

# Preface

The creation of substitutes to repair damaged tissues and organs dates back to the beginning of recorded history [1]. Several ancient civilizations dabbled in tissue repair; for example, Indian physicians created primitive skin grafts as long ago as 800 BC. It has been only within the past century that surgical understanding of vessel anastomosis and aseptic surgical technique have enabled transplantation and replacement of tissues [2].

There are many techniques for harvesting natural tissue for transplant use. The “gold standard” for natural transplantable tissue is called autograft tissue. This type of tissue is transferred from one site to another in the same individual. If one is lucky enough to have a genetically identical twin, also known as a monozygotic twin, this individual can serve as a source of isograft tissue. Autograft/isograft tissue use is associated with many problems. For example, additional surgery at the “donor” site can result in complications, including infection, inflammation, and chronic pain. In addition, the quantity of material that can be harvested from the donor site is limited.

Another source of transplantable tissue is known as allograft tissue. In this case, tissue is transferred from one person to another. Over 20 different types of tissue, including cartilage, cornea, hearts, kidney, liver, lung, and pancreas, have been successfully transplanted between different individuals. Unfortunately, this type of tissue use is also associated with many difficulties. The most significant problem with allograft transplantation is providing an adequate amount of organs for all of the patients who need them. There are currently over 80,000 people on waiting lists for allograft transplantation in the United States [3]. Because of this supply limitation, more than 10,000 people have died in recent years on waiting lists for allograft organs and tissues. In addition, the body’s immune system generates acute vascular rejection and chronic rejection processes that degrade transplanted material in days, weeks, months, and years after implantation [4]. The long-term immunosuppressive therapy typically used to counter the rejection process may itself lead to tumor formation.

There is also a risk of infectious disease transmission from the allograft donor to the allograft recipient [5]. Although allograft tissue may be treated using gamma irradiation, electron beam radiation, freeze-drying, ethylene oxide, or tissue freezing methods, the risk of disease transmission persists [6]. In addition, many methods that are used to reduce disease transmission also decrease viability of the tissue.

The risks of infection after transplantation of allograft tissue are not theoretical. For example, in November 2001, a 23-year-old otherwise healthy Minnesota man died from an *Clostridium sordellii* infection after undergoing transplantation of allograft femoral condyle tissue. That Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) traced the allograft tissue to a commercial tissue bank, CryoLife, Inc., in Kennesaw, Georgia. CryoLife was ordered to recall its allograft tissue and was temporarily shut down by the FDA. The CDC then asked orthopedic surgeons to report infections associated with allograft transplantations. The CDC identified 26 allograft-related infections, 11 of which were *Clostridium septicum* or *Clostridium sordelli* infections that involved allograft tissue processed by CryoLife. It has been estimated that the risk of HIV transmission with allograft bone is one case in 1.6 million. Similarly, one case of hepatitis B transmission and three cases of hepatitis C transmission have been clinically correlated with allograft tissue transplantation. Xenografts, or grafts from animals are rare, as these grafts allow transfer of animal pathogens (bacteria, viruses, fungi, and prions) to humans.

The growing demand for tissue substitutes and the continuing limitations of natural tissue substitutes have led to the development of a field known as tissue engineering. This field was pioneered by Robert S. Langer, Joseph P. Vacanti, and Anthony Atala at the Massachusetts Institute of Technology and Harvard University. The materials used in tissue engineering include living cells, natural materials, and synthetic materials. Tissue engineered materials are created by placing living cells within scaffolding that is meant to guide cell growth, differentiation, and development. The cell-seeded structure is then placed in a bioreactor that provides oxygen and nutrients, which enables cells to multiply within the scaffold. The tissue substitute is then implanted in an environment that will permit the tissue to possess normal structure and/or exhibit normal function.

Current tissue engineering processing techniques have yet to overcome several limitations. First, cell division is not rapid and the scaffold seeding process is difficult. In addition, it is very difficult to create tissue substitutes that contain more than several cell layers because bioreactors cannot provide sufficient nutrients to thicker structures. Growth in a bioreactor usually ceases after the tissue is 100  $\mu\text{m}$  thick. These problems have severely limited the clinical use of tissue substitutes fabricated using conventional methods. As a result, only been a handful of tissue substitutes created using conventional tissue engineering methods have been approved by the FDA for use in the United States.

