3.0 Emergence and Evolution of a Shared Concept

It is unclear who first used the term "tissue engineering" to mean what it does today. Not surprisingly for a coinage that seems so natural in hindsight, a number of the individuals interviewed for this study suggested that the term may have been invented several times independently before it came into sufficiently broad usage that a wide range of researchers can be expected to have encountered it in publications or in discussion. Indeed, the first appearance of the term in print of which the study team is aware – also the earliest revealed through a PubMed search – was an incidental, almost offhand usage in a 1984 publication that described the organization of an endothelium-like membrane on the surface of a long-implanted, synthetic ophthalmic prosthesis.[34]

However, the origin of "tissue engineering" as it is recognized today can be clearly traced to a specific individual. In 1985, Y.C. Fung, a pioneer of the field of biomechanics and of bioengineering more broadly, submitted a proposal to NSF for an Engineering Research Center to be entitled "Center for the Engineering of Living Tissues".[35] Fung's concept drew on the traditional definition of "tissue" as a fundamental level of analysis of living organisms, between cells and organs:

> The study of organs and organ systems has historically been the domain of the physiologist and physician. There is, therefore, a relative wealth of practical information about organs, codified in terms of medical practice. On the other hand, tissues are composed of cells, having specialized internal organelles and, ultimately, chemical constituents. The composition of the cell and its constituents has been dealt with by cell biologist and biochemist *[sic]*. There are relatively few focused efforts at bridging the gap between these extremes. A clear understanding of phenomena at the tissue level is prerequisite to the engineering of tissues *[emphasis in original]*…

Fung's proposal was not accepted. Nevertheless, the concept of an engineering approach to the level of biological organization between cells and organs surfaced again at NSF in the spring of 1987, at a panel meeting convened to review proposals to the Bioengineering and Research to Aid the Handicapped (BRAH) Program within the Engineering Directorate. Fung was present at this meeting, and is recalled as having volunteered the term "tissue engineering" in the course of a discussion that was seeking to crystallize the concept.[36]

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[34] Wolter JR, Meyer RF, "Sessile Macrophages Forming Clear Endothelium-like Membrane on Inside of Successful Keratoprosthesis", *Trans Am Ophthalmol Soc* 1984;82:187-202. "After observing the facts of the present case, one is drawn to the conclusion that the reactive cellular components contribute toward the eye's purpose by attempting to prevent light scattering even under totally unusual conditions…. Nature impresses us with a great variety of reactive possibilities in the adaptation of its tissues to new conditions and substances. Sound progress in medicine is easiest when we work along with the physiological currents of beneficial reaction and adaptation. To understand the direction and limits of nature's reactions is always the first step toward progress in *tissue engineering* [emphasis added]. It is in this sense that the observations in the unusual present case will contribute to progress in the creation of artificial windows in the shell of the eye with the aim to maintain and possibly also to correct vision." Interestingly, the chapter on the cornea in *Principles of Tissue Engineering* does not cite this paper, even though, despite 16 years of scientific progress, it retains its predecessor's focus on the body's response to corneal replacements made of purely synthetic materials, placing it similarly outside of the TE mainstream.

[35] "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.

[36] Allen Zelman, interview, July 17, 2001; Y.C. Fung, interview, August 23, 2001.

Further discussions between the program directors for the BRAH Program, which looked at whole organs, and the Directoratefor Engineering's Biotechnology (BIOTECH) Program, which focused on the cellular level, led to the convening of a special Panel Meeting on Tissue Engineering at NSF on October 28, 1987. For this meeting, Allen Zelman, a Program Director for BRAH, prepared a draft definition of tissue engineering:

> The term "tissue engineering" indicates a new inter-disciplinary initiative which has the goal of growing tissues or organs directly from a single cell taken from an individual.

