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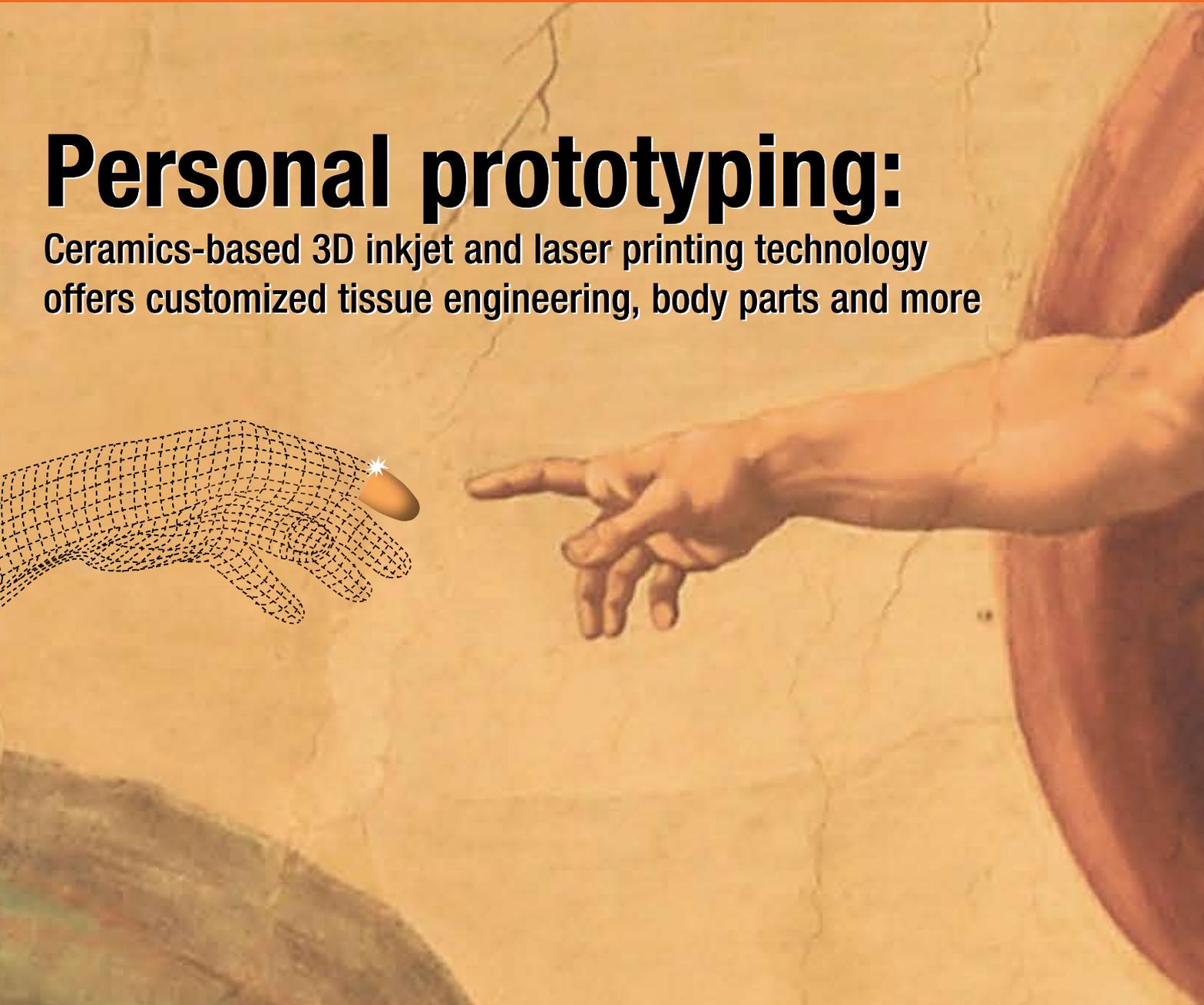
bulletin

emerging ceramics & glass technology

MAY 2009

Personal prototyping:

Ceramics-based 3D inkjet and laser printing technology offers customized tissue engineering, body parts and more



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Personal prototyping:

Ceramics-based 3D inkjet and laser printing technology offers customized tissue engineering, body parts and more

Joanna Marshall

Introduction

Just a few decades ago, the diagnosis of a condition such as osteosarcoma would have left a patient with only one option: amputation. Today, surgeons can take advantage of the amazing advancements in biometallurgy that give patients the chance to retain a limb through the use of surgical implants.