Several investigators have recently examined the use of rapid prototyping technologies to overcome the limitations associated with current tissue engineering processing methods. This technology was originally developed over a quarter century ago for the fabrication of prototypes of machine tools, automotive parts, and military devices. The term “rapid prototyping” is used to describe the fabrication of three-dimensional structures through additive joining of materials in a layer-by-layer manner as opposed to conventional subtractive processes. Recent studies have shown that printing techniques and other rapid prototyping methods may be used to process cells and scaffold materials in order to create patient-specific tissue substitutes. Data

obtained from magnetic resonance imaging or computed tomography of a given patient may be employed in order to create models of the injured, damaged, or missing tissue. Customized implants created using printing techniques may possess suitable features geometry, weight, and biological properties for treatment of a certain patient. Surface features may be incorporated into prostheses in order to increase diffusion of nutrients to cells on the prosthesis surface and promote desirable tissue-implant interactions. In addition, many rapid prototyping technologies can be placed near clinical facilities; specialized or dedicated fabrication environments are typically not required. The typical feature size, advantages, and disadvantages for common rapid prototyping and printing techniques are provided in Table 1.

Patients and surgeons are demanding more individualized, “patient-specific” treatments for trauma, injury, aging, and disease processes. The printing technologies described in this volume offer tremendous potential for the fabrication of tissue substitutes with appropriate mechanical and biological properties for treatment of a given patient. We anticipate that the use of printed biomaterials in medicine, surgery, and dentistry will become more significant in the next several years.

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**Table 1** Rapid prototyping and printing technologies used for additive processing of biomaterials

Technique	Feature size (μm)	Advantages	Disadvantages
Rapid prototyping robotic dispensing system (RPBOD)	400–1,000	Compatible with many materials; Biological molecules may be included	Precise control of precursor material properties essential; Freeze drying required
Robocasting	100–1,000	Compatible with many materials	Precise control of precursor material properties essential
Selective laser sintering (SLS)	500	Microporous structures may be produced; Compatible with several materials; Rapid processing rate	Precursor material must be in powder form; High processing temperatures involved; Powdery surface finish; Completed part may contain trapped powder
Precise extrusion manufacturing (PEM)	200–500	Precursor material must be in pellet form	High processing temperatures involved; Difficult to prepare structures with microscale porosity
Low-temperature deposition manufacturing (LDM)	400	Biological molecules may be included	Use of solvent required; Freeze drying required
Multi-nozzle deposition manufacturing (MDM)	400	Compatible with several materials; Biological molecules may be included; Low processing temperatures involved	Use of solvent required; Freeze drying required
TheriForm™	300	Microporous structures may be produced; Compatible with many materials; Rapid processing times	Precursor material must be in powder form; Powdery surface finish; Completed part may contain trapped powder
3D Bioplotter	250	Compatible with several biomaterials; Biological molecules may be included	Low mechanical strength; Low accuracy; Slow processing rate
3D Fiber-deposition technique	250	Precursor material must be in pellet form	High processing temperatures involved; Difficult to prepare structures with microscale porosity
Fused deposition modeling (FDM)	250	Good mechanical strength; Good control of internal microstructure; Good control of external microstructure	High processing temperatures involved; Filament precursor material; Difficult to prepare structures with microscale porosity
Stereolithography apparatus (SLA)	250	Compatible with many materials; Rapid processing rate	Material must be biocompatible and capable of photopolymerization; Requires use of ultraviolet light

3-dimensional printing™	200	Compatible with several materials; Microporous structures may be produced; Water may be used as a binder; Rapid processing rate	Precursor material must be in powder form; Completed part may contain trapped powder; Powdery surface finish; Post processing steps usually required; Low mechanical strength;
3-D inkjet printer	180	Compatible with several materials; Good control of internal microstructure; Good control of external microstructure	Multiple processing steps necessary
Two photon polymerization	<1	Control of external and internal morphology; Requires use of infrared light	Material must be biocompatible and capable of photopolymerization
Modified from "Rapid Prototyping of Artificial Tissues and Medical Devices," Boland, Thomas; Ovsianikov, Aleksandr; Chickov, Boris N.; Doraiswamy, Anand; Narayan, Roger J.; Wai Yee Yeong; Kah Fai Chua, Advanced Materials & Processes, 165(4):51-53, 2007.			

Printed Biomaterials

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