Appendix 1: Approach to Data Collection

Literature Review

Bibliographic searches, general Internet searches, advice from expert informants, and citations and other leads within retrieved documents pointed to a wide range of professional, institutional and popular literature relevant to the study. Documents of the following types were reviewed:

- ***Articles in peer-reviewed scientific journals,*** including review articles and original research papers published in general scientific and medical journals such as *Science*, *Nature*, and the *New England Journal of Medicine* as well as in biological, medical and engineering specialty and subspecialty journals such as *Journal of Cellular Biochemistry*, *Journal of Vascular Surgery*, *Journal of Biomedical Materials Research*, and *Tissue Engineering*.

- ***Conference agendas and proceedings,*** including key events such as the 1987 NSF special panel meeting, 1988 Granlibakken TE workshop, the 1992 Keystone symposium, and the 2001 BECON symposium.

- ***Prospectuses, promotional materials and other documents from professional societies and private-sector development initiatives,*** such as the Tissue Engineering Society and the Pittsburgh Tissue Engineering Initiative.

- ***Program announcements, project abstracts, reports and background documents from Federal funding agencies and collaborative initiatives,*** including NSF, NIH, NIST, and NASA, and the NIH BECON and interagency MATES initiatives.

- ***Annual reports and miscellaneous documents from private foundations*** such as the Whitaker Foundation.

- ***Special task force reports,*** notably including the January 2002 WTEC Panel Report on Tissue Engineering Research.

- ***Announcements, bulletins, research abstracts, course syllabi and other materials from academic programs in tissue engineering.***

- ***Textbooks,*** including two recently-published, comprehensive volumes: *Principles of Tissue Engineering, 2nd Ed. (Academic Press, 2000)* and *Methods of Tissue Engineering (Academic Press, 2002)*.

- ***Promotional materials and annual reports from companies engaged in tissue engineering.***

- ***Articles from trade publications and general-interest periodicals*** such as *The Scientist, Scientific American*, *Discover*, *Business Week*, and *Time*.

- ***A convenience sample of TE-related patents*** identified through exploratory searches of the US Patent and Trademark Office database, using the term "tissue engineering" or the names of researchers or organizations prominent in the field as search terms.

Expert Interviews

An iterative process of literature review, Internet searches, and discussions with expert informants produced a list of 126 individuals presently or formerly active as participants in or observers of TE, including researchers based in academia, researchers and managers from private companies, present and former program managers for funding agencies, and investment and venture capital professionals. The study team was able to interview a total of 46 people from this list, either in person or by telephone, including most of the individuals identified by consensus among our informants as especially influential in shaping the field during the earliest years of its emergence.

A master protocol of study questions was developed, from which separate interview guides were derived for use in discussions with individuals working in academic, government, and corporate settings. A complete list of interviewees can be found in Appendix 3, and copies of the interview protocols can be found in Appendix 4.

Bibliometric Analysis

A formal bibliometric analysis was carried out by CHI Research, Inc., using reference sets of publications and patents identified as related to tissue engineering. Full details are provided in a separate Appendix 5 to this report.[140]

Search for Data on Research Sponsorship

To inform analysis of NSF's role as a research sponsor in the emergence of tissue engineering, an attempt was made to collect systematic data on the quantity and character of related research projects funded and on the amount of money expended by Federal agencies in support of TE. Sources utilized included the following:

- ***RaDiUS***, a comprehensive database on Federally-funded research and development, maintained by the RAND Corporation.
- ***Project databases of individual Federal agencies***, including NSF, NIH and NASA.
- ***Documents provided by program managers*** at Federal agencies.
- ***Bibliometric analysis of funding acknowledgments*** in published papers and patents.

It became apparent from intensive exploratory analysis of RaDiUS and the agency-specific project databases that there is no way to construct either a definitive list of TE projects funded by the Federal government or to calculate anything more than an order-of-magnitude estimate of the amount of funding provided for TE by the government. In part, this is a consequence of the boundary-drawing problem, and of the related difficulty of specifying a search filter that is both sensitive and specific for TE-related research. However, technical limitations of these databases – notably in the consistency of the largely investigator-reported data on which these systems are based – imposed severe constraints on the analysis as well.

