Executive Summary

This report examines the emergence of the research field of tissue engineering (or TE), focusing on developments in the United States. Its purpose is to document the evolution of tissue engineering into a distinct area recognized as such by scholars, to document the involvement of the Directorate for Engineering at NSF, and to evaluate the significance of the Directorate for Engineering's role in the broader context of the field's evolution. A graphical genealogy of the field is also provided as a separate wall chart.

Tissue engineering represents the confluence of a complex array of pre-existing lines of work from three quite different domains: the worlds of clinical medicine, engineering, and science. Its most obvious precursors lie in the clinical domain, and are best understood as specific examples of general problem-solving strategies employed by physicians. However, tissue engineering is also remarkable for the breadth of its "footprint" in fundamental and applied biomedical research, in areas such as cell and developmental biology, basic medical and veterinary sciences, transplantation science, biomaterials, biophysics and biomechanics, and biomedical engineering. Key developments in the prehistory of tissue engineering are reviewed briefly for several clinical areas, including vascular grafts, skin grafts, therapies for kidney, pancreatic and liver failure, and bone and cartilage repair.

The origin of the term "tissue engineering", and of the concept *as we know it today* can be traced to bioengineering pioneer Y.C. Fung of the University of California at San Diego (UCSD), who led the UCSD team that submitted an unsuccessful proposal to NSF in 1985 for an Engineering Research Center Program award under the title "Center for the Engineering of Living Tissues". Fung proposed the term again at a 1987 panel meeting that was considering future directions for the NSF's Directorate for Engineering Bioengineering and Research to Aid the Handicapped Program; strong interest in the concept within NSF led to a special panel meeting on tissue engineering at NSF in the fall of 1987 and then to the Lake Granlibakken, CA workshop of 1988, the first formal scientific meeting of this emerging field. This workshop, and succeeding symposia in 1990 and 1992 , helped "seed" the scientific literature with this new concept. More widespread awareness of the term tissue engineering appears to have followed with the 1993 publication of a review article in *Science* by Robert Langer and Joseph Vacanti, a paper which cites, among others, funding support from NSF.

The definitions of the concept presented in the published proceedings of the Granlibakken workshop and in the Langer/Vacanti review have provided the framework within which most researchers who published later have situated their work. Langer and Vacanti defined tissue engineering as "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function", and identified three general strategies employed in tissue engineering: use of isolated cells or cell substitutes, use of tissue-inducing substances, and use of cells placed on or within matrices. However, actual usage of the term reflects an ongoing ambiguity in scope and focus, notably with respect to how far applications can stray into purely molecular (rather than cellular) approaches and still be considered tissue engineering, and with respect to the role of hybrid and external organ replacement devices. Experts interviewed in the study used the recently-coined terms "reparative medicine" and "regenerative medicine" largely as synonyms of "tissue engineering."

During the years since 1987, the number of researchers who consider themselves to be working in tissue engineering has grown substantially, as newly-trained and established researchers have entered the field, as established researchers have come to recognize their existing lines of work as tissue engineering, and as the scope of tissue engineering has implicitly expanded when adjacent fields report advances that address core challenges in tissue engineering.

Based on discussions with figures prominent in the tissue engineering community, the single most influential research paper in the field from a substantive point of view is a 1988 paper, also by the Langer/Vacanti team, that described the method of using resorbable polymer matrices as a vehicle for cell transplantation. This method rapidly became the most important enabling technology and organizing concept in the field and catalyzed a flurry of work on a wide range of tissue and organ systems, overshadowing to some extent fundamental efforts to address other knowledge gaps in areas such as scaffold materials, cell sourcing, immune response, chemical signaling, vascularization, bioreactors and bioprocessing, tissue preservation, and methods for characterization and functional assessment of bioengineered tissues.

Given the range of topics/foci characteristic of the field, we find an assortment of investigators pursuing work in TE. Analysis of a sample of 231 individuals representing a majority of non-physician faculty active in tissue engineering as well as a selection of prominent clinician-researchers and individuals active in the corporate sector pointed to some generalizations about the cadre of tissue engineers (please see Appendices 1 and 2 for a discussion on methodology and for the list of tissue engineers). While not meant to be an exhaustive listing of tissue engineers, some trends are apparent. They are indeed predominantly engineers, with chemical engineering the most frequent field of their training by a wide margin, followed by bioengineering and mechanical engineering. Current academic department affiliations are also strongly weighted toward engineering, but with bioengineering or biomedical engineering the leading disciplinary affiliation by a wide margin, followed by chemical engineering and, distantly, by mechanical engineering. Biological science affiliations are few, and are weighted toward basic medical science departments. Clinical and clinical science affiliations are strongly weighted toward surgery and surgical specialties, notably orthopedics.