However, these metal prostheses – for example, to replace a femur bone – would take months to produce, are extremely heavy and are astronomically expensive. More importantly, these prostheses are not accurate replicas of the original bone, leading to a high incidence of postoperative complications.

Researchers like Roger Narayan, a bright, young MD and Ph.D. who conducts research in the department of biomedical engineering at the University of North Carolina–Chapel Hill are hoping to improve patient’s prospects by incorporating innovative materials and cutting-edge laser technologies to produce near perfect replicas of the body’s own structures in a remarkably short amount of time.

Narayan, with the help of his colleagues, seems to have a gift for harnessing state-of-the-art technology and using it to improve time-tested but imperfect procedures – such as the inkjet and laser-printing technologies outlined in the following article

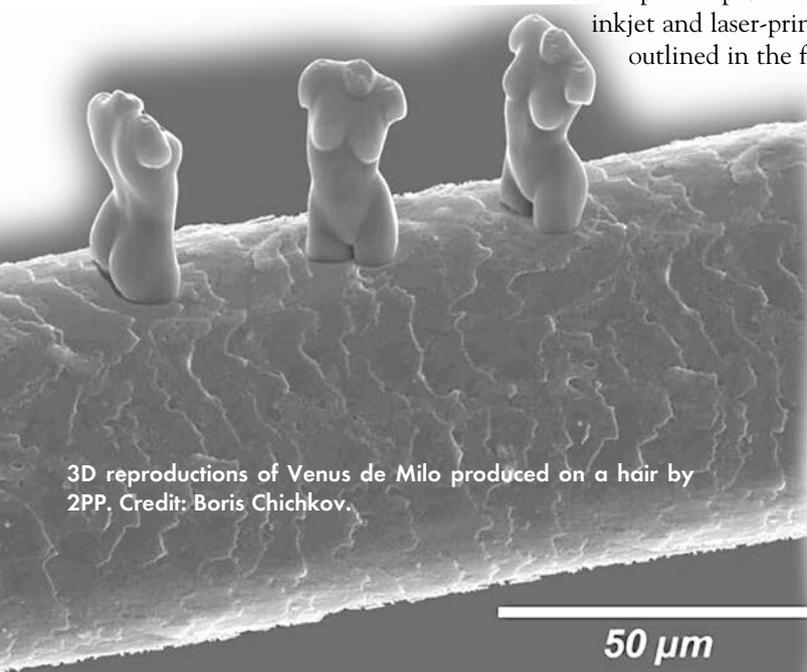
– to make a more precise version of the traditional immunoassay. He has found real-world uses for his 3D laser technology in everything from body parts to bioadhesives to nanoneedles (capable of penetrating the skin to deliver drugs or collect blood with virtually no pain).

Narayan, in conjunction with cohorts, such as Boris Chichkov at Laser Zentrum Hannover, specializes in the study of a technique known as rapid prototyping. Their rapid-prototyping technique is “two-photon polymerization,” used in combination with a novel hybrid polymer, to provide a mechanism by which nearly any computerized image or model can be translated into a 3D object.

In the case of the total femur replacement, a preoperative CT image of a patient’s bone would be “printed” into a glass-like powder that hardens as the laser hits it. This process of additive fabrication – one layer at a time – eventually results in a complete, near-exact replica of the original femur made of a heat resistant, durable and mechanically sound material that mimics the actual bone far better than metallic materials.

Additionally, a prototype that may have previously taken months to construct can now be fabricated in a matter of hours. This application alone would be reason enough to give rapid prototyping a close look. However, the implications of an extremely-high-resolution biomimetic fabrication system span far beyond prostheses.

High-resolution production is the key to accurately reproducing any body part, and it is an ability that 2PP does better than any other prototyping system. This high resolution is due to the a special laser’s ability to make one molecule to harden, yet leave those a few molecules away in their powdered form. This is a task accomplished using a “femtosecond” laser system. The femtosecond laser works on the principle that the shorter a laser pulse is, the higher the power it can emit. Chichkov described the femtosecond laser’s



3D reproductions of Venus de Milo produced on a hair by 2PP. Credit: Boris Chichkov.