Interestingly, in his "statement of the problem", Zelman pointed to the avoidance of immune rejection through the growth of tissues or organs from a patient's own cells as the key benefit of tissue engineering. Zelman envisioned the development of a large and vigorous new industry producing internal organs, but tempered this vision with the *caveat* that production of complex internal organs, such as the kidney, "would be considered far too ambitious as a starting point" and that "tissues, being more simple than organs, should be investigated initially".[37]

During the discussions at the October 28 meeting, Maurice Averner, Program manager for NASA's Controlled Ecological Life Support Systems Program, proposed another definition of tissue engineering: the production of large amounts of functional tissues for research and applications through the elucidation of basic mechanisms of tissue development combined with fundamental engineering production processes. This definition reflected the tenor of the discussion more generally, in which problems of production and distribution of tissue-engineered materials featured prominently. In the end, however, after different opinions were expressed concerning how precise and explicit a field definition needed to be, no formal definition was adopted; further clarification on this point was left as a task for an envisioned workshop.[38]

Subsequent to this meeting, a Forum on Issues, Expectations, and Prospects for Emerging Technology Initiation was held in Washington, DC, under the sponsorship of the Division of Emerging Engineering Technologies within NSF. This forum recommended that tissue engineering be designated as an emerging engineering technology, and that a workshop be held to identify appropriate areas for research in this technology. This proposed workshop, organized by Zelman, Frederick Heineken, and Duane Bruley –all of NSF—was held at Granlibakken Resort, Lake Tahoe, California, in February 1988.[39]

With the exception of a re-publication of the 1984 ophthalmology paper in another ophthalmology journal in 1985, the next known appearance of the term "tissue engineering" in print was in the proceedings of the Granlibakken workshop.[40] A preface to these proceedings defined the term more broadly than did any of the provisional definitions floated up to that point, to encompass a wider range of potential therapeutic interventions that could be enabled by research carried out under this new perspective:

> "Tissue Engineering" is the application of principles and methods of engineering and life sciences toward fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain, or improve tissue function.

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[37] Zelman A, "Tissue Engineering: A Fundamentally New Concept in Health Care", internal discussion memo, first draft, Sept. 22, 1987, courtesy of NSF.

[38] Skalak R, notes from Panel Meeting on Tissue Engineering , Oct. 28, 1987, courtesy of NSF.

[39] Heineken FG, Skalak R, "Tissue Engineering: A Brief Overview", *J Biomech Eng* 1991 May;113(2):111-2.

[40] Skalak R, Fox CF, *eds.*, *Tissue Engineering* (New York: Alan R. Liss, Inc., 1988).

> The basic point of the above definition is that tissue engineering involves the use of living cells plus their extracellular products in development of biological substitutes for replacements as opposed to the use of inert implants. The definition is intended to encompass procedures in which the replacements may consist of cells in suspension, cells implanted on a scaffold such as collagen and cases in which the replacement consists entirely of cells and their extracellular products.

The term did not appear in the title or abstract of an indexed biomedical journal again until 1989,[41] after the proceedings of the February 1988 Granlibakken workshop had been published in book form, but again representing the publication of meeting proceedings. Abstracts of the April 1990 UCLA symposium (later to become the Keystone symposia) in tissue engineering were published in 1990[42] and selected papers in 1991.[43]

At the 1992 UCLA symposium on tissue engineering, Eugene Bell defined tissue engineering in terms of a more specific list of goals:

1) providing cellular prostheses or replacement parts for the human body;
2) providing formed acellular replacement parts capable of inducing regeneration;
3) providing tissue or organ-like model systems populated with cells for basic research and for many applied uses such as the study of disease states using aberrant cells;
4) providing vehicles for delivering engineered cells to the organism; and
5) surfacing non-biological devices.[44]

These early meeting proceedings can be said to have "seeded" the term tissue engineering into the biomedical literature. However, on the whole, interviews conducted for the present study made clear that broad awareness of the term "tissue engineering", and its usage as a unifying concept for a wide range of concurrent lines of research, can be dated to the publication of a review paper by Robert Langer and Joseph P. Vacanti in the May 14, 1993 issue of *Science*.[45] This paper acknowledges NSF support, as well as support from other sources.

Langer and Vacanti referenced the definition from the Granlibakken proceedings, presenting it in condensed form:

> Tissue engineering is an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function.

Thus, perhaps the single most cited and influential paper in the field, cites the Granlibakken workshop and builds upon its pioneering definition of the tissue engineering. With this definition as a foundation, they added substance to the notion of common themes underlying a seeming diversity of research by identifying three general strategies for the creation of new tissue – the use of:

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41 Matsuda T, Akutsu T, Kira K, Matsumoto H, "Development of Hybrid Compliant Graft: Rapid Preparative Method for Reconstruction of a Vascular Wall", *ASAIO Trans* 1989 Jul-Sep;35(3):553-5.

