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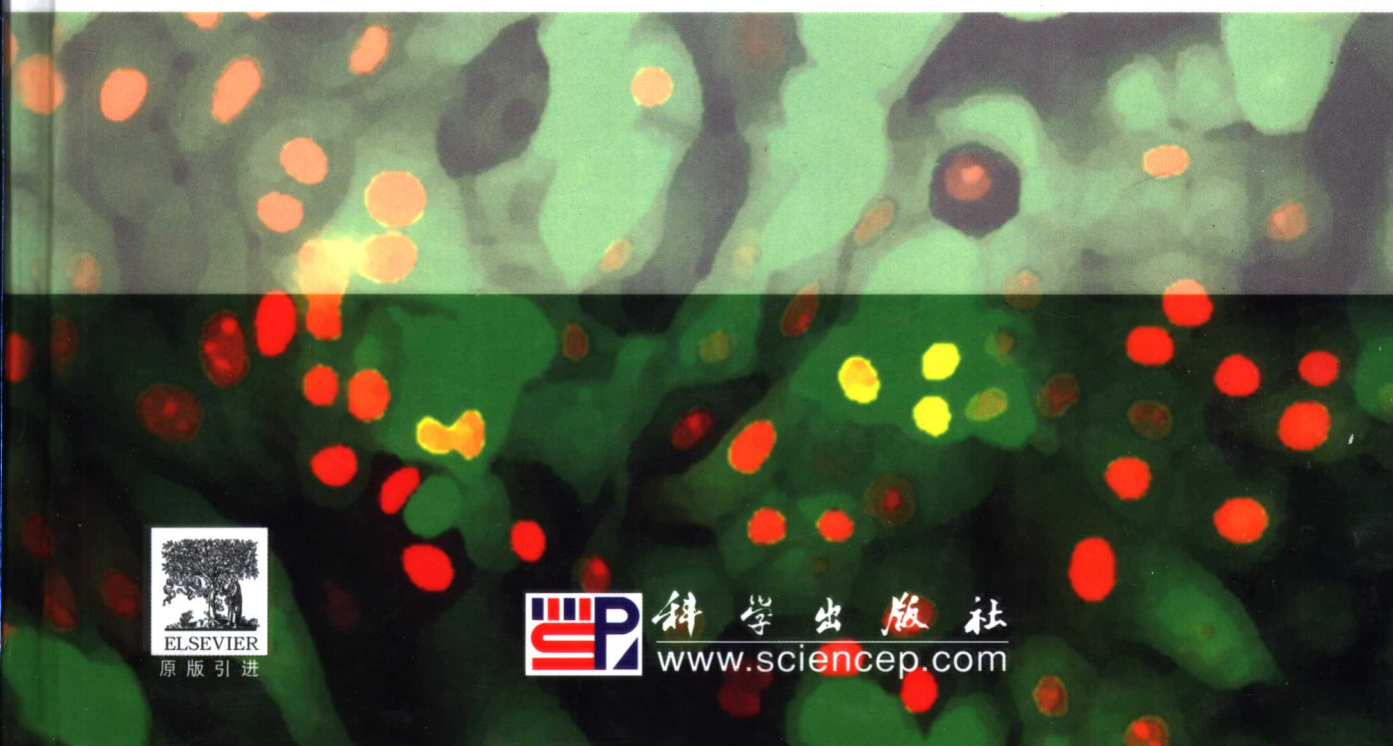
Tissue Engineering: Fundamentals and Applications

组织工程：基础与应用

〔日〕筏义人



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[日] 筏义人

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导　读

组织器官的缺损和功能障碍（老化、受损伤或病态）是危害人类健康的主要因素之一，也是引起人类疾病和死亡的最主要原因。目前临床用于组织缺损和功能障碍的修复和治疗方法主要是自体组织器官的移植、异体组织器官的移植、异种组织器官的移植和采用人工替代物等几种。自体组织器官虽然是最理想的移植供源，可以避免移植后发生免疫排斥，但从患者自体获取移植供体不但供源有限，而且如同雪上加霜，会给患者造成更大的伤害。异体组织器官移植虽可大大丰富组织器官的供源，但是异体组织器官引起的免疫排斥反应常常是导致移植失败的主要原因。异种组织器官移植可以很好地解决组织器官供源缺乏的问题，但异种组织和器官间的组织相容性问题和免疫排斥问题一直是造成移植失败的主要原因；此外，异种组织器官移植还存在着伦理问题和动物与人类疾病交叉传染的隐患。人工替代物则往往是与天然组织器官只具有相似形态的惰性物质，而并不具备组织器官真正的功能；有时还会因这样的人工替代物在体内是异物而引起机体的异物反应。所以至今临床实际上还没有一个十全十美的方法可以真正解决缺损或功能障碍组织和器官的修复与治疗问题。因此，如何从根本上解决缺损或功能障碍组织和器官的修复与治疗问题，已成为国际科技界，特别是国际生命科学研究领域科学家们积极探索的前沿性研究课题。