Personal prototyping

power most concisely by writing that “the total power of every power station in Germany combined, including both solar and wind are expected to approach 120 gigawatts by the year 2010 ... The peak power of the modern laser can exceed 200 gigawatts.”

So, for one-quadrillionth of a second, a beam containing more energy that it takes to run the most populous country in the European Union is focused (with an error of less than 100 nm) upon an atom, with the intention of having it absorb two photons nearly simultaneously. This process of near-simultaneous two-photon absorption allows the atom to achieve a unique excitation state where polymerization can occur. Conversely, in the areas (or in this case, molecules) where the laser is not focused, the polymerizing chemical reaction is not initiated and no polymerization occurs.

The end-result of this is visible in Chichkov’s amazing creation of several identical replicas of the Venus de Milo

neatly arranged upon a single human hair.

One promising application of this technique is the creation of nanoscaffolds to support tissue regeneration. The nanoscaffold’s ability to support tissue growth is dependant on qualities such as pore size within the scaffold, density, longevity and consistent reproducibility. Although each of these characteristics is vitally important, they change with the type of tissue that is being grown. Therefore, each nanoscaffold created by 2PP could be customized to the ideal growth conditions of a given cell type.

Current research is centered on investigating the possibility of seeding these scaffolds with patient-derived epithelial or stem cells, and providing growth factors and differentiation signals to induce regeneration of tissue. As the cells divide they remain attached to the scaffold and it supports their initial 3D conformation while its open structure enables blood circulation, diffusion

of nutrients and neovascularization. The scaffold functions as a provisional matrix to support the cells as they grow into their proper conformation.

The techniques discussed below by Narayan could soon enable researchers to map and create an image of a blood vessel, prototype a nanoscaffold replica (seeded with vascular endothelium and supplemented with various growth factors) and eventually transplant the newly formed blood vessel into the patient.

And, if it can be done with blood vessels, it is easy to imagine what else might be possible.

Joanna Marshall is a doctoral student at the Ohio State University College of Medicine. Her research focuses on the molecular mechanisms of human disease. She began her research at Nationwide Children’s Hospital in Columbus but is now a part of OSU’s Center for Microbial Interface Biology where she is currently studying drug development for the treatment of malaria.

Two Photon Polymerization: An Emerging Method for Rapid Prototyping of Ceramic–Polymer Hybrid Materials for Medical Applications

Roger Narayan

Rapid prototyping is a manufacturing technique that has developed over the past quarter century for additive layer-by-layer fabrication of three-dimensional structures. In recent work, researchers at the University of North Carolina and Laser Zentrum Hannover have exam-

ined rapid prototyping of ceramic–polymer hybrid materials to create microscale patient-specific medical prostheses, microscale medical devices and scaffolds for tissue engineering.

Scientists and technicians originally created rapid prototyping more than a quarter century ago for fabrication of machine-tool prototypes using computer-aided design models. This technique allows for fabrication of 3D structures by selectively connecting solid, liquid or powder materials in a layer-by-layer manner. Numerous rapid-prototyping

techniques, including fused deposition modeling, stereolithography, laser-direct writing and inkjet printing, have been used to process materials for biosensor, drug delivery, tissue engineering and other medical applications.

Several factors are involved in selection of an appropriate rapid-prototyping technique for a given application, including material selection, resolution, fabrication time and cost. For example, there is a trade-off between feature resolution and fabrication time. Because structures fabricated by rapid prototyping are built in a layer-by-layer manner, a reduction in the size of the features requires an increase in the number of build layers. Instead of using rapid prototyping to directly fabricate a medical device, rapid prototyping can be used to create a mold. Molding

allows one to reproduce the structure in larger numbers or fabricate structures out of materials that are incompatible with the rapid-prototyping technique.

Rapid prototyping allows direct fabrication of structures with complex or unique architectures.¹⁻¹⁰ For example, patient-specific medical devices can be prepared using data acquired from computed tomography, magnetic resonance imaging, or other imaging techniques.¹⁴ Custom implants may be created, which possess appropriate geometry and size for a given patient. These implants can be designed with pores or other features in order to promote tissue-implant integration. Rapid prototyping also can be used to assist with surgical planning.⁵ Rapid prototyping allows a surgeon to physically examine and perform studies on structures relevant to a given operation.