42 "19th Annual UCLA Symposium: Tissue Engineering. Abstracts", *J Cell Biochem Suppl* 1990;14E:227-56.

43 "Tissue Engineering. Selected Papers from the UCLA Symposium of Tissue Engineering. Keystone, Colorado, April 6-12, 1990", *J Biomech Eng* 1991 May;113(2):111-207.

44 Bell E, "Tissue Engineering, an Overview", pp. 3-15 in Bell E, *ed.*, *Tissue Engineering: Current Perspectives* (Boston, MA: Birkhäuser, 1993).

45 Langer R, Vacanti JP, "Tissue Engineering", *Science* 1993 May 14;260:920-6.

- isolated cells or cell substitutes;
- tissue-inducing substances; or
- cells placed on or within matrices.

In the body of the paper, they briefly introduced ongoing efforts across a wide range of organ systems, classified by their embryologic origin – as ectoderm, endoderm, or mesoderm. Finally, they concluded by identifying further common themes, this time in the form of enabling knowledge or technologies of broad significance that should be targets for future research, in the areas of cell biology, cell sourcing and preservation, and materials.

The number of PubMed title/abstract "hits" on the term "tissue engineering" first exceeded 10 in 1994, the year after the Langer/Vacanti review appeared (see Table 1) . The number of appearances doubled in 1996, and again in 1998 and 1999, reaching 153 in 1999 and continuing to grow to 214 in 2000.[46] This figure surely understates the extent to which researchers associated the concept "tissue engineering" with their work; once the concept is established, there is no reason for a researcher to call it out explicitly in titles or abstracts unless there is a specific point to be made by doing so.

[46] Bibliometric analysis by CHI Research, Inc.

Table 1. Number of papers using the term "tissue engineering" in their titles or abstracts since 1984[47]

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

The definitions elaborated during the 1987-93 period provided the basic terms of reference for discussions of tissue engineering through the 1990s. Tissue engineering researchers seeking to situate their work within a broader context typically cited either the Granlibakken workshop definition or the Langer/Vacanti framing of the field. Even those who did not directly cite these sources offered definitions that reflected some combination of the elements contained in the definitions outlined here, with the exception of Eugene Bell's final point about surfacing non-biological devices, which seems to have been ignored for the most part.

These early definitions left at least two important ambiguities. One involved the role of cells in tissue engineering. In many formulations of the concept, the unique aspect of tissue engineering compared to traditional biomedical engineering or to pharmaceutical development was that its products incorporated living cells. Bell's 1992 definition, allowing for "acellular replacement parts capable of inducing regeneration", reflected an emerging recognition that physiologic reactions to biomaterials were not necessarily just a nuisance to be suppressed, but might under some circumstances offer a means of inducing useful adaptations in the body. However, this conceptual advance also blurred the distinction between this new field and the studies of acellular biomaterials that had been a mainstay of biomedical engineering and materials science. Langer and Vacanti went one step further, defining the use of "tissue-

[47] See Bibliometric Analysis by CHI Research Inc., Appendix 5

inducing substances" more generally as one of the strategies of tissue engineering. Including growth factors or other "signaling molecules" within the domain of tissue engineering represented progress toward an integrated understanding of the factors that govern tissue development *in vivo*, but also broke down the boundaries between tissue engineering and modern pharmaceutical research, which draws increasingly on the latest findings of cellular and molecular biologists. In the words of tissue engineer Jeffrey Hubbell, "Doing tissue engineering with factors to stimulate cells in the body is really just fancy drug delivery. One is delivering a drug – like a protein, a morphogenic factor – that stimulates cellular responses at a site with the goal of ending up with some overall tissue reconstruction or regeneration at that site."[48]

A second ambiguity concerned the role of hybrid devices in tissue engineering, and the related question of whether therapeutic products of tissue engineering were necessarily intended to be implanted into the body. Several lines of research typically referred to as tissue engineering pursue the development of external bioreactors that can replace critical metabolic functions. From both a conceptual and a historical perspective, this work arguably represents an incremental advance on the dialysis machine. The long-term vision of researchers working on hybrid devices typically extends to more compact, self-contained versions that can be implanted. However, even when miniaturized, current "bioartificial organs" remain more machines than living organs, closer to today's mechanical artificial heart than to the vision of an adaptive biological implant that is seamlessly incorporated into the body's reparative and homeostatic mechanisms.