组织工程是将工程学原理同细胞学和组织生物学原理相结合，以替代有缺损和功能障碍组织和器官的科学。它是通过将自体细胞或干细胞在生物材料所制备的、具有与所需修复的组织或器官相同形态结构的支架上进行体外培养扩增、构建成细胞和生物材料构成的三维空间复合体后，再植入体内的病损部位，使之繁衍、生长，最终达到修复与重建组织或器官、恢复功能目的的生物工程技术。由组织工程再造的组织和器官可以同人工替代物一样进行大批量的生产，用它们进行修复与重建的组织和器官不但不会发生免疫排斥反应，而且还可具有与天然组织与器官相同的功能。所以组织工程的提出、建立和发展，将改变传统的以创伤修复创伤的治疗模式，为最终实现无损伤修复创伤和真正意义上的功能重建开辟新的途径。组织工程被认为是最有望彻底解决缺损或功能障碍组织和器官的修复治疗手段。组织工程是在生命科学和工程学原理与方法相结合基础上研究、发展而成的，用于修复、增进和改善人体损伤组织或器官形态和功能，展示了人们有能力再造具有复杂组织结构和生理功能的器官的能力，也标志着医学将走出组织、器官移植的范畴，进入制造组织、制造器官的新时代。成为生命科学发展史上的一个新里程碑。

组织工程的核心是建立由细胞和生物材料构成的三维空间复合体。其目标是应用细胞生物学、分子生物学、材料学的技术和工程学的原理和方法构建具有生命力的组织和器官，从而实现在形态、结构和功能等各方面对缺损和功能障碍组织器官的永久性置换和替代，最终改善人们的健康和生活质量。组织工程包括种子细胞、生物材料、构建组织和器官的方法和技术、组织工程的临床应用等多个基本要素，它是一门建立在细胞生物学、生物材料学和分子生物学三大学科上，又融汇了生物信息学、生物化学工程学、

遗传学、工程学、生物力学、生物电子学、计算机模拟和科学，以及临床医学等多学科的交叉边缘科学，因此在组织工程的研究中必须进行各相关高技术的交叉、结合和渗透，使其最终能够演化、发展和衍生成为新的高技术学科，并产生巨大的社会效益和经济效益。鉴于组织工程是一门多学科交叉的边缘学科，是相关高技术交叉、渗透和发展的产物，因此，可以认为组织工程已成为一个国家医学发展水平的重要标志之一。所以组织工程自被提出以来，得到了世界各国极大的反响和重视，成为二十世纪九十年代以来各国争相开展的重要研究课题。如今，诸多以“组织工程”命名、或者辟有“组织工程”专栏的刊物已经产生，并且正在逐渐增加。国际组织工程学会也已成立，这对组织工程学科的发展起了极大的推动作用。如今，国际上自最早在实验室获得组织工程化软骨的成功以来，已相继成功地构建了组织工程化骨、肌腱、血管、气管、神经、皮肤、肌肉、输尿管、心脏瓣膜等等，其中具有部分功能的组织工程化皮肤已经达到了产业化水平，组织工程化肝脏、胰腺、血液的研究也取得了很大的进展。

