We intensively appreciate the importance of vascular requirements of tissues, the impact of hypoxia and revascularization on repair, the background of a chronic wound environment, and the role of bacterial clusters and infection. The reconstructive surgeon values the powerful role of autologous donor tissues versus the needs for allogenic tissues and allotransplantation, the induction of tolerance, and the effect of immunogenicity. For these reasons, we are perfectly positioned to analyze and investigate, and guide and lead in the further developments in tissue engineering and regenerative medicine.

## Expert Commentary

**James Chang, MD**

*Drs Vranckx and Den Hondt, highly regarded experts in tissue engineering from Belgium, have provided an excellent update on this exciting topic.*

*Plastic and reconstructive surgeons continue to face shortages of tissue after trauma, tumor resection, and/or congenital absence. While many areas of medical research have embraced tissue engineering, it is likely that reconstructive surgery applications for this strategy will be among the first to reach widespread use.*

*Tissue engineering is an interdisciplinary scientific field that combines the principles of life sciences and engineering toward the development of biological substitutes that will serve to restore, maintain, or improve tissue function. It is a nascent field, now evolving to many possible tissues. It has drawn intense academic and commercial interest because of its translational (bench-to-bedside) potential.*

*The critical challenges for applying tissue engineering to reconstructive microsurgery relate to the cells, the scaffold, and the ultimate product, the tissue. As the authors have presented, the field of tissue engineering, and the purpose of all research papers, can be divided into these three components. The authors also rightfully focus on the need for vascularization, decellularization of tissues as scaffolds, and the use of stem cells to accelerate re-seeding and proliferation.*

*The ultimate success of tissue engineering will be established when the body incorporates the new tissue, and normal structure and function are again restored. In some tissues such as bone, the structure is the function. In more complex tissues such as skeletal muscle, coordination and control of contractile forces must be re-created.*

*Tissue engineering has made rapid advances in its short span. Given the examples in this chapter: skin, urethra and bladder, bone, trachea, and the cardiovascular system, we are on the cusp of seeing this research progress translate into clinical benefits. Other tissue substitutes such as for tendon, nerve, and cartilage, will likely follow as the science and technology of tissue engineering reach translation. All of us look forward to the advances that will give us new tissues with which to reconstruct our patients.*