Once the roster of tissue engineers was completed, the database of NSF awards accessible through FastLane was searched for evidence of NSF support for the listed researchers.

---

[140] *Bibliometric Analysis of Core Papers Fundamental to Tissue Engineering*, CHI Research Inc., March 25, 2002.

Although it was impossible to develop a precise quantitative accounting of the roles of different research sponsors, the available data, combined with qualitative information obtained via interviews of program officers, funded researchers and other observers, provided substantial qualitative insight.

Review of NSF Historical Data

We also analyzed data in the NSF Awards Database provided via CD-ROM by Linda Parker for five key researchers: Eugene Bell, Howard Green, Robert Langer, Jay Vacanti, and Ioannis Yannas. A total of 28 records were retrieved for these 5 names. The breakdown of awards is as follows:

Eugene Bell: 19 awards
Howard Green: no awards
Robert Langer: 4 awards
Jay Vacanti: no awards
Ioannis Yannas: 4 awards

Based on the information provided in the database, it is unclear which Directorate at NSF sponsored these awards. For many of these awards, the records are so old they are tracked instead by a 'historical' number HST#, rather than under a Directorate heading. Abstracts for these awards are also missing, which make it difficult to understand the precise scope of each award.

Only one of Langer's 4 awards retrieved by the database actually pertains to tissue engineering and describes "Novel Degradable Polymers for Cellular Adhesion." The other 3 awards are more specifically related to his work on drug delivery technology, which Langer himself considers a largely separate line of work from his efforts in tissue engineering.

In the case of Yannas and Bell, it appears that the awards listed in the NSF database supported research in basic and developmental biology, which are no doubt important inputs to the development of tissue engineering and most certainly contributed to the efforts of these two researchers in developing the methods and materials which allowed them to develop their early skin substitutes. Adoption of this viewpoint shows NSF as a key supporter of Eugene Bell in the years prior to his major discoveries in skin replacement technology. It should also be noted, however, that though NSF appears to have provided some initial support to these researchers, none of the awards listed represent work that directly related to the development of the first living skin equivalents, which took place in the late 1970's and early 1980's. Again, however, without the grant abstracts, this is a surface judgment based only on the title of the award and not necessarily the substance of the research.

Thus, based on the information contained in this database, combined with our previous analysis of NSF award abstracts listed in FastLane, we do not believe there to be convincing evidence to support additional discussion in our final report which cites NSF has having provided a framework for key advances in tissue engineering (for these researchers or otherwise). It is true that there are some records missing, post-1996, which are contained under separate heading at NSF. However, given the late date of these awards, we do not believe that these provide evidence that NSF provided *early* support to enable fundamental advances in the field.

Construction of Roster of Tissue Engineers

To enable an analysis of genealogic relationships among researchers active in tissue engineering, a roster of tissue engineers was constructed with information about their training and employment. (Appendix 2). The majority of the information in this table was extracted from documents obtained via Google search of the World Wide Web, including investigators' CVs and laboratory pages,

departmental overviews and histories, news reports, and a variety of other articles and documents. References located via PubMed were used to identify research collaborations not otherwise documented and to corroborate relationships suggested by other sources. Additional information was obtained from other sources identified above under "Literature Review".

As with data on research project funding, the absence of a precise definition of the field makes decisions about the inclusion of a given individual somewhat arbitrary. Our selection was intended to include individuals who have identified themselves as active in the field, usually by describing their own work with the term "tissue engineering", and for whom TE-related work constitutes an important component of their overall portfolio of activity. 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 meet these criteria.

In addition, the list includes several of the most prominent physician-researchers in the field, along with a small sampling of individuals in the corporate sector. In general, less information was available on the web about physicians whose primary academic appointments were in clinical departments than about faculty in engineering or basic science departments, and almost no information was available about employees of private companies.

A few deceased individuals who played prominent roles in the emergence of the field are included in the roster.