A number of patient-specific prostheses have been developed using rapid prototyping techniques. For example, Singare et al.^{6,7} fabricated a titanium jaw prosthesis using stereolithography and molding processes; this prosthesis was subsequently implanted in a human patient. Subburaj et al. fabricated a patient-specific prosthetic ear by fused deposition modeling and molding for clinical use.⁸ Stereolithography also has been used to directly fabricate small bones with complex structures, including the scaphoid and lunate bones in the wrist.⁹

Several rapid-prototyping techniques rely on thermal changes of extruded material. For example, fused deposition modeling involves extrusion of melted materials (e.g., polyesters) into thin filaments, which subsequently join together on cooling. Filament thickness may be varied between 0.05 mm and 0.70 mm. Filament materials include polymers, such as polyethylene and polypropylene. Metals and ceramics also have been used.² Structures prepared using fused deposition modeling typically exhibit poor mechanical properties and high porosities.

Other rapid prototyping techniques involve selectively melting thin layers of powders. For example, in selective

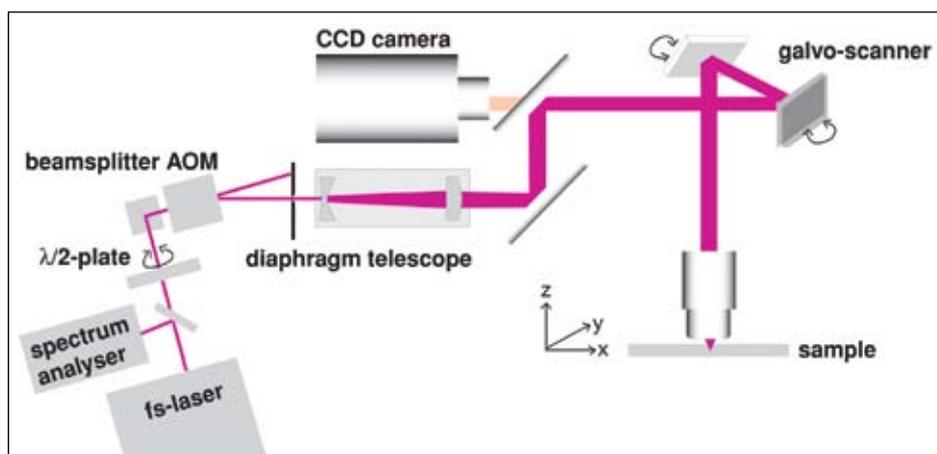


Figure 1. Schematic diagram of 2PP system. Femtosecond laser pulses are aimed at photo sensitive resin. The structures is fabricated by moving the the laser focus in the xy plane using a galvo scanner, while the sample stage moves in the z direction.

laser sintering, a powder is brought to a temperature near its melting point. A small increase in temperature produced by the laser causes localized melting. This technique has been utilized to process polymers, metal, and ceramics into complex porous matrices that can be used to repair bone defects. However, materials processed using selective laser sintering commonly exhibit uneven surface roughness properties and high porosities. In addition, only a limited number of materials are compatible with this technique.⁴

One of the disadvantages of fused deposition modeling and selective laser sintering is that relatively high operating temperatures (above melting temperature of the material) are required. Proteins can be denatured and other biological molecules can be altered at these high temperatures. Low-temperature deposition manufacturing involves freezing of a liquid precursor. The frozen pattern is subsequently freeze-dried, which serves to preserve the pattern under typical atmospheric conditions. One of the benefits of LDM is that this technique does not alter the structure and activity of biological materials.^{11,12}

3D printing involves layer-by-layer joining of material in powder form. Many ceramics and polymers (e.g., poly(glycolic acid)) have been processed using this technique. An inkjet printer deposits an adhesive or a

binder (e.g., chloroform for polymers), which serves to selectively join the powder together. The Envisiontec 3D Bioplotter system involves patterning the material of interest into a bath with similar density. Because the bath is of the same density as the patterned material, the structure is suspended in the bath and needs no structural supports.¹³ A wide variety of materials are compatible with the 3D Bioplotter technique.^{10,14}

Inkjet printing is able to pattern cells, nutrients, growth factors and scaffold materials into 3D tissue substitutes. This technique involves forcing fluid out of the nozzle using heat (thermal inkjet printing) or mechanical vibrations of a lead zirconate titanate transducer (piezoelectric inkjet printing). Inkjet printing may be used to pattern materials with features as small as 30 μm . Several factors, including ink viscosity, surface tension and droplet size determine resolution of the inkjet-processed pattern.