## REFERENCES


1. Lee AY, Mahler N, Best C, et al. Regenerative implants for cardiovascular tissue engineering. Transl Res 2014;163:321–41.
2. Langer R, Vacanti JP. Tissue engineering. Science 1993;260:920–6.
3. Vranckx JJ. Tissue engineering and gene transfer for wound repair. Thesis dissertation, KU Leuven, 2007.
4. Vranckx JJ, Yao F, Eriksson E. Gene transfer of growth factors for wound repair. In: Rovee D, Maibach H, editors. The epidermis in wound healing. Boca Raton, FL: CRC Press; 2004. p. 265–83.
5. Harrison R, St-Pierre JP, Stevens MM. Tissue engineering and regenerative medicine: a year in review. Tissue Eng 2014;20:1–16.
6. Fisher MB, Mauck RL. Tissue engineering and regenerative medicine: recent innovations and the transition to translation. Tissue Eng 2013;19:1–13.
7. Fuchs JR, Nasseri BA, Vacanti JP. Tissue engineering: a 21st century solution to surgical reconstruction. Ann Thorac Surg 2001;72:577–92.
8. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med 1971;285(21):1182–6.
9. Singer A, Clark RA. Cutaneous wound healing. N Engl J Med 1999;341:738–46.
10. Metcalfe A, Ferguson M. Harnessing wound healing and regeneration for tissue engineering. Biochem Soc Trans 2005;33:413–17.
11. Griffith LG. Emerging design principles in biomaterials and scaffolds for tissue engineering. Ann NY Acad Sci 2002;961:83–95.
12. Vranckx JJ, Den Hondt M, Delaere P. Prefabrication and prelamination strategies for complex tracheal and laryngeal defects. J Reconstr Microsurg 2014;30(3):145–52.
13. Miller JS, Stevens KR, Yang MT, et al. Rapid casting of patterned vascular networks for perfusable engineered three-dimensional tissues. Nat Mater 2003;2:265–70.
14. Gauvin R, Chen Y-C, Lee JW, et al. Microfabrication of complex porous tissue engineering scaffolds using 3D projection stereolithography. Biomaterials 2012;33:3824–34.
15. Haraguchi Y, Shimizu T, Sasagawa T, et al. Fabrication of functional three-dimensional tissues by stacking cell sheets in vitro. Nat Protoc 2012;7:850–4.
16. Gilbert TW, Sellaro TL, Badylak SF. Decellularization of tissues and organs. Biomaterials 2006;27(19):3675–83.
17. Song JJ, Guyette JP, Gilpin SE, et al. Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med 2013;19:646–8.
18. Spradling A, Drummond-Barbosa D, Kai T. Stem cells find their niche. Nature 2001;414:98–104.
19. McCulloch EA, Till JE. Perspectives on the properties of stem cells. Nat Med 2005;11(10):1026–8.
20. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–76.
21. Rolletschek A, Wobus AM. Induced human pluripotent stem cells: promises and open questions. Biol Chem 2009;390:845–9.
22. Liang L, Bickenbach JR. Somatic epidermal stem cells can produce multiple cell lineages during development. Stem Cells 2002;20:21–31.
23. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–7.
24. Jiang Y, Jahagirdar BN, Reinhardt RL, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. Nature 2002;418:41–9.
25. Barry FP, Murphy JM. Mesenchymal stem cells: clinical applications and biological characterization. Int J Biochem Cell Biol 2004;36:568–84.
26. Blau HM, Brazelton T, Weimann JM. The evolving concept of a stem cell, entity or function. Cell 2001;105:829–41.
27. Miura M, Miura Y, Padilla-Nash HM, et al. Accumulated chromosomal instability in murine bone marrow mesenchymal stem cells leads to malignant transformation. Stem Cells 2006;24:1095–103.
28. Lin Y, Weisdorf DJ, Solovey A, et al. Origins of circulating endothelial cells and endothelial outgrowth from blood. J Clin Invest 2000;105:71.
29. Yoder MC, Mead LE, Prater D, et al. Redefining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. Blood 2007;109:1801.
30. Kalka C, Masuda H, Takahashi T, et al. Transplantation of ex vivo expanded endothelial progenitor cells for therapeutic neovascularization. Proc Natl Acad Sci USA 2000;97:3422–7.
31. Hendrickx B, Verdonck K, Van den Berge S, et al. Integration of blood outgrowth endothelial cells in fibroblast sheets promotes full thickness wound healing. Stem Cells 2010;28(7):1165–77.
32. Kannan RY, Salacinski HJ, Sales K, et al. The roles of tissue engineering and vascularisation in the development of microvascular networks, a review. Biomaterials 2005;26:1857–75.