我国早在上世纪九十年代就将组织工程列为“国家重点基础研究发展规划”、“国家高技术研究发展计划”和“国家自然科学基金”等国家级科研项目，投入了大量的人力、物力和财力，开展了从中央到地方的组织工程研究。我国如今已成为国际上组织工程研究的先进国家之一，有些方面的研究还达到国际领先水平，2005 年 10 月还在上海举办了国际组织工程学会的第八届年会。然而十多年的研究经验也使我们认识到，从体外到体内的研究，实际存在着诸多从未发现和注意过的因素正在影响着组织工程化组织的形成过程与组织构建效果，因此仅凭现有组织工程理论与技术，是难以达到从结构与功能上构建完全再生的组织或器官这一目标的。例如，虽然我国的第一个具有部分功能的组织工程皮肤产品也已基本通过了国家食品药品监督管理局（SFDA）的审查，并即将进入试产；呈现出了组织工程化产品良好的临床效果和应用前景。但是这第一代组织工程皮肤还没有毛孔，与天然皮肤有很大的差异的。今后的组织工程研究层面必须从单纯的种子细胞、生物材料研究，提升到大动物体内的组织构建研究；在研究目标上，也必须从单纯地追求与正常组织结构的相似性，发展到突出重视构建组织的功能完整性。应用组织工程技术，构建具有形态与功能完美统一的组织工程化组织和器官，已成为组织工程学新一阶段发展的主要方向。在种子细胞、生物材料、生长因子、组织构建及临床手术等各项技术得到进一步改进和发展后，更多更好的、能与天然组织器官具有相似功能的各种组织工程化产品都会在不久的将来投入临床应用和产业化生产。

本书作者筱义人教授是日本组织工程研究的先驱者，也是国际知名的生物材料和组织工程专家。他毕业于著名的日本京都大学，又先后在京都大学获得了工学博士和医学博士学位，所以是难得的兼具坚实工学和医学基础和专业知识的学者。筱义人教授长期在京都大学的医用高分子中心（后改名为“生体医疗工学研究中心”和“再生医学研究所”）从事高分子反应、高分子表面化学、医用高分子、人工脏器和药物释放体系方面的研究工作，所以又具有丰富的研究经验和宽广的知识面。他曾撰写过多部有关组织工程和再生医学的著作，本书《组织工程：基本原理与应用》是他有关组织工程的又一部著作。正是鉴于他特殊的教育和研究背景和经历，所以能从工程学和医学等多个不同学科的角度对组织工程的过去、现在和未来进行总结和评价。在本书中通过引用大量的文献资料，他既全面地介绍了“组织工程”的概念及其优点和良好的应用前景，介绍了与

工程化组织相关的动物和人体组织与器官，介绍了在细胞、生物材料、构建组织器官的方法和技术上的新进展，同时也指出了要达到“理想组织工程化组织”所面临的挑战、困难和可能遇到的障碍。因此，本人认为：筱义人教授的《组织工程：基本原理与应用》一书，是一本将组织工程理论和实践很好结合起来，兼具介绍、评论和前景展望的著作。它提示大家在开展组织工程研究时，一定不能忘了该学科的多学科交叉的特点；必须从各个学科、多角度地去观察问题、思考问题，以及通过多学科的结合去解决问题。所以本书不但对从事组织工程的研究人员，而且对从事生物材料、细胞生物学、临床医学及其它学科的学生和研究人员都将是一本十分有益和难得的参考书。

作为国际生物材料和组织工程研究方面的知名科学家，筱义人教授经常应邀出席或主持各种国际学术会议。2005 年 10 月他应邀出席了在上海举办的国际组织工程学会第八届年会。照片就是在会议期间组织的浦江夜游时筱义人教授（左 2）同 ***Biomaterials*** 杂志主编 D. F. Welliams 教授（左 1）、夫人 O. Peggy（中），以及本人（右 2）、夫人贝建中（右 1）的合影。

王身国　研究员
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序　言

现行的临床技术，特别是器官移植和人工器官，对于那些因意外事故、创伤和癌症需要重建患病或受损的器官和组织的患者，或因先天性畸形需要矫正的患者，是非常好的挽救生命和延续生命的治疗方法。长期以来，大多数科学家和临床医师认为受损或丧失的组织只能通过器官移植或完全的人工组织来替代。尽管手术的技术、抑制免疫排斥和术后护理的进步提高了手术成功率和人们的生活质量，但是依然存在有像移植部位病变、供体短缺和组织排斥等器官移植所产生的问题。鉴于上述原因，各种各样的合成和天然材料已被开发出来替代丧失的组织，但结果仍不尽如人意，例如，人工器件的长期性能就是非常令人担忧的问题。通过肾透析对后期肾衰竭的治疗完全是依靠非生理的驱动力，不能模仿由肾小管细胞完成的主动分子运转。为治疗乳腺癌进行乳房切除术或乳房肿瘤切除术后，用于胸部重建的硅树脂可能会引起异物反应和感染。为了降低上述反应，自体的脂肪组织已被临床用于修复脂肪组织，然而这种治疗方法也存在一些问题，移植脂肪组织可能会被吸收而导致体积减小。由于这些仍然没有解决的重大问题和进一步改进治疗方法的需要，推动了以创造新组织为目标的研究。利用组织工程可以修复、取代或重建组织和器官，是非常有应用前景的研究方向。组织工程是从病人的活组织切片分离特殊细胞，在三维支架上精确控制条件培养，然后转移到病体所需的位置，以引导新组织在支架内形成；而支架则随着时间的推移被身体吸收。