Stereolithography involves polymerization of resins that contain photoinitiator molecules and monomers upon exposure to ultraviolet laser radiation. In this technique, a tray is submerged into a bath containing monomers and photoinitiator molecules. Excitation of the photoinitiator molecules on ultraviolet light exposure leads to crosslinking of the monomer. The laser selectively polymerizes the liquid resin to

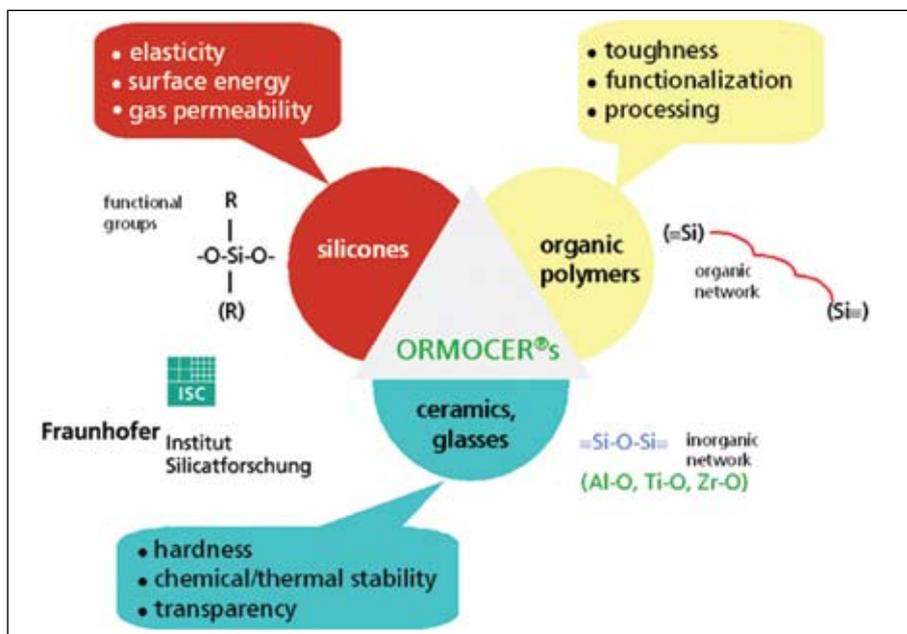


Figure 2. The 2PP system uses special formulations of Ormocer ceramic-hybrid materials to tailor the properties of the finished prototype.

generate a layer of solidified material. The table is subsequently lowered and another layer is selectively cured. This process is repeated until the desired three-dimensional structure is obtained. The minimum layer thickness is limited by the curing depth, which is dependent on the material and laser energy.² Ceramics or metals also can be added to the photocurable resin.¹⁵

Finding the right materials

We have used a unique form of stereolithography, two-photon polymerization, to create microstructured medical devices, patient-specific medical prostheses and scaffolds for tissue engineering (Figure 1). In 2PP, excitation of photoinitiator molecules is induced by spatial and temporal overlap of photons from a femtosecond laser.¹⁶ A so-called virtual state is created for several femtoseconds after nearly simultaneous absorption of two photons. Electronic excitation by two nearly simultaneous photons is comparable to electronic excitation by a single photon with a higher energy. This process displays a quadratic dependence on the incident intensity, such that negligible absorption takes place except in the vicinity of the focal volume. Polymerization by free radicals occurs in the vicinity of

the focal volumes. By moving the laser focus, we have been able to achieve the direct writing of 3D structures. We can also tune the resolution by changing the size of the numerical aperture. 2PP has the capability of achieving resolutions less than 100 nm.¹⁷

One class of materials that is compatible with 2PP is Ormocer (organically modified ceramic) materials (Figure 2). These inorganic–organic hybrid materials are created by sol–gel methods. Ormocer materials were originally developed by the Fraunhofer Institute (Fraunhofer Institut für Silicatforschung, Würzburg, Germany). The ceramic components crosslink to form a Si–O–Si network by condensation and controlled hydrolysis, and the polymeric components crosslink by photo, thermal or redox processes. A three-dimensional network is formed by crosslinking of organic and inorganic components, which prevents separation of the material.³

