

# Printing organs cell-by-cell

*3-D printing is growing in popularity, but how should we regulate the application of this new technology to health care?*

Howard Wolinsky

Welcome to the body shop, where machines are busy constructing new organs, one cell at a time. 3-D bioprinters, cousins to the common inkjet printer, squirt cells into a scaffold, printing and nurturing an organ until it can be transplanted into a patient. 3-D bioprinting<sup>†</sup> might sound like science fiction, but the technology is already in the early stages of development and use. It builds on experience and advances made in bioengineering to enable the more efficient and cheaper production of tissues, organs, and body parts. However, if it goes mainstream, 3-D bioprinting is likely to raise challenging legal and ethical issues, as well as to come up against regulatory hurdles.

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This new focus on the potential benefits and risks of 3-D bioprinting comes as a result of the increasing attention being paid to the new technology in the press. Last year, for example, researchers at Weill Cornell Medical College in New York, USA, reported that they had printed and grown a replacement ear that could be used for reconstructive surgery on children born with malformed outer ears (<http://www.news.cornell.edu/stories/2013/02/bioengineers-physicians-3-d-print-ears-look-act-real>). In Ann Arbor, researchers at the University of Michigan’s C.S. Mott Children’s Hospital

reported last year that in a medical first they had used a 3-D printer to produce a splint to treat the trachea and bronchus of a child with tracheobronchomalacia, which causes deadly breathing problems (<http://www.uofmhealth.org/news/archive/201305/baby’s-life-saved-groundbreaking-3d-printed-device>). These and other stories—both successful and tragic—are creating a high profile for bioprinting.

Bioprinting replacement parts for the human body expands upon techniques pioneered by bioengineers: growing new skin from a patient’s own body to replace skin lost to severe burns, for instance, or creating tubular structures such as blood vessels, urethras or windpipes, and hollow organs, such as the bladder and stomach. Bioengineers have also been making progress in growing specific tissues for solid organs such as heart muscle or liver tissue.

In the meantime, bioprinting—the cell-by-cell construction of organs—could further advance the field and become a standardized method to generate human tissue. According to bioengineer and urologist Anthony Atala, Director of the Wake Forest Institute for Regenerative Medicine in Winston-Salem, NC, USA, the technology enables researchers to step up their efforts from artisanal to industrial. “Bioprinting allows you to scale up the technology so you can make many [cells] at the same time in an automated manner instead of by hand. And it allows you better reproducibility because it’s so computer driven, and therefore, you don’t have the variance”, he said. Atala has been bioengineering organs for more than 20 years and has worked with

3-D bioprinting as a tool during the past decade.

Darryl D’Lima, a bioengineer and orthopedic surgeon at the Scripps Research Institute in La Jolla, CA, USA, said that skin and cartilage are low-hanging fruit for this approach. “The technical challenges for the most part have been solved. The hurdles are in my opinion just regulatory”, he said of his work on artificial cartilage to be used in knee surgery. However, printing complex organs is still some way off. “Bioprinted livers and kidneys may actually save lives, but technically it is so challenging that the technology may be 10–20 years away”, D’Lima explained. “If you’re printing a kidney, you have to hook it up not only to the blood supply, but also to the plumbing for the urinary system. If you’re printing the heart, you have to print not only the tissue, but also the electrical conducting portions of the heart”.

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In his bioengineering approach, Atala said he removes a very small piece of tissue from the patient, less than half the size of a postage stamp, from which cells are scraped off, seeded in an appropriately shaped 3-D mold, and then incubated. “Think of it as making a layer cake”, Atala explained. “Then you place this scaffold with the cells in an incubator which is an oven-like device that has the same conditions as the human body: 37 degrees centigrade, 95% oxygen.

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<sup>†</sup>Correction added on 15 July 2014 after first online publication: “The technology” was changed to “3-D bioprinting”.

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The ultimate goal for bioengineering—and now bioprinting—is to make whole solid organs from scratch, but this still is not feasible. Until then, many researchers think that tissue patches and partial replacements may be enough to restore organ function. One strategy to achieve this would be the so-called cassette replacement. After all, most organs do not have to work at full steam all the time; failures typically do not affect the body until about 90% of function is lost. "You don't even need one kidney", Atala explained. "So if you have above one finger [of kidney tissue] rolled up, you get yourself out of dialysis. We're creating these cartridges or cassettes that we can implant and can boost your organ functionality".