33. Cao Y, Vacanti JP, Paige KT, et al. Transplantation of chondrocytes utilizing a polymer-cell construct to produce tissue-engineered cartilage in the shape of a human ear. Plast Reconstr Surg 1997; 100(2):297–302.
34. Walles T. Tracheobronchial bio-engineering: biotechnology fulfilling unmet medical needs. Adv Drug Deliv Rev 2011;63(4–5): 367–74.
35. Nayyer LL, Patel KH, Esmaeili A, et al. Tissue engineering: revolution and challenge in auricular cartilage reconstruction. Plast Reconstr Surg 2012;129(5):1123–37.
36. Markeson D, Pleat JM, Sharpe JR, et al. Scarring, stem cells, scaffolds and skin repair. J Tissue Eng Regen Med 2015;9(6):649–68.
37. 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;194:413–28.
38. Massagé P, Vandenhof B, Vranckx JJ. Full face resurfacing of third degree burns with artificial dermis: barriers and opportunities. J Plast Reconstr Surg 2006;59:1–12.
39. Mansbridge J. Tissue-engineered skin substitutes. Exp Opin Biol Therapy 2002;2:25–34.
40. Rosso F, Marino G, Giordano A, et al. Smart materials as scaffolds for tissue engineering. J Cell Physiol 2005;203:465–70.
41. Sheridan RL, Tompkins RG. Skin substitutes in burns. Burns 1999;25:97–103.
42. Naughton GK, Mansbridge JN. Human-based tissue-engineered implants for plastic and reconstructive surgery. Clin Plast Surg 1999;26:579–86.
43. Rheinwald JG, Green H. Serial cultivation of strains of human epidermal keratinocytes: the formation of keratinizing colonies from single cells. Cell 1975;6:331–43.
44. Rheinwald JG, Green H. Formation of a keratinizing epithelium in culture by a cloned cell line derived from a teratoma. Cell 1976;6:317–30.
45. O'Connor NE, Mulliken JB, Banks-Schlegel S, et al. Grafting of burns with cultured epithelium prepared from autologous epidermal cells. Lancet 1981;1:75–8.
46. Hefton JM, Madden MR, Finkelstein JL, et al. Grafting of burn patients with allografts of cultured epidermal cells. Lancet 1983;2: 428–30.
47. Dantzer E, Braye FM. Reconstructive surgery using an artificial dermis (Integra): results with 39 grafts. Br J Plast Surg 2001;54: 659–64.
48. Hunt JP, Hunter CT, Brownstein M, et al. Host priming, not target antigen type, decides rejection rate in mice primed with MHC-II "knock-out" cultured keratinocytes. J Surg Research 1998;76: 32–6.
49. Rouabhia M. Permanent skin replacement using chimeric cultured sheets comprising xenogeneic and syngeneic keratinocytes. Transplantation 1996;61:1290–300.
50. Huang ZM, Zhang YZ, Kotaki M, et al. A review on polymer nanofibers by electrospinning and their applications in nanocomposites. Compos Sci Technol 2003;63:2223–53.
51. Powell HM, Supp DM, Boyce ST. Influence of electrospun collagen on wound contraction of engineered skin substitutes. Biomaterials 2008;29:834–43.
52. Vermeulen P, Dickens S, Degezelle K, et al. A plasma-based biomatrix mixed with endothelial progenitor cells and keratinocytes promotes matrix formation, angiogenesis, and reepithelialization in wounds. Tissue Eng Part A 2009;15(7):1533–42.
53. Dickens S, Vermeulen P, Hendrickx B, et al. Regulable VEGF165 overexpression by ex vivo expanded keratinocyte cultures promotes matrix formation, angiogenesis and healing in porcine full thickness wounds. Tissue Eng Part A 2008;14(1):19–27.
54. Vranckx JJ, Hoeller D, Velander PE, et al. Cell suspension cultures of allogenic keratinocytes are efficient carriers for ex vivo gene transfer and accelerate healing of full thickness wounds by overexpression of hEGF. Wound Rep Regen 2007;15:657–64.
55. Pham C, Greenwood J, Cleland H, et al. Bioengineered skin substitutes for the management of burns: a systematic review. Burns 2007;33(8):946–57.
56. Farnham SB, Cookson MS. Surgical complications of urinary diversion. World J Urol 2004;22:157–67.
57. Atala A, Bauer SB, Soker S, et al. Tissue-engineered autologous bladders for patients needing cystoplasty. Lancet 2006;367: 1241–6.