Ormocer materials exhibit outstanding chemical and thermal stability. They remain stable up to 350 C in an oxygen atmosphere and 415°C in a nitrogen atmosphere.¹⁸ Moreover, the mechanical properties of Ormocer materials are available in a large variety of formulations. As a result, the

mechanical properties of Ormocer materials can be tailored for a given medical application. For example, the Young’s modulus values for Ormocer materials can be varied between those of ceramics and those of polymers by modifying several parameters, including filler concentration, spacer length connecting the organic and inorganic crosslinking sites, amount of organic network modifying elements and amount of inorganic network-modifying elements.¹⁸

Many materials prepared by sol–gel processing demonstrate a large amount of shrinkage during curing, which can lead to cracks or other defects. Ormocer materials exhibit low amounts of shrinkage because of the presence of a strong inorganic network. Furthermore, fillers can be used to minimize shrinkage. In-vitro studies suggest that Ormocer materials exhibit good compatibility with cells.^{19,20} Due to their excellent biological, chemical, and mechanical properties, Ormocer materials are currently approved for use as dental resins in the United States and Europe.

The benefits of 2PP

2PP provides several advantages over chemical isotropic etching, injection molding, reactive ion etching, surface micromachining, bulk micromachining, micromolding, lithography-electroforming replication and other conventional processes for scalable production of medical devices. First, raw materials needed to prepare Ormocer materials are widely available and inexpensive. Second, the 2PP process can be set up in a conventional “dirty” manufacturing environment. Third, Ormocer materials have already gained widespread acceptance in Europe and the United States for use in dentistry. Finally, two photon polymerization of Ormocer microscale medical devices is a rapid single-step process, as opposed to other laborious multiple-step techniques.

Recent studies by researchers at the University of North Carolina and Laser Zentrum Hannover shows that 2PP may be used for rapid prototyping of medical devices, prostheses and scaffolds for

tissue engineering with microscale features that are difficult to achieve with conventional fabrication methods.

This technique has been used to fabricate total ossicular prostheses for treatment of hearing loss. The malleus, incus and stapes are small bones in the middle ear that serve to transmit sounds from the tympanic membrane to the inner ear. Diseases of the middle ear, including tympanosclerosis and otosclerosis, may result in fixation or damage of the ossicles. The most commonly used material for restoring sound conduction in the middle ear is the patient's own incus bone. However, patients suffering from chronic middle ear disease may not have tissue available for use. Ossicular replacement prostheses must undergo small-scale movement between the tympanic membrane and the inner ear as well as appropriate cell compatibility.

Mass-produced implant designs do not take individual patient anatomy (e.g., anatomical alterations because of middle-ear disease) into account. Figure 3 is an optical micrograph of a total ossicular replacement prosthesis with a head diameter of 4 mm, shaft diameter of 2 mm and length of 6 mm that was fabricated using 2PP.²¹ The prosthesis was implanted and removed from the middle ear in a cadaver. Conelike microscale features (Figure 4) were incorporated into the implant design to



Figure 3. Placement of a 2PP-made Ormocer total ossicular prosthesis into a cadaver head. The Ormocer ossicular replacement prosthesis lies against the posterior canal wall.

facilitate cell–implant interaction and minimize tympanic membrane perforation. Other design features, including head geometry, footplate geometry and weight also can be optimized to align and minimize rotation of the prosthesis.

Two photon polymerization of ceramic–polymer hybrid materials also has been used to create scaffolds for

tissue engineering (Figure 5).¹⁹ The demand for substitutes for damaged or diseased tissues has led to the growth of tissue engineering. Tissue engineering is a technology for replacing damaged or diseased tissues, which involves placing cells within 3D scaffolds that are fashioned out of ceramics, polymers or natural materials.¹⁰ The scaffold mate-

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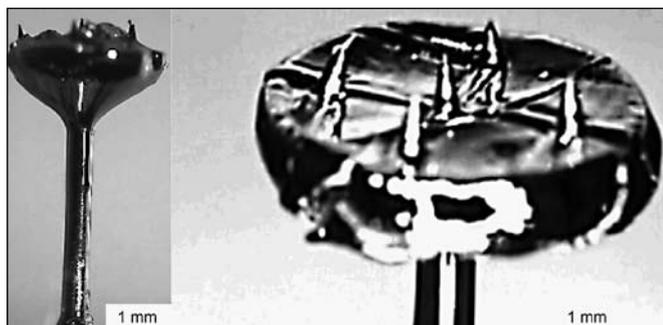


Figure 4. Grasping microscale cone structures have been added to 2PP total ossicular replacement prosthesis.

rial is seeded with cells and placed into a bioreactor to foster cell growth and differentiation. The cell-seeded scaffold is then implanted into the body.