This brave new world of bioengineering and bioprinting, however, is fraught with potential regulatory and ethical problems. Bioprinting is in many ways a special application of the broader field of 3-D printing of physical objects to make replacement parts for all kinds of consumer and industrial goods. Bioprinters themselves are actually modified inkjet printers, as the range of sizes of ink globules and human cells are roughly the same: between 8 and 100 microns. In fact, D'Lima noted that he spent some time persuading the computer and printer manufacturer, Hewlett-Packard, to provide his lab with a printer on which virtually all parameters could be modified, so he can better control the size of the droplets.

Today, many libraries, schools, shops, and museums are exploring "regular" 3-D printing with their patrons. The Smithsonian, for example, offers a download of President Abraham Lincoln's life mask (<http://3d.si.edu/>). Conventional 3-D printing has been touted as a means of democratizing manufacturing, one layer at a time. Hobbyists buy or assemble 3-D printers for a few hundred dollars and create and share files of

printable objects on the Internet. The files for the "Liberator" handgun, designed and made available for free by the non-profit digital publisher and 3-D R&D firm Defense Distributed, is perhaps the best-known example. The Liberator triggered an intense debate about the US Constitution's First Amendment on free speech and publishing rights, and about the Second Amendment, which many interpret as the right to own a gun. The US Department of State eventually put a stop to the free distribution of the Liberator plans, maintaining the blueprints violated its International Traffic in Arms Regulations.

Even for more mundane things, copyright, patent, and trademark holders are becoming concerned about the sharing of plans for commercial parts. Gartner Inc, a market research group, forecasts that by 2018, 3-D printing will result in the loss of at least US \$100 billion per year in intellectual property globally. "The very factors that foster innovation—crowdsourcing, R&D pooling and funding of start-ups—coupled with shorter product life cycles, provide a fertile ground for intellectual property theft using 3-D printers", according to Peter Basiliere, Gartner's research director, author of *Predicts 2014: 3D Printing at the Infection Point* (<https://www.gartner.com/doc/2631234>).

Julie Nichols Matthews, a partner at the law firm Edwards Wildman Palmer LLP in Chicago, IL, USA, who specializes in intellectual property (IP) and copyright law, has been following developments in the 3-D printing of commercial objects. "There are questions as to whether the technology will become ubiquitous and how it will affect manufacturers of products that can be scanned, 3-D printed, and easily distributed and sold without authorization". She added that the same concerns could impact 3-D bioprinting. "Inventors of novel bioprinted materials and devices likely have significant concerns about piracy, quality control and unauthorized products, so it will be critical for them to actively pursue patent protection".

So far, D'Lima noted that IP theft has not been an issue for bioprinting, but he conceded that it might become a problem. He said that file formats generally are customized to hardware and not likely to be pirated. "We write our own code to control the printheads and the motion of the controller. If anyone gets access to our files, they will also need the exact same hardware for everything to work. At the moment, the hardware is the challenge rather than the file

format", he explained, adding that, "[i]f someone comes up with a successful blueprint of a very difficult organ, that might be worth protecting".

As the example of the Liberator handgun demonstrates, there is also potential for abuse. "What happens when complex enhanced organs involving non-human cells are made? Who will control the ability to produce them? Who will ensure the quality of the resulting organs?" Basiliere asked. Ikhlaq Sidhu, founding chief scientist at the Coleman Fung Institute for Engineering Leadership at the University of California, Berkeley, USA, made a similar point: "Every time we develop some technology that is powerful, we introduce power into the hands of people who didn't have that power before. And then it takes us some time to catch up with what are the rules that you use to govern what people can do with that power", he said. "The power didn't exist before, and you never really had the questions. There will be people who will figure out the limits of this and what you can do with it. And because you can do it doesn't mean you should do it. And that's a question that has to be resolved, after the fact".

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Gabor Forgacs, scientific founder of the bioprinting company Organovo Inc (San Diego, CA, USA) and a bioprinting pioneer from the University of Missouri (Columbia, MO, USA), explained that it is more difficult to bioprint tissue than inanimate objects, but he has no doubt that people will try: "There are numerous examples from the history of science and technology that if something was possible to do, somebody did it. Sometimes it was positive and sometimes it was negative", he said. "And still it was done".

Atala agreed that all technologies have the potential to be abused. "That's where regulation is important. And ethical debate is important, always. We take that very seriously", he said. "You want to make sure that the trials are done correctly and also make

sure that the technologies are used adequately and appropriately". For that reason, regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency are expected to play a key role in the development of bioprinting technologies.