为了避免混淆，简单地解释一下组织工程、再生医学、细胞治疗和胚胎干细胞之间的关系。近年来，因为多功能细胞被预期能分化为任何细胞从而形成体内的任何组织和器官，因此胚胎干细胞引起了人们强烈的关注。例如，帕金森症和胰岛素依赖性糖尿病也许可以通过胚胎干细胞而治愈，这种新兴的疗法被称为“再生医学”。在一些病例中，将细胞注射到病体中也足以起到治疗效果，这被称为“细胞治疗”。然而对于许多丧失的是有三维结构、大而复杂组织或器官的病例，因为注射的细胞会从注射点迅速扩散，仅仅注射细胞就会变得无效。这种情况下，我们就必须提供一个具有导向和一定结构的物质作为细胞粘附、扩展、分化，以形成新组织的基质，这就是组织工程的原理。因此我们可以说再生医学包含了利用细胞进行治疗的两个概念：一个是细胞治疗（不用支架），另一个是组织工程（有支架辅助）。显然，经由胚胎干细胞创建三维复杂的组织器官也需要组织工程技术，但是要使细胞生物学达到可以广泛使用胚胎干细胞的程度，还有很长的一段路要走。

在组织工程发展的历程中，有很多重要事件是值得纪念的。1987 年春天，美国国家科学基金会（NSF）的工程理事会召开了一个以生物工程未来方向为主题的座谈会[1]。研究的目标是一个交叉领域，会上确定了用“组织工程”这个术语来命名他们的成就。正是 1987 年春天的这个座谈会产生了第一个书面用语“组织工程”。在这个座谈会的基础上，1987 年 10 月美国国家基金会又召开了一次组织工程专家讨论会。在修复外科医生和生物材料工程师的创议和努力下，美国诞生了组织工程学科。1993 年，

Langer 和 Vacanti 提出了将工程学和生命科学的原理相结合制备生物替代物，用于修复和提高组织功能的组织工程概念 [2]，展示了组织工程学科的多学科领域的性质。同样，组织工程的目标是建立细胞—支架的复合结构，以诱导患者的组织再生和修复。由此，组织工程吸引了许多科学家和外科医生，他们希望通过这种革命性的治疗方法，极大地提高全世界成千上万人的生活质量。毫无疑问，早期的工作也已经成功地证明了可通过生物降解的聚合物支架上的细胞实现新组织的再生。

Lysaght 和 Reyes 在 2001 年写的一篇评论显示，在 2001 年初 70 多个公司的 3300 位科学家和医务人员从事组织工程 R&D，这些公司的年支出总额超过了 6 亿美元 [3]。自 1990 年以来，这个领域的投资总额超过了 35 亿美元，并且许多新的公司也加入了这一行列。其中有 16 家从事这一领域的新公司已经开始公开销售证券，募集市场资金 26 亿美元。然而直到写这本书为止，组织工程的概念已经提出大约 20 年了，全面开展研究大概也有 15 年了，组织工程依然没能提供很多用于医疗的产品，也没有太多成功的公司生产这些产品。Lysaght 和 Hazlehurst 在 2004 年发表的一篇评论中写到 [4]：

……最近，也就是 2003 年 2 月，一个持有正常怀疑态度的经济学家报道，“这是组织工程激动人心的时刻。培养人体部分器官的技术正在迅速的提高；培养人体皮肤已经成为可能，人们正在付出更大的努力来发展像心血管和整个肝脏等更加复杂的结构”(The Economist, February 1, 2003)。这样一个有益的治疗手段自然是有着广阔的市场前景的，但是一些资深专家渐渐意识到研究与现实的脱节，这一脱节很难带来一个愉快的结局。……

组织工程要想成为现实，技术知识和技能必须发展。许多研究领域对于组织工程的成功起着至关重要的作用。世界上许多组织工程研究中心致力于细胞技术的研究。这些工程化的组织可以产生于同体细胞或异体细胞。异体细胞可以在一个地方大规模地生产，而同体疗法可能导致更多服务性行业的发展，这里着重强调的是地方或区域性的细胞库（或类似机构）。也许因为这个差异，两个主要从事异体产品的大型美国公司（ATS 和 Organogenesis）在 2002 年破产。破产的主要原因之一也许是他们高估了昂贵的组织工程产品的市场而进行的过度投资。在控制成本的医疗环境条件下，只有那些既能极大提高生活质量、又可减少费用的技术才会向前发展。

在一篇评论中，Breuer 等做了如下描述 [5]：

……任何组织工程项目的最终目标都是成功的临床应用和新组织的应用。Shin'oka 等已经将这种技术用到创建组织工程化的心血管，并且为 40 多个患有复杂的先天性心脏病的孩子进行同源血管移植用做静脉管……他们用 PGA 和 经过 PLLA 强化的 ε-己内酯[P(CL/LA)]或 P(CL/LA)聚合物来构建血管移植……1999 年 5 月，Shin'oka 做了他的第一例手术。手术效果非常好，并且对这些患者进行了长期的跟踪调查。一些术后血管造影术、计算机控制〔X 线〕断层扫描术或核磁谱检测显示没有发现移植扩张和破裂，也没有组织工程自体移植并发症。尽管组织学的评估不太可能，但是通过图片的分析没有发现组织硬化和微硬化现象。Shin'oka 的结果显示了医学组织工程的临床效果和可行性。尽管 Shin'oka 和 Dohmen 等人取得了出色的结果，心脏血管组织工程技术的临床应用依然没有通过美国标准。为确保组织工程产品的 FDA 临床试验，必须建立临床前试验的标准。心血管组织工程研究的迅速发展已经远远超过了管理机构通过完善政策

来管理产品开发的能力。临床前期的研究工作可以为临床应用提供坚实的基础，对于这个前途光明的技术的理性和可靠的发展是必要的。

作为 Shin'oka 研究组的一位合作工程师，写这本书的目的是想讨论一下为什么组织工程的发展如此缓慢，以及为什么临床应用如此有限。这本书包括四章，第一章介绍了当前组织工程研究的概况，这章对那些对组织工程满怀热情但又对这一领域相对陌生的读者大有裨益。有关组织工程的动物实验和人体实验的最新进展在第二章作了描述。这也许会帮助读者理解组织工程应用的最新状况，同时也了解为什么只有小部分组织工程被应用于患者。这意味对组织工程的临床应用而言依然处于初级阶段，需要各个领域做出更多的贡献。第三章涵盖了大量的已发表的有关组织工程领域基本技术的科学论文。然而由于该领域发表论文的数量非常巨大，本书参考的论文相对来说非常有限。最后一章，也是这本书最重要的一章，主要探讨了哪些技术是阻碍组织工程临床应用的真正瓶颈，与有关当前组织工程研究文献简洁汇编的第二、第三章有着本质的不同。相比之下，第四章包含了本书作者关于发展组织工程的一些想法和建议，这些想法和建议是作者在对生物材料、药物传输、人工器官和组织工程研究的长期实验基础上所产生的。此外，由于这本书是由多位不同撰稿人所写的章节合并而成的，本书的写作风格也与其它组织工程的书籍有所不同。

作者希望本书对组织工程成为一种革命性的治疗方法，特别是对未来的受损和丧失组织的修复以及具有复杂结构新组织重建的研究，提供一个基本指导。

参 考 文 献

1. C. W. Patrick Jr, A. G. Mikos, and L. V. McIntire, Eds, *Frontiers in Tissue Engineering*, Pergamon, 1998.
2. R. Langer and J. P. Vacanti, Tissue engineering, *Science*, **260**, 920 (1993).
3. M. J. Lysaght and J. Reyes, The growth of tissue engineering, *Tissue Engineering*, **7**, 485 (2001).
4. M. J. Lysaght and A. L. Hazlehurst, Tissue engineering: The end of the beginning, *Tissue Engineering*, **10**, 309 (2004).
5. C. K. Breuer, B. A. Mettler, T. Anthony, V. L. Sales, F. J. Schoen, and J. E. Mayer, Application of tissue-engineering principles toward the development of a semilunar heart valve substitute, *Tissue Engineering*, **10**, 1725 (2004).

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（王身国　译）

Preface

Current clinical technologies, especially donor transplants and artificial organs, have been excellent life-saving and life-extending therapies to treat patients who need to reconstitute diseased or devastated organs or tissues as a result of an accident, trauma, and cancer, or to correct congenital structural anomalies. For long, most scientists and clinicians believed that damaged or lost tissues could only be replaced by organ transplantation or with totally artificial parts. Although advances in surgical techniques, immunosuppression, and postoperative care have improved survival and quality of life, there are still problems associated with the use of biological grafts, such as donor site morbidity, donor scarcity, and tissue rejection. With regard to prostheses, a variety of synthetic and natural materials have been developed for replacement of lost tissues, but the results have not always been satisfactory. For instance, there is a great concern over the long-term performance of artificial devices. Treatments for end-stage renal failure by kidney dialyzers are based solely on unphysiological driving forces and are not able to mimic active molecular transport accomplished by renal tubular cells. Silicone for breast reconstruction after surgical mastectomy or lumpectomy for treatment of breast cancer may cause foreign body reactions and infection. Autologous adipose tissues have been clinically used to regenerate adipose tissues in depressed regions in the breast, but this therapy has problems of absorption and subsequent volume loss of transplanted adipose tissues. Such serious problems remaining unsolved and the need for improved treatments have motivated research aimed at alternative approaches creating new tissues. Tissue engineering emerged as a promising alternative in which organs or tissues can be repaired, replaced, or regenerated. The tissue engineering paradigm is to isolate specific cells through a small biopsy from a patient, to grow them on a three-dimensional scaffold under precisely controlled culture conditions, to deliver the construct to the desired site in the patient's body, and to direct new tissue formation into the scaffold that can be absorbed over time.

To avoid confusion, a brief explanation will be required for the relationship among tissue engineering, regenerative medicine, cell therapy, and embryonic stem (ES) cells. In recent years, ES cells have attracted surprisingly much attention because the pluripotent cells are anticipated to be able to differentiate into any cells responsible for formation of all kinds of tissues and organs present in the body.

For instance, Parkinson's disease and insulin-dependent diabetes might be cured using ES cells. This emerging therapy is called "regenerative medicine". In some limited cases, injection of cells to patients is sufficient for the medical treatment. This is termed "cell therapy" or "cellular therapy". However, in many other cases where lost tissues or organs have three-dimensional, bulky complex structure, cell injection alone is not effective as a cure because of quick scattering of injected cells from the site of injection. In such cases, we have to provide a guiding and scaffolding framework for cells to adhere to, expand, differentiate, and produce matrices for neotissue formation. This is the principle of tissue engineering. We can say therefore that regenerative medicine involves two concepts both of which make use of cells for therapies. One is cellular therapy (no use of scaffold) and the other is tissue engineering (assisted by scaffold). Obviously, the creation of three-dimensional complex tissues starting from ES cells also needs the technology of tissue engineering, but it will be several decades before advances of cell biology enable the widespread human use of ES cells.

It is worthwhile historically reflecting on what has happened in tissue engineering. In the spring of 1987, the Engineering Directorate of the National Science Foundation (NSF) of USA held a Panel discussion focusing on future directions in bioengineering. The target research areas appeared to overlap and the Panel coined the term "tissue engineering" to consolidate their efforts. It was this panel meeting in the spring of 1987 that produced the first documented use of the term "tissue engineering". On the basis of this initial Panel discussion, a Panel meeting on Tissue Engineering was held at the NSF in October 1987 [1]. The United States gave birth to the field of tissue engineering through pioneering efforts in reparative surgery and biomaterials engineering. In 1993, Langer and Vacanti presented an overview on tissue engineering showing how this interdisciplinary field had applied the principles of engineering and the life sciences to the development of biological substitutes that restore and improve tissue function [2]. As such, the goal of tissue engineering is to create cell–scaffold constructs to direct tissue regeneration and to restore function through the delivery of living elements, which become integrated into the patient. Since then, tissue engineering has attracted many scientists and surgeons with the hope of revolutionizing methods of healthcare treatment and dramatically improving the quality of life for millions of people throughout the world. Indeed, earlier work has successfully demonstrated creation of new tissues by using cells on biodegradable polymer scaffolds.