The linkage of TE research with clinical medicine, although inevitable and desirable in view of the goals of the endeavor, nevertheless has also served as something of an obstacle to the sharpening of a definition of tissue engineering as an academic discipline. For example, orthopedic surgeons have been investigating many different kinds of implant that may promote bone regeneration. From a clinical perspective, what matters is not so much whether the active agent in an implanted matrix consists of stem cells, bone morphogenetic proteins, or gene therapy vectors, but whether it is therapeutically effective. Similarly, a nephrologist may view the dialysis machine, the external biohybrid "artificial kidney" or functional, histocompatible "microrenal" units created via nuclear transplantation as possibilities along a seamless spectrum of therapeutic options rather than in terms of the radically different underlying technologies they represent.

Recent developments in nomenclature reflect this persistent ambiguity in scope and focus. The National Institutes of Health Bioengineering Consortium (BECON) symposium on tissue engineering, held at NIH in June, 2001, was entitled "Reparative Medicine: Growing Tissues and Organs". The proceedings of the symposium offer multiple competing – and to some extent conflicting – definitions of reparative medicine, of tissue engineering, and of the relationship between the two. At one extreme, reparative medicine is defined very broadly as "the replacement, repair, or functional enhancement of tissues and organs", a definition that is not much narrower than all of clinical medicine, although most of the examples cited have a surgical flavor; tissue engineering is viewed as one strategy among many for reparative medicine.[49] At the other, reparative medicine is defined as a synonym for tissue engineering:

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[48] Henry CM, "Drug Delivery", *Chemical & Engineering News* 2002 Aug 26;80(34):39-47. NSF has itself, on at least one occasion, extended the definition of tissue engineering beyond even this point, to encompass the use of controlled release polymers to deliver anticancer drugs in the brain. "Nifty 50: Tissue Engineering", http://www.nsf.gov/od/lpa/nsf50/nsfoutreach/htm/n50_z2/pages_z3/45_pg.htm (URL verified December 31, 2002).

[49] Sipe JD, "Tissue Engineering and Reparative Medicine", pp. 1-9 in Sipe JD, Kelley CA, McNicol LA, *eds*., Reparative *Medicine: Growing Tissues and Organs* (Annals of the New York Academy of Sciences, vol. 961, June 2002).

> Reparative medicine, sometimes referred to as regenerative medicine or tissue engineering, is the regeneration and remodeling of tissue *in vivo* for the purpose of repairing, replacing, maintaining or enhancing organ function, and the engineering and growing of functional tissue substitutes *in vitro* for implantation *in vivo* as a biological substitute for damaged or diseased tissues and organs.[50]

This definition of tissue engineering is noteworthy for excluding extracorporeal bioartifical organs, and indeed, such devices gain only a passing mention in the proceedings,[51] which otherwise cover a very broad scope.

The term "regenerative medicine", offered as a further synonym, appears to have been coined by William Haseltine, to capture for promotional purposes his view of the future of medicine.[52] Contrary to the usage at the BECON symposium, Haseltine's conception positions TE as a subset – a "thread" or "phase" – of regenerative medicine, not as a synonym for it, emphasizing the *in vitro* construction of human organs for implantation, using specialized biocompatible materials, signaling molecules, and adult human cells. In practice, however, there is little to distinguish Haseltine's "regenerative medicine" from other conceptions of tissue engineering.

Despite these alternative forms of the term, however, the true sentiment of the field appears to have been captured early on at the NSF meetings of 1987 and 1988. It is this concept of the field, which has been carried on by its leading proponents and remains highly referenced today.

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[50] Nerem R, Sage H, Kelley CA, McNicol LA, "Symposium Summary", pp. 386-9 in Sipe JD, Kelley CA, McNicol LA, *eds*., Reparative *Medicine: Growing Tissues and Organs* (Annals of the New York Academy of Sciences, vol. 961, June 2002).

[51] Niklason LE, Ratcliffe A, *et al*., "Bioreactors and Bioprocessing: Breakout Session Summary", pp. 220-2 in Sipe JD, Kelley CA, McNicol LA, *eds*., Reparative *Medicine: Growing Tissues and Organs* (Annals of the New York Academy of Sciences, vol. 961, June 2002).

[52] Haseltine WA, "The Emergence of Regenerative Medicine: A New Field and a New Society", *e-biomed: The Journal of Regenerative Medicine* 2001;2:17-23.