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Thomas Boland, at the University of Texas at El Paso and co-founder and chief science officer at TeVido BioDevices, which is working on custom bioprinted implants and grafts for breast-cancer patients made from their own fat cells, thinks that regulatory agencies are not yet ready to deal with bioprinting: "The FDA is struggling with this. Nobody yet knows how to deal with this. Regulation probably will develop a device at a time, maybe simpler organs or skin, maybe adipose will go first before they move onto more complex organs", he said. Forgacs also said that regulators are not yet knowledgeable about bioprinting: "If you go to the FDA and you say, "Hey, I am building functional tissues by bioprinting," they will have no clue what that is", he said. "As with everything new, they will really have to sit down, scratch their heads, and then come up with something. I think there has to be something spectacular for the FDA to really pay attention to this, and I don't think at this point they really do".

Forgacs hopes that Organovo's bioprinted liver patch for drug toxicity testing will eventually attract the attention of the regulator. If bioprinted liver patches are predictive for drug toxicity, it could result in major savings in time and money in developing new drugs. "The FDA will come in big time when we get to the point that we will start thinking about altogether eliminating the animal trials. Because if this technology works, why do we need the animal trials? Why not just start with more and more refined and anatomically correct little liver tissues or kidney tissues or whatever, and forget about animal trials altogether. And that's when the FDA's role will become critical", he said.

Sharon Presnell, chief technology officer at Organovo, said that the ways in which bioprinting will change how new drugs are

developed will impact regulation. For the first time, she said, researchers will test new medicines on living human tissues before testing them on humans, and this will help in the move away from animal models, as promoted by the FDA and the European Medicines Agency, addressing protest by animal rights activists. However, it will also permit researchers to obtain more accurate forecasts of outcomes in humans. "Time will tell if 3-D human systems that are being developed can at least partially displace the animal models. That's going to be driven by data, over time", she said.

David Rosen, head of the Life Sciences Industry Team and FDA practice at the global law firm Foley & Lardner LLP, who worked for 15 years at the FDA, said bioprinting, especially whole organs, poses new regulatory issues that are different from traditional medical devices and pharmaceuticals. "Is it just tissue, or is it a drug or device? FDA is challenged in evaluating the safety and efficacy of a much more complex product that's multifunctional, operating as a drug and a device, as it doesn't fall into any of the traditional frameworks they've developed", he explained. An FDA spokeswoman declined comment because bioprinting "is still in the research stage".

Other potential abuses of bioprinting are also conceivable, notably in sports. "There is a lot of money involved. There is much more money involved for performance enhancement than there is for medical treatment", D'Lima, who is a consultant to the World Anti-Doping Agency on the use of stem cells for doping, said. "We're talking about people who train to the point of exhaustion, to the point of injury. Their risk-benefit ratio is completely different from what average people would accept". D'Lima also mentioned a conference on computers and art that he attended where an artist described his plans to bioprint human tissue in art: "This was pure art. He wanted the tissue to be living. So it's like living sculpture but made with themselves. Where do you draw the line between research for science and using human tissue for art?"

Nancy King, Co-Director of the Center for Bioethics, Health, & Society at Wake Forest, who works with Atala and his bioprinting programme, added that bioprinting potentially poses a far bigger ethical issue: social justice—whether new therapies will be available to all patients or just to wealthy people

who can afford them. She also pointed out that bioprinting organs could blur the line between treatment and prevention; namely, whether whole organs need to be replaced or whether cartridges of bioprinted tissue would suffice to boost their function. "You might not know that your kidneys are really failing until you start feeling bad, when you've lost 80 or 90% of function. But when you find that out, do you need a whole replacement or can you just get this cartridge, and can that bring you back over the threshold?" King explained. "And what if we all start having comprehensive examinations every year because these regenerative techniques have gotten so good? Then you might get a "preventive" intervention like this, which is a lot easier than going on dialysis and a lot easier than getting a kidney transplant". King argued that there might be a need to put limits on providing organ enhancements. "How many organ replacements are appropriate before you've extended life so much that we've changed the trajectory of human life?" she asked.

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Andrew Hessel, a synthetic biologist and researcher at Autodesk Inc, a 3-D design software company, said that technology always has upsides and downsides, but things get tricky for bioprinting because it could involve organisms that replicate. "This means that good products are easy to manufacture, even for a global market. It also means that something bad can be impossible to eradicate once it exists", he said, though he pointed out that, "Today, because life science is a digital technology, we get plenty of digital breadcrumbs to understand where people went, how, and why. And we can close off the paths to places we don't want people to go again. Best practices get baked into the software and computer-controlled hardware". As such, Hessel is generally upbeat about the future of 3-D bioprinting. "People will experiment with themselves, for fun, pleasure, or profit—or just because. If our history with computing is any guide, the positive applications of these technologies will far outweigh the bad".