More than 70 universities are represented in the list of institutions from which tissue engineers in this sample set received their non-clinical doctorates and more are sure to exist. Of the major institutions with groups of researchers in this list pursuing tissue engineering, MIT trained the largest number of individuals, 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. When postdoctoral training relationships are traced as well, the relative weight of MIT in this group increases further. Finally, within this cohort the great majority of individuals active in tissue engineering are involved on a part-time basis, simultaneously maintaining a number of lines of research both in tissue engineering and in other areas.

A separate analysis of key genealogic relationships within this emerging field is also described. Discussions with experts in the field, document review, and analysis of funding abstracts pointed to six major centers of activity in the United States, the focus of the study, as having played central roles in research or training since the earliest days of the field. These six were selected for further analysis and included: Boston (MIT and Harvard), the University of California at San Diego, Rice University, Georgia Tech/Emory University, Columbia University, and the University of Pennsylvania. Research suggests that, to date, MIT has played the most prominent role, and within MIT the laboratory of Robert Langer. There is fair but not complete overlap between the key players identified in the bibliometric review and the literature review.

While academia remains the primary source of fundamental advancement in the field, the corporate sector has also played a notable role in the development of this unique field, mostly due to the high level of corporate R&D funding injected into the field as compared to the relatively small influx of funds from the federal government. Given TE's traditional perception as a high-risk investment, few agencies in the government were willing to support early work in the field forcing those pursuing research objectives to locate alternate sources of funding, such as by bootstrapping funds from other grants, patent revenue, or by bringing their ideas to the private sector. Corporate R&D has focused on the creation of proprietary intellectual content centered on the challenges of bringing products to market, and less on the solution of broader challenges in science or engineering. Today, there are over 70 start-up companies in the field specializing in structural, metabolic, and cellular TE applications, and other enabling technologies, many of these with founding links to major universities with TE programs.

Patenting in the area is increasing steadily. 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. Most of the patents are coming from US inventors and assignees. The bulk of the innovation is coming from the US (especially from MIT, Advanced Tissue Sciences, and Regen Biologics Inc.). Over seventy percent of the global tissue engineering patents are invented in the US, followed by 18% in Europe (led by Germany and UK) and 6% in Japan. The highest cited patents are also US-based. MIT has the most highly cited patents. Among the most effective patenting companies is Regen Biologics Inc., which has 8 of its 11 patents among the highly cited set.

Today tissue engineering remains an eclectic mix of topical foci and research styles, with work of an *ad hoc* character continuing to play a strong role not only in the corporate sector but in academia as well. An important contribution of engineers during the events that led to the emergence of the field in the 1980s was to articulate the need for rationalization and systematization of the field. However, to date little progress has been made in this respect. Assessed in terms of the number and character of its products that have either reached or approached commercialization, tissue engineering has made only incremental progress toward its ultimate goal of developing practical and viable therapeutic products.

The National Science Foundation, in particular the Directorate for Engineering, appears to have played an important role in the emergence of tissue engineering as a recognized field of activity, and in shaping the character and determining the direction of the field. Prescient leaders in the Directorate, such as Allan Zelman and Frederick Heineken, were instrumental in making tissue engineering a priority within their Divisions and in gaining the support and involvement of other agencies in TE activities, such as the MATES working group and the WTEC study on TE.

In terms of financial support, the amount of NSF funding for tissue engineering has been growing over time, but represents a relatively small fraction of the total resources available to support academic research in the field. In terms of absolute dollar amounts, a more important early sponsor of institutional development in support of tissue engineering has been the Whitaker Foundation, through its role in building the field of biomedical engineering, and especially in providing institutional development funds for the creation and expansion of bioengineering departments. The Directorate for Engineering has been able to leave a mark on the field, however, through its provision of support to several important conferences, workshops, and other networking activities since the field's inception. They have also provided targeted support to Tissue Engineering Centers at MIT, the University of Washington, and the Georgia Institute of Technology—groups that currently represent hubs of training and research activity in the field.

The NSF Directorate for Engineering has also provided important early career development support for a large number of promising young researchers in tissue engineering, a role that may not be fully appreciated by researchers who have not themselves been direct beneficiaries of NSF's support. NSF also appears to have played a role in bringing the biomechanics community into this emerging field in a timely way, and more recently, is working to address a key gap in the field by exerting a similar effort to engage biologists. The role of Frederick Heineken in particular is key in the Directorate especially in initiating cross-agency coordination. This is reflected in NSF's recent collaborations with other federal agencies, through the Multi-Agency Tissue Engineering Science Working Group (MATES) which also sponsored a WTEC report to document international Tissue Engineering research, and with the National Institutes of Health's National Institute for Biomedical Imaging and Bioengineering (NIBIB).