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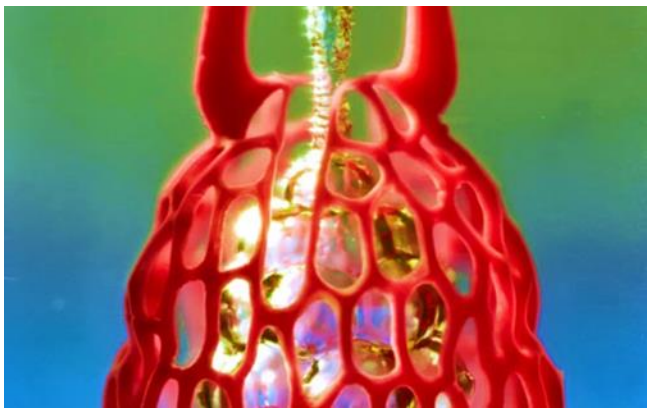
3D bioprinting in medicine



3D printing in medicine is usually associated with the production of medical devices such as hip implants and prosthetic limbs. However, new research is applying 3D printing to living cells and proteins, to print new tissues and organs for medical use in a process known as 3D bioprinting. This POSTnote gives an overview of 3D bioprinting and the associated biological, manufacturing, regulatory and ethical implications.

Overview

- 3D bioprinting is a type of 3D printing that prints an ink made from biological material, such as living cells and proteins.
- This technology could potentially be used to print new and bespoke organs, such as skin or bladders, on demand for transplantation to relieve the donor organ shortage.
- It is currently unclear whether the EU Advanced Therapy Medicinal Products and Medical Devices regulations would apply to bioprinted organs or whether such products would be considered an entirely new class of medicines.
- The adoption and widespread use of this technology would raise a range of logistical, financial and ethical challenges, such as manufacturing dynamics, treatment accessibility and human enhancement.

Background

The current strategy for treating organ damage or failure is to replace the organ with one from a donor. While the current donation rate is improving, the waiting time for an organ can be several years.[1] Patients who receive donor organs face a lifetime regimen of immunosuppressive drugs, lifestyle changes and a high risk of organ rejection.[2,3]

Regenerative medicine is the branch of medicine that looks at regenerating or replacing cells, tissues or organs to repair damage caused by trauma or disease, rather than using donor organs.[4] The government supports regenerative medicine through UK Research and Innovation (UKRI), which since 2012 has provided £80m of funding for regenerative medicine and supporting technologies, with a further £44m coming from the National Institute for Health Research (NIHR).[5] Research is also driven in this area by the Cell and Gene Therapy Catapult and its Cell Therapy Manufacturing Centre, established in 2018.[6]

One branch of regenerative medicine, known as tissue engineering (TE), aims to replace diseased tissues by developing implantable, synthetic tissue substitutes.[7] These tissues are made from the natural biological building blocks found within the body, including cells and structural proteins such as collagen.[8] Currently licenced TE therapies available on the NHS include limbal stem cell transplantation to treat some forms of blindness,[9] and autologous chondrocyte implantation for arthritis.[10,11] Many scientists consider the ultimate goal of TE to be the creation of whole synthetic tissues and organs,[12] but the field is still in the early stages of development.

Applying tissue engineering to medicine

A key advantage of TE therapies is that they are tailored individually to each patient. Although this approach improves treatment efficacy, it is also a factor restricting the pace of research and development within TE, as personalisation is slow, expensive, and requires specialist laboratories.[13] As a result, this research is currently limited to small-scale applications. There is increasing interest in technologies that can scale-up and standardise production of TE therapies to overcome these issues and accelerate the pace of research.[14] An example of such a technology is an applied form of 3D printing known as 3D bioprinting.[15]

3D printing and 3D bioprinting

3D printing is a form of additive manufacture whereby objects are produced by the selective, incremental layering of material to form a 3D structure.[16] There are three main ways that 3D

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Box 1: 3D liver cells to restore liver function
Work at the University of Edinburgh has shown that liver cells (hepatocytes and endothelial cells) derived from human stem cells can be grown into small 3D self-assembled spheres for researching human liver disease. These may also have potential clinical uses: recent studies have shown that when liver spheres were implanted under the skin of immune competent mice with a type of liver disease, human liver proteins were detected in their blood, and recipients displayed substantially better liver function.[17] Work is ongoing to investigate the use of bioprinting to scale up the number of spheres that can be produced for clinical studies.

printing can be applied in medicine: printing of pharmaceuticals;[18] printing of structural medical devices; and 3D bioprinting, which uses living cells and biocompatible materials (biomaterials) to print living tissue-like structures in three dimensions. The following section defines and distinguishes the latter two techniques and highlights some of the main technical challenges associated with the bioprinting process.