58. Adamowicz J, Kowalczyk T, Drewa T. Tissue engineering of urinary bladder – current state of art and future perspectives. Cent European J Urol 2013;66(2):202–6.
59. Raya-Rivera A, Esquiliano DR, Yoo JJ, et al. Tissue-engineered autologous urethras for patients who need reconstruction: an observational study. Lancet 2011;377(9772):1175–82.
60. Romagnoli G, De Luca M, Faranda F, et al. Treatment of posterior hypospadias by the autologous graft of cultured urethral epithelium. N Engl J Med 1990;323:527–30.
61. Quarto R, Mastrogiacomo M, Concedda R, et al. Repair of large bone defects with the use of autologous bone-marrow stromal cells. N Engl J Med 2001;344:385–6.
62. Warnke PH, Springer IN, Wiltfang J, et al. Growth and transplantation of a custom vacularised bone graft in a man. Lancet 2004;364: 766–70.
63. Warnke PH, Wiltfang J, Springer IN, et al. Man as living bioreactor: fate of an exogenously prepared customized tissue-engineered mandible. Biomaterials 2006;27:3163–7.
64. Delaere PR, Van Raemdonck D. The trachea: the first tissue-engineered organ? J Thorac Cardiovasc Surg 2014;147(4): 1128–32.
65. Delaere P, Vranckx JJ, Verleden G, et al. Tolerance in a vascularized tracheal allotransplant. N Engl J Med 2010;362(2):138–45.
66. Delaere PR, Vranckx JJ, Den Hondt M, et al. Tracheal allograft after withdrawal of immunosuppressive therapy. N Engl J Med 2014;370(16):1568–70.
67. Kojima K, Vacanti CA. Generation of a tissue-engineered tracheal equivalent. Biotechnol Appl Biochem 2004;39:257–62.
68. Omori K, Nakamura T, Kanemaru S, et al. Regenerative medicine of the trachea: the first human case. Ann Otol Rhinol Laryngol 2005;114(6):429–33.
69. Nakamura T, Sato T, Araki M, et al. In situ tissue engineering for tracheal reconstruction using a luminar remodeling type of artificial trachea. J Thorac Cardiovasc Surg 2009;138:811–19.
70. Sato T, Araki M, Nakajima N, et al. Biodegradable polymer coating promotes the epithelization of tissue-engineered airway prostheses. J Thorac Cardiovasc Surg 2010;139:26–31.
71. Macchiarini P, Jungebluth P, Go T, et al. Clinical transplantation of a tissue-engineered airway. Lancet 2008;372:2023–30.
72. Jungebluth P, Moll G, Baiguera S, et al. Tissue-engineered airway: a regenerative solution. Clin Pharmacol Ther 2012;91(1): 81–93.
73. Orlando G, Soker S, Stratta RJ. Organ bioengineering and regeneration as the new Holy Grail for organ transplantation. Ann Surg 2013;258:221–32.
74. Jungebluth P, Alici E, Baiguera S, et al. Trachea-bronchia transplantation with a stem-cell seeded bioartificial nanocomposite: a proof of concept study. Lancet 2011;378:1997–2004.
75. Vogel G. Trachea transplants test the limits. Science 2013;340: 266–8.
76. Elliot MJ, De Coppi P, Speggiorin S, et al. Stem cell based tissue engineered tracheal replacement in a child: a 2-year follow up study. Lancet 2012;380:994–1000.
77. Zopf DA, Hollister SJ, Nelson ME, et al. Bioresorbable airway splint created with a three-dimensional printer. N Engl J Med 2013; 368(21):2043–5.
78. Guthrie CC. End-results of arterial restitution with devitalized tissue. JAMA 1919;73:186–7.
79. Shin'oka T, Imai Y, Ikada Y. Transplantation of a tissue-engineered pulmonary artery. N Engl J Med 2001;344:532–3.
80. McAllister TN, Matruszewski M, Garrido SA, et al. Effectiveness of haemodialysis access with an autologous tissue-engineered vascular graft: a multicentre cohort study. Lancet 2009;373:1440–6.
81. Hibino N, McGillicuddy E, Matsumara G, et al. Late-term results of tissue-engineered vascular grafts in humans. J Thorac Cardiovasc Surg 2010;139:431–6.
82. Olausson M, Patil PB, Kuna VK, et al. Transplantation of an allogeneic vein bioengineered with autologous stem cells: a proof-of-concept study. Lancet 2012;380:230–7.
83. Vrtovec B, Poglajen G, Lezaic L. Effects of intracoronary CD34+ stem cell transplantation in nonischemic dilated cardiomyopathy patients: 5-year follow-up. Circ Res 2013;112(1):165–73.
84. Bolli R, Chugh AR, D'Amario D, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 2011;378:1847–57.