One of the greatest challenges of tissue engineering is nutrient transport. In large scaffolds, cell viability is impaired as a result of limited access to nutrients. Ormocer materials support the growth of several cell types, including neuroblastlike cells and human epidermal keratinocytes.¹⁹⁻²¹ These results suggest that Ormocer materials do not impair cell viability or cell growth, and tissue engineering scaffolds fabricated using 2PP support cell attachment.

Microfine needles

2PP may also be used to fabricate microneedles for transdermal

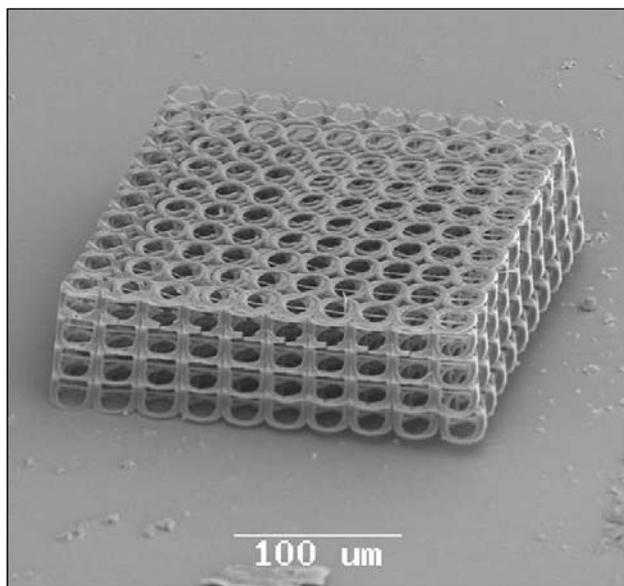


Figure 5. High porosity Ormocer tissue-engineering scaffold fabricated using 2PP. These scaffolds can be seeded with cells and engineered to promote cell growth.

drug delivery. Protein- and nucleic acid-based drugs and vaccines for cancer, diabetes and other chronic diseases recently have been developed. However, these agents cannot be delivered using pills or other oral

delivery methods, because the liver may metabolized them before reaching systemic circulation. These agents can be administered intravenously using hypodermic needles. Administration of drugs using hypodermic needles involves pain to the patient and tissue damage at the injection site. One new method for delivery of drugs and vaccines involves the use of microneedles, which are miniaturized hypodermic needles that have at least one dimension less than 500 μm .³ These devices penetrate the outer layers of the epidermis, which typically prevents the transport of many agents through the skin.

Microneedles do not interact with nerve endings, which are located in a deeper layer of the skin known as the dermis.²²⁻²⁵ A scanning electron micro-

graph of a microneedle array created by 2PP of Ormocer materials is shown in Figure 6. Microneedle arrays can be used to provide drug delivery at higher rates than individual microneedles. Arrays of in-plane and out-of-plane hollow microneedles with various aspect ratios also have been fabricated using 2PP. In compression load testing studies, Ormocer microneedle arrays penetrated cadaveric porcine adipose tissue without fracture.

A fine future

The medical and research community is developing complex tools for diagnosis and treatment of medical conditions. Soon, patient-specific prostheses, drug delivery devices and artificial tissues will become routine components of medical care. 2PP and other rapid-prototyping techniques provide capabilities for fabrication of patient-specific devices, microscale medical devices and complex tissue-engineering scaffolds. These techniques are capable of producing medical microdevices with a larger range of sizes, shapes and materials than conventional microfabrication techniques. We anticipate that rapid prototyping of medical devices will be translated into the medical device industry and the clinic in the coming years. ■

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Figure 6. Ormocer microneedle array fabricated using 2PP. Arrays such as this can provide painless drug delivery and patient testing.

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