3D printing of structural medical devices

3D printing is currently used to produce customised surgical implants to replace knees and hip joints,[19–21] external supports (orthoses),[16,22] and surgical guides for clinicians.[23] These devices may be printed with polymers or metals.[24,25] Recent innovations in 3D printed joint replacements involve the incorporation of microscopic sponge-like designs onto the product surface to encourage bone cells to grow into the device when implanted, or the addition of antibacterial compounds such as silver.[26]

3D bioprinting

3D bioprinting is a technology that prints biomaterials and cells to form a tissue-like material. The cells and biomaterials used in this technique are referred to as the "bioink", which is printed to generate complex biological structures capable of mimicking the tissues found within the body.[27] Bioprinting techniques are currently under study to produce tissue models for disease research. These models can also be used for testing potential new drugs as an alternative to animal testing.[28,29] Work is also underway to apply these techniques to the creation of new medical treatments (see Box 1).[30,31] The use of bioprinting processes to produce tissue-like materials is part of a process known as 'biofabrication'.[32]

Stages of the biofabrication process

There are three important stages in the development of a biofabricated construct (printed tissue or organ): imaging and design, bioink selection, and printing and maturation.[32,33]

Imaging and design

The first stage of the process requires the creation of a virtual computer-aided design (CAD) file. This contains the necessary 3D information needed to inform the printer where and what to print during manufacture.[34] The CAD software can translate medical images, such as MRI scans, into virtual 3D formats.

Bioink selection

A critical element of the bioprinting process is the design of the bioink, which is the component printed to make the structure. The ideal bioink should:

- hold the right physical properties in order to be printed,[35]
- react (gel) on demand, to form a 3D shape,[36]
- be biocompatible, and not degrade into toxic products,[37]
- have mechanically similar properties to living tissue,[38]
- support the growth of cells in the ink and in the body.[39]

Examples of materials with these properties include natural proteins such as gelatin and silk. These are made into a liquid solution that can gel on demand to form a semi-solid material once printed.[40] As the bioink will form a tissue-like structure it may also contain living cells, but the addition of cells to the bioink makes it more delicate and thus more difficult to print.

Box 2: Novel bioprinting techniques
New applications have been developed to enable the production of quicker, more defined bioprinted structures using existing bioprinting methods. These include:

- **Reactive jet impingement**. Developed at Newcastle University. It uses a multivalve printhead to eject two different liquid bioinks. These collide and react in mid-air, forming a gel which falls onto the print substrate. This allows quick valve printing of a gel bioink with cell concentrations approaching those found in some human tissues.[41]
- **Suspended layer additive manufacturing**. Developed at the Universities of Huddersfield and Birmingham. It uses a microextrusion printer to print delicate 3D structures within a bed of supportive gel. Once the print has solidified, the gel can be washed away, leaving the printed structure intact.[42]

Printing and Maturation

Various bioprinting techniques are available, with each using a different mechanism for ejecting the bioink.[33] Three commonly used bioprinting methods include:

- **Inkjet printing**. Uses liquid bioinks that gel after printing. They work by increasing the pressure of the bioink to jet it out of the printhead. They print at the highest detail (resolution) due to their ability to print single cells, but cannot print bioinks with a high cell concentration as the cells can clump and block the printhead.[43,44]
- **Valve printing**. Also uses liquid bioinks. This works by opening/closing the print nozzle on demand to allow the bioink to be deposited. They print at a lower resolution than inkjet printers but can print bioinks of a larger range of cell concentrations.[45]
- **Microextrusion**. Uