reflecting its intellectual origins, the proposal envisioned a program of research with a strong biomechanics and engineering flavor. Although this proposal was not accepted, the UCSD research program continued to develop through support from other sources, notably the Whitaker Foundation, and the tissue engineering concept stayed alive, to be raised by Fung at the spring 1987 review panel meeting of NSF's Bioengineering and Research to Aid the Handicapped Program.

The development of the UCSD Program was bolstered during this period by the arrival from Columbia University in 1988 of two other pioneering researchers in biomechanics and the study of the microcirculation – Richard Skalak and Shu Chien. As Director of Columbia's Bioengineering Institute, Skalak had been a participant in the special Panel Meeting on Tissue Engineering at NSF in October

[108] "A Proposal to the National Science Foundation for An Engineering Research Center at UCSD, CENTER FOR THE ENGINEERING OF LIVING TISSUES", UCSD #865023, courtesy of Y.C. Fung, August 23, 2001.

1987, and helped to coordinate the Granlibakken workshop in February 1988 along with Fung and Fred Fox of the University of California, Los Angeles. Additional UCSD researchers represented at the Granlibakken workshop were John Hansbrough and Savio L.Y. Woo. Hansbrough, a surgeon and leader in research on burn treatment, had begun to investigate skin substitutes in the mid-1980s and maintained an active line of research in this area until his untimely death in 2001. Although not a member of the bioengineering program proper, Hansbrough held an affiliation with the cross-departmental UCSD Institute for Biomedical Engineering (now the Whitaker Institute of Biomedical Engineering).[109] Woo, an engineer who has focused on biomechanics of connective tissue, led the Orthopedic Bioengineering Laboratory at UCSD until his departure in 1990 for the University of Pittsburgh.

At present, the Department of Bioengineering at UCSD supports a wide range of fundamental and applied research that is relevant to tissue engineering. Core faculty who specifically identify their research as focused at least in part on tissue engineering include:

- Sangeeta Bhatia MD, PhD (PhD in Health Sciences and Technology, MIT, 1997, under Mehmet Toner) is Associate Professor of Bioengineering and head of the Microscale Tissue Engineering Laboratory, focusing on hepatic tissue engineering and BioMEMS (biological micro-electro-mechanical systems).

- Shu Chien, MD, PhD, formerly of Columbia University, is Professor of Bioengineering and Medicine, and Director of WIBE, leads the Vascular Bioengineering Laboratory, investigating molecular mechanisms by which mechanical forces affect cellular functions such as proliferation, migration and apoptosis.

- Andrew McCullough (PhD in Theoretical and Applied Mechanics, University of Auckland, NZ, 1986) is Professor of Bioengineering, and leads the Cardiac Mechanics research group. Group member Jeffrey Omens (PhD in Applied Mechanics and Engineering Sciences (Bioengineering), UCSD, 1988, under Y.C. Fung) is Associate Adjunct Professor of Medicine and Bioengineering.

- Bernhard Palsson, PhD, Professor of Bioengineering, joined the department in 1995 from a prior faculty position at the University of Michigan, and leads the Genetic Circuits research group; his TE-related work focuses on tissue engineering of bone marrow.

- Robert Sah, MD, ScD (Medical Engineering and Medical Physics in the HST Program at MIT under Alan Grodzinsky, 1990) is Associate Professor of Bioengineering and leads the Cartilage Tissue Engineering laboratory.

- John A. Frangos (PhD in Chemical Engineering (Bioengineering) at Rice University under Larry McIntire, 1987) was an active member of the department core faculty from 1994-2002; he is currently Adjunct Professor, and continues to lead research on bone and vascular tissue engineering as president of the new La Jolla Bioengineering Institute.

[109] The UCSD Institute for Biomedical Engineering, which was renamed the Whitaker Institute for Biomedical Engineering (WIBE) in 1999 in recognition of support from the Whitaker Foundation, is a cross-departmental unit that promotes and coordinates interdisciplinary research at the interfaces of engineering, biology and medicine. The Institute includes among its membership faculty from the Department of Bioengineering as well as other departments from the schools of engineering, medicine and natural science and other affiliated organizations. WIBE, directed by Shu Chien, has identified "tissue engineering research" as one of its major research thrusts.

Rice University

At Rice University, faculty active in tissue engineering are based in the Institute of Biosciences and Bioengineering (IBB) and the Department of Bioengineering, both chaired by Larry McIntire. The IBB was founded in 1986, and serves as a coordinating mechanism for cross-disciplinary research in biological, chemical and engineering disciplines involving researchers at Rice and at Texas Medical Center, the Johnson Space Center, industry, and other collaborators. Early efforts to organize a research focus in tissue engineering at Rice were bolstered by a special opportunity award from the Whitaker Foundation to IBB in 1994, and a large development grant from the Whitaker Foundation in 1996 made possible the creation of the Department of Bioengineering.

McIntire completed his PhD at Princeton University in 1970, with a thesis in the area of fluid dynamics. In connection with artificial heart-related research in Houston during the 1970s, he became involved in studies of the effects of hemodynamics on blood coagulation, later extending that work to effects on endothelial cells and blood vessels. Within this still-ongoing line of work, he has supervised the PhD research of the following individuals who have established independent careers in tissue engineering, including:

- Jeffrey Hubbell (PhD in Chemical Engineering, 1986), now Professor of Biomedical Engineering and director of the Institute for Biomedical Engineering at the Eidgenössische Technische Hochschule (ETH) in Zürich

- John A. Frangos (PhD in Chemical Engineering, 1987)

- Timothy M. Wick (PhD in Chemical Engineering, 1988), currently Associate Professor of Chemical Engineering at Georgia Tech, and a member of the Georgia Tech/Emory Center for the Engineering of Living Tissues

- B. Rita Alevriadou (PhD in Chemical Engineering, 1992), currently Assistant Professor of Biomedical Engineering at Johns Hopkins University

- Charles W. Patrick, Jr. (PhD in Chemical Engineering, 1994), now Assistant Professor and Director of Research, Department of Plastic Surgery, MD Anderson Cancer Center, and Adjunct Assistant Professor in the Department of Bioengineering at Rice University

- Julia M. Ross (PhD in Chemical Engineering, 1995), now Associate Professor of Chemical and Biomedical Engineering at the University of Maryland, Baltimore County

Another cornerstone of the tissue engineering program at Rice has been Antonios Mikos, who earned his PhD in chemical engineering under Nicholas Peppas at Purdue, then completed a postdoctoral fellowship with Robert Langer at MIT. Mikos joined the faculty at Rice in 1992 and is now John W. Cox Professor of Bioengineering and Chemical Engineering. Mikos leads a broad research program known especially for contributions to bone tissue engineering and to the further development of polymer and scaffolding technology for TE applications. In 1993 he created the continuing education course “Advances in Tissue Engineering” that continues to be offered annually at Rice. Mikos lab alumni active in tissue engineering include:

- Susan Ishaug-Riley (PhD in Chemical Engineering, 1996), who joined the staff of Advanced Tissue Sciences

- Susan Peter (PhD in Chemical Engineering, 1998), who joined the staff of Osiris Therapeutics

- Vasilios Sikavitsas (postdoctoral fellow) who is now Assistant Professor of Chemical Engineering and Materials Science at the University of Oklahoma

- Aaron Goldstein (postdoctoral fellow) who is Assistant Professor of Chemical Engineering at Virginia Polytechnic Institute and State University

- Julia Babensee (postdoctoral fellow) who is Assistant Professor of Biomedical Engineering at Georgia Institute of Technology, and is active in the Georgia Tech/Emory Center for the Engineering of Living Tissues

Other Rice core faculty in TE include:

- Kyriacos Athanasiou (PhD under Van Mow, Columbia University, 1989), leads the Musculoskeletal Bioengineering Laboratory.

- Kyriacos Zygourakis, PhD, Professor of Bioengineering and Chair of the Chemical Engineering Department, maintains a research track in TE as part of a diverse research program in bioengineering and chemical engineering.

- Jennifer West (PhD thesis under Jeffrey Hubbell during his tenure at the University of Texas at Austin, 1996) is Associate Professor in the Department of Bioengineering.

Other Rice alumni active in TE include:

- Konstantinos Konstantopoulos (PhD in Chemical Engineering under J. David Hellums, 1995), now Assistant Professor of Chemical Engineering at Johns Hopkins University

- Brenda K. Mann, (PhD in Chemical Engineering, under Jacqueline V. Shanks, 1997), now Assistant Professor in the Keck Graduate Institute of Applied Life Science, Claremont, CA

Georgia Institute of Technology / Emory University

The Georgia Tech/Emory Center for the Engineering of Living Tissues (GTEC) is a National Science Foundation-sponsored Engineering Research Center established in 1998 within the context of an evolving institutional framework for research and education in biomedical engineering linking the Georgia Institute of Technology with the Emory University School of Medicine. A key milestone in the development of bioengineering at Georgia Tech was the 1993 receipt of a Whitaker Foundation Biomedical Engineering Development Award, which provided funds for faculty and institutional development and the creation of a new PhD program. Today, the major institutional elements in which bioengineering is centered are the Parker H. Pettit Institute for Bioengineering and Bioscience (IBB) at Georgia Tech and the joint Georgia Tech/Emory Wallace H. Coulter Department of Biomedical Engineering.

Both GTEC and IBB are led by Robert Nerem, who joined the Georgia Tech faculty in 1987. Nerem received his PhD from Ohio State University in 1964, and served on the faculty of the Department of Aeronautical and Astronautical Engineering at Ohio State and the Department of Mechanical Engineering at the University of Houston before coming to Georgia Tech. He has been active in bioengineering research for more than thirty years, starting with work on cardiovascular fluid dynamics and expanding into the study of the effects of physical forces on anchorage-dependent mammalian cells, especially as found in blood vessels. Nerem was represented at the 1988 Granlibakken workshop with a paper on the implications for the development of endothelialized synthetic vascular grafts of cell responses to shear stress.

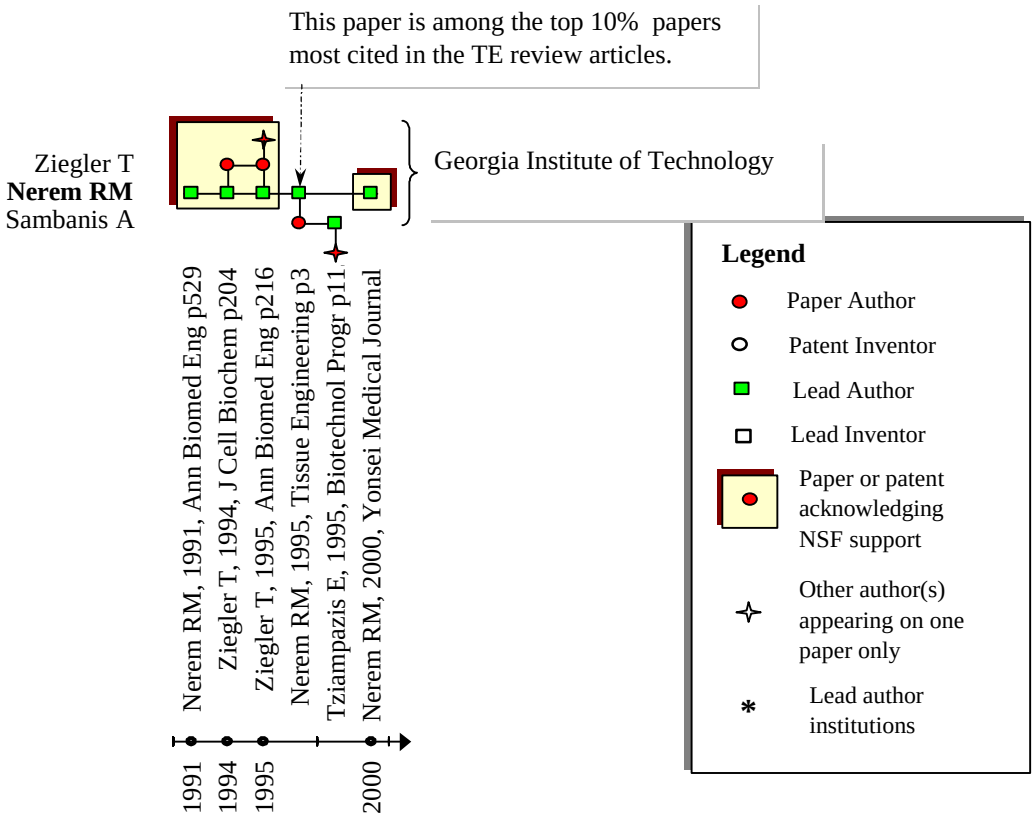

Figure 5.1: Nerem has been active in bioengineering for more than 25 years. He has conducted fundamental research on problems in cardiovascular fluid dynamics. This Figure shows his work on the influence of physical forces on anchorage-dependent mammalian cells, with much of this work focusing on the cells which make up a blood vessel, and some work on modeling the pancreas. (From CHI Report Appendix 5)

The Georgia Tech/Emory tissue engineering program was initiated in 1994 and expanded with the support of the NSF ERC award beginning in 1998. GTEC lists 29 faculty participants, whose primary faculty appointments are concentrated in the joint Biomedical Engineering department, the Mechanical Engineering department at Georgia Tech, and the Surgery and Orthopedic Surgery departments at Emory.

Georgia Tech/Emory alumni active in tissue engineering include:

- Kacey Marra, now Assistant Professor of Surgery at the University of Pittsburgh, and Janine Orban, now a research scientist at the DePuy Orthobiologics division of Johnson & Johnson, former postdoctoral fellows of Elliot Chaikof

- Naomi Chesler, currently Assistant Professor of Biomedical Engineering at the University of Wisconsin, Madison, who carried out postdoctoral research with David Ku and Zorina Galis

Columbia University

Bioengineering studies have been ongoing at Columbia University since 1962, notably in the areas of cardiac and orthopedic biomechanics, although a formal department of biomedical engineering was not created until 2000. Three of the leaders in the development of bioengineering at Columbia have played prominent roles in the emergence of tissue engineering.

Richard Skalak received his PhD in civil engineering and engineering mechanics from Columbia in 1954, and joined the faculty in that department upon completing his doctorate. His early research was focused on fluid mechanics, but by the mid-1960s he began to combine engineering mechanics and biomedical sciences in a series of pioneering investigations, notably in the area of blood rheology. As noted previously, Skalak was a participant in the special Panel Meeting on Tissue Engineering at NSF in October 1987, and helped to coordinate the 1988 Granlibakken workshop. Skalak served as director of Columbia's Bioengineering Institute, a forerunner of today's academic department, until his departure for the University of California at San Diego in 1988. He died in 1997.

Following completion of his medical training in Taiwan, Shu Chien came to the United States to study physiology at Columbia, receiving his PhD in 1957 with a thesis on the role of the sympathetic nervous system in compensatory mechanisms to hemorrhage. Chien continued this line of research as a faculty member at Columbia, and by the mid-1960s was focusing on blood rheology. Starting in the late 1960s he conducted important work in this area in collaboration with Richard Skalak. Shu Chien moved to UCSD in 1988 as well, where he has continued his research on blood rheology at the molecular and cellular level, and has served as director of WIBE and chair of the Department of Bioengineering.

Van C. Mow earned his doctorate in applied mechanics at Rensselaer Polytechnic Institute in 1966. As a faculty member at RPI in the early 1970s, he began to focus on orthopedic biomechanics. He joined the Department of Orthopedic Surgery at the Columbia University College of Physicians and Surgeons and the Department of Mechanical Engineering in the School of Engineering and Applied Sciences at Columbia in 1986, and currently serves as director of the Orthopedic Research Laboratory and chairman of the new Department of Biomedical Engineering. Mow participated in the Granlibakken workshop in 1988. Former Mow doctoral students active in tissue engineering include:

- Kyriacos Athanasiou (PhD, 1989), now Professor of Bioengineering at Rice University
- Gerard Ateshian (PhD, 1991), currently Professor of Mechanical Engineering and Bioengineering at Columbia
- Louis Soslowsky (PhD, 1991), currently Associate Professor of Bioengineering at the University of Pennsylvania
- Farshid Guilak (PhD, 1992), now Assistant Professor of Orthopedic Surgery at Duke University

University of Pennsylvania

The University of Pennsylvania has offered graduate degrees in bioengineering since 1961, and its Department of Bioengineering, established in 1973, was one of the earliest in the field. Penn currently offers a PhD program track in Cell and Tissue Engineering. More generally, however, as one of the most productive bioengineering departments, with long-standing research activities in many aspects of the application of mechanics to biomedical problems, the bioengineering department at Penn has trained a number of researchers currently active in tissue engineering.

Current Penn bioengineering faculty active in tissue engineering include:

- Paul Ducheyne (PhD in Materials Science, Katholieke Universiteit Leuven), Professor of Bioengineering
- Keith Gooch (PhD in Chemical Engineering, Penn State, 1995, under John A. Frangos), Assistant Professor of Bioengineering

- Steven Nicoll (PhD in Bioengineering, University of California, Berkeley and San Francisco, 2000), Assistant Professor of Bioengineering

- Solomon Pollack (PhD in Physics, University of Pennsylvania, 1961), Professor of Bioengineering

- Louis Soslowsky (PhD in Engineering Mechanics, Columbia, 1991, under Van C. Mow), Associate Professor of Bioengineering

Penn bioengineering alumni active in the field include:

- Fred Allen (PhD, 1996, under Solomon Pollack) is Assistant Professor of Biomedical Engineering at Drexel University

- Kristen Billiar (PhD, 1998, under Michael Sacks) worked at Organogenesis after completing her doctorate, and is now Assistant Professor of Biomedical Engineering at Worcester Polytechnic Institute

- Andres Garcia (PhD, 1996, under David Boettiger and Paul Ducheyne) is Assistant Professor of Mechanical Engineering at Georgia Tech and a participant in GTEC

- Kevin Healy (PhD, 1990, under Paul Ducheyne) is Associate Professor of Bioengineering and Materials Science and Engineering at the University of California, Berkeley

- Clark Hung (PhD, 1995, under Solomon Pollack) is Assistant Professor of Biomedical Engineering at Columbia University

- David Kohn (PhD, 1989, under Paul Ducheyne) is Associate Professor of Biologic and Materials Sciences at the University of Michigan School of Dentistry

- Michelle LaPlaca (PhD, 1996, under Lawrence Thibault) is Assistant Professor of Biomedical Engineering at Georgia Tech, and a member of GTEC

- Helen Lu (PhD, 1998, under Solomon Pollack) is Assistant Professor of Biomedical Engineering at Columbia University

- David Shreiber (PhD, 1998, under David Meaney) is Assistant Professor of Biomedical Engineering at Rutgers University

Chemical Engineering graduates from Douglas Lauffenburger's tenure at the University of Pennsylvania have been noted previously.

5.3 Collaborations Among Tissue Engineers

We examined patterns of co-authorship for several prominent authors in tissue engineering in order to understand the nature of collaboration occurring in the field. Through an analysis of primary and secondary authors on a selection of tissue engineering papers, CHI Research found several core collaborations which appear to have produced fruitful results. Appendix 5 summarizes CHI's conclusions about co-authorship patterns. The analysis revealed the interweaving of public and private knowledge and the public and private sectors in the development of tissue engineering research. Figure 5.3 is included as an illustration (with Figure 5.2 as legend). The Figure shows that Jay Vacanti and Langer are prominent not only because of their highly cited *Science* paper referred to above; nor because they have

double or triple the number of papers compared to any other lead author; but also because of the highly collaborative nature of their work. Nine of the other lead authors shown 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.

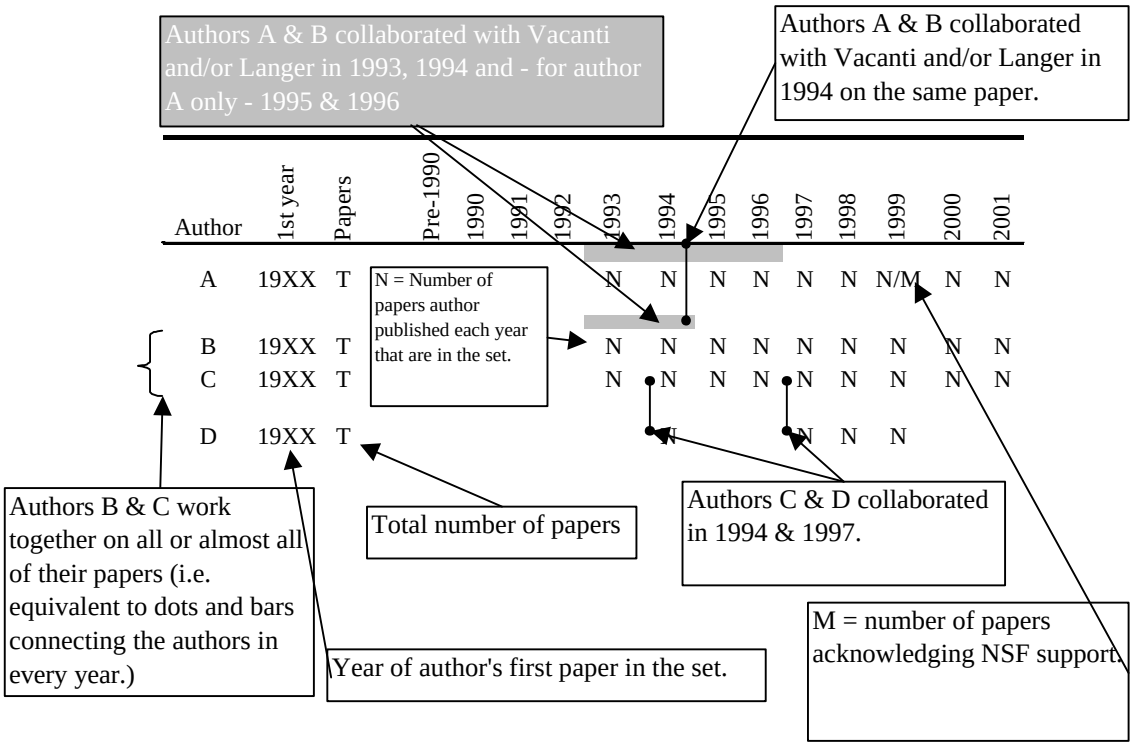

Figure 5.2: Legend for Overview of Lead Author Coauthorship (to explain Figure 5.3)

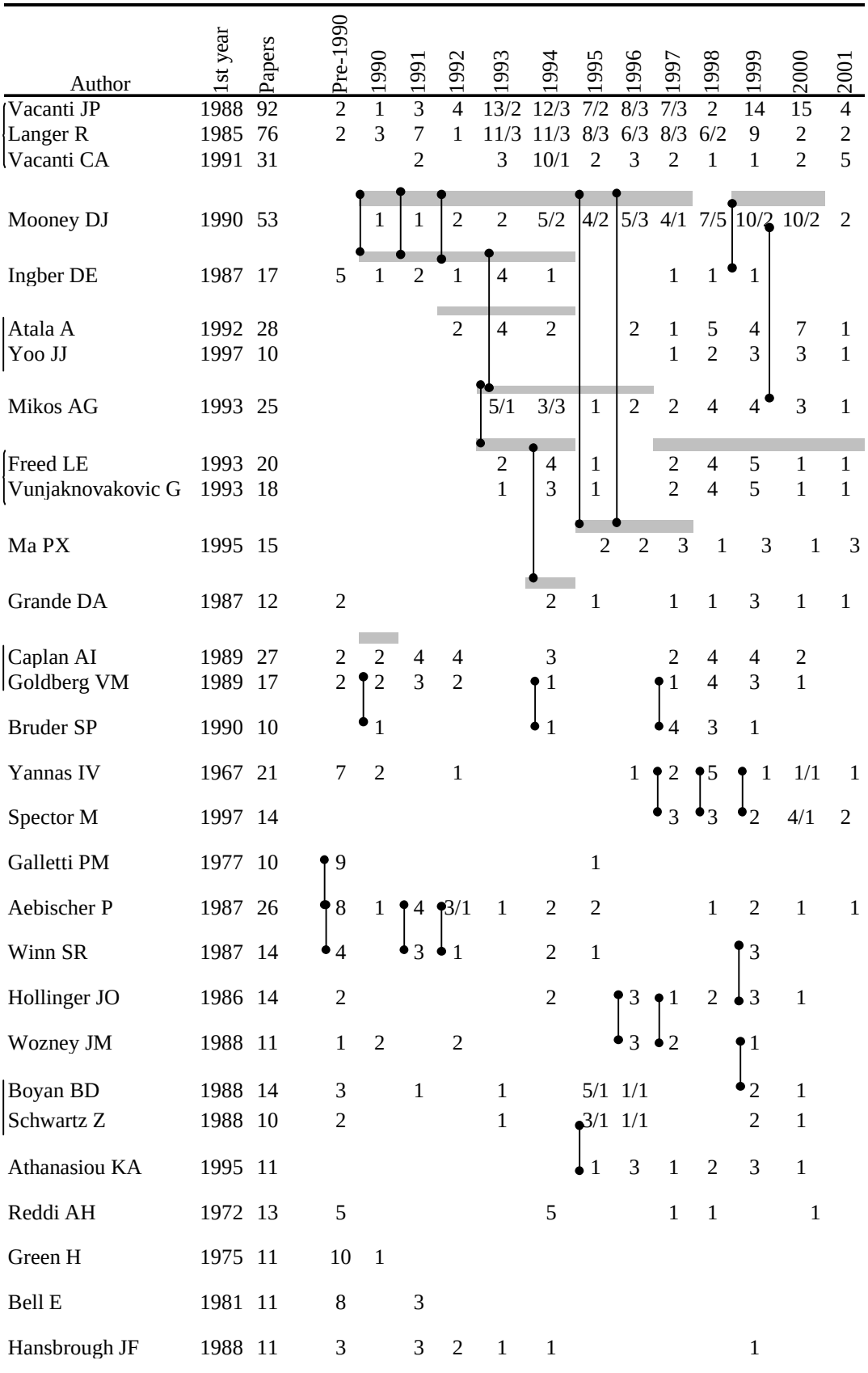

Figure 5.3: Overview of Lead Author Coauthorship Patterns