A review article by Lysaght and Reyes in 2001 demonstrated that at the beginning of 2001, tissue engineering R&D was being pursued by 3300 scientists and support staff in more than 70 companies with a combined annual expenditure of over $600 million [3]. Furthermore, the aggregate investment in the sector since 1990 exceeded $3.5 billion and the sector witnessed the entry of many new startup firms. As many as 16 startup firms focusing on this sector reached the milestone of initial public offerings (IPOs) and had a combined market capitalization of $2.6 billion. However, until the time of writing, tissue engineering has not yet delivered many products for better healthcare nor many successful companies making them,

although the tissue engineering concepts have been around for 20 years, with serious activity for about 15 years. Lysaght and Hazlehurst wrote in a review published in 2004 [4]:

> . . . As recently as February 2003, the normally skeptical *Economist* reported, "these are exciting times for tissue engineers. The technology for growing human body parts is advancing rapidly. Already it is possible to cultivate sheets of human skin. And huge efforts are underway to develop even more complex structures, such as heart valves and whole organs such as the liver" (*The Economist*, February 1, 2003). Such highly favorable media treatment has its benefits, but research-minded professionals increasingly recognized a disconnect with the realities. And such disconnects rarely lead to happy endings. . . .

Technical knowledge and skill must develop if tissue engineering is to become a successful reality. Numerous research areas are critical for the success of tissue engineering. Many research centers of tissue engineering in the world have devoted much of their efforts to challenges in cell technologies. Engineered tissues are possibly produced from both autologous and allogeneic cells. Allogeneic products are amenable to large-scale manufacturing at single sites, while autologous therapies will likely lead to more of a service industry, with a heavy emphasis on local or regional cell banking/expansion. Probably because of this difference, two large American companies (*e.g.*, ATS and Organogenesis) focused on allogeneic products, but bankrupted in 2002. One of the major reasons for the bankruptcy may be their overinvestment in the overestimated market for their expensive tissue engineering products. In a cost-controlled healthcare environment, only those technologies capable of providing a major enhancement to quality of life and a reduction in expenditure will be driven forward.

In a review article, Breuer *et al.* described as follows [5]:

> . . . The holy grail of any tissue-engineering project would be the successful clinical application and use of the neotissue. Shin'oka *et al.* have applied the techniques used in creating a tissue-engineered heart valve to construct autologous vascular grafts for use as venous conduits in more than 40 children with varying forms of complex congenital heart disease. . . . They used a copolymer of either PGA and ε-caprolactone [P(CL/LA)] or P(CL/LA) reinforced with poly-L-lactide (PLLA) to construct their tubular grafts. . . . Shin'oka's first operation was performed in May 1999. Immediate postoperative results have been excellent, and there are now long-term follow-up results for these patients. Serial postoperative angiographic, computerized tomography, or magnetic resonance imaging examinations revealed no dilatation or rupture of grafts, and there have been no complications related to the tissue-engineered autografts. Although histological evaluation is not possible, no unwanted calcification or microcalcification has been found by current imaging studies in these patients. Shin'oka's results demonstrate the clinical utility and feasibility of tissue engineering in medicine. . . . Despite the excellent results of Shin'oka

> *et al.* and Dohmen *et al.*, the clinical application of cardiovascular tissue-engineering techniques is premature by U.S. standards. The development of standards for preclinical trials to provide justification for establishing FDA clinical investigations of tissue-engineered products is in its infancy. The rapid development of cardiovascular tissue-engineering research has far outpaced the ability of regulatory agencies to develop policies to govern product development. The completion of preclinical studies that provide a firm foundation on which to base clinical trials is essential for the rational and responsible development of this promising technology. . . .

The motivation for writing this book was to address, as a collaborative engineer of the Shin'oka team, the reason why progress in tissue engineering has been so slow, with still so limited clinical applications of engineered tissues. This book is composed of four chapters. Chapter 1 provides an overview of contemporary tissue engineering research. This chapter will be helpful to readers new to the field who are very enthusiastic about tissue engineering. The most recent advances in animal experiments and human trials associated with tissue engineering are described in Chapter 2. This may help readers to understand current activities of tissue engineering applications, but readers will also learn how small numbers of engineered tissues have been applied to patients. This means that tissue engineering is still at an early stage in terms of clinical applications and needs much more of a contribution from different fields. Chapter 3 covers a large number of scientific papers published on basic technologies related to the tissue engineering area. However, the number of papers referred to in this book had to be drastically limited because of the extraordinarily vast number of publications in this field. The last chapter, the most important in this book, is devoted to demonstrating which technologies are the real bottlenecks that retard the clinical application of tissue engineering. Chapter 4 is therefore substantially different from Chapters 2 and 3 which are a brief compilation of literature on current tissue engineering research. In contrast, Chapter 4 involves thoughts and suggestions of the author of this book for developing the engineering systems needed to produce functional engineered tissues on the basis of his long-standing experience in research, including absorbable biomaterials, drug delivery, artificial organs, and tissue engineering. This writing style discriminates this work from other tissue engineering books that mostly consist of many chapters written by different contributors.

The author wishes that this book will serve as a base for directing future research of tissue engineering toward revolutionizing healthcare, especially repair of damaged and lost tissues as well as regeneration of neotissues with complex structures.

REFERENCES

1. C.W. Patrick Jr, A.G. Mikos, and L.V. McIntire, Eds, *Frontiers in Tissue Engineering*, Pergamon, 1998.
2. R. Langer and J.P. Vacanti, Tissue engineering, *Science*, **260**, 920 (1993).
3. M.J. Lysaght and J. Reyes, The growth of tissue engineering, *Tissue Engineering*, **7**, 485 (2001).

4. M.J. Lysaght and A.L. Hazlehurst, Tissue engineering: The end of the beginning, *Tissue Engineering*, **10**, 309 (2004).
5. C.K. Breuer, B.A. Mettler, T. Anthony, V.L. Sales, F.J. Schoen, and J.E. Mayer, Application of tissue-engineering principles toward the development of a semilunar heart valve substitute, *Tissue Engineering*, **10**, 1725 (2004).

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List of Abbreviations

MATERIALS

Synthetic Polymers

PGA	poly(glycolide), poly(glycolic acid)
PLA	poly(lactide), poly(lactic acid)
PLLA	poly(L-lactide), poly(L-lactic acid)
PDLLA	poly(D,L-lactide), poly(D,L-lactic acid)
PGLA(PLGA)	glycolide-lactide copolymer(lactide-glycolide copolymer)
PCL	poly(ε-caprolactone)
P(LA/CL)	lactide-ε-caprolactone copolymer
PEG [PEO]	poly(ethylene glycol) [poly(ethylene oxide)]
PTFE	polytetrafluoroethylene
PTMC	poly(1,3-trimethylene carbonate)

Natural Polymers

HAc	hyaluronic acid or hyaluronate
CS	chondroitin sulfate
GAG	glycosaminoglycan
PHA	poly(β-hydroxyalakanoate)
FN	fibronectin
LN	laminin
FGF	fibroblast growth factor
bFGF	basic fibroblast growth factor
BMP	bone morphogenetic protein
EGF	epidermal growth factor
VEGF	vascular endothelial growth factor
TGF	transforming growth factor
KGF	keratinocyte growth factor
ALP	alkaline phosphatase
OP	osteopontin
OCN	osteocalcin
MMP	matrix metalloprotease
GFP	green fluorescent protein
EGFP	enhanced GFP
IL	interleukin
RGD	arginine-glycine-aspartic acid

Ceramics

HAp	hydroxyapatite
TCP	tricalcium phosphate

Low-molecular-weight molecules

GA	glutaraldehyde
WSC	water soluble carbodiimide
EDAC	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
NHS	N-hydroxysuccinimide

TISSUES

ECM	extracellular matrix
CNS	central nervous system
PNS	peripheral nervous system
ACL	anterior crucial ligament
SIS	small intestine submucosa

CELLS

ES	embryonic stem
MSC	mesenchymal stem cell, marrow-derived stem cell
BMSC	bone marrow-derived stem cell, bone marrow-derived mesenchymal stem cell, bone-marrow stromal cell
ADAS	adipose-derived adult stem
NSC	neural stem cell
MNC	mononuclear cell
EPC	endothelial progenitor cell
EC	endothelial cell
HUVEC	human umbilical vein endothelial cell
UC	urothelial cell

CELL CULTURE

2-D	two dimensional
3-D	three dimensional
FCS (BFS)	fetal calf serum (bovine fetus serum)
PBS	phosphate buffered solution
DMEM	Dulbecco's modified Eagle's medium
MEM	Minimal essential medium
AA	ascorbic acid
PRP	platelet-rich plasma

RWV	rotating-wall vessel
RT–PCR	reverse transcription polymerase chain reaction

MISCELLANEOUS

BSE	bovine spongiform encephalitis
PERV	porcine endogenous retrovirus
GTR	guided tissue regeneration
GBR	guided bone regeneration
MW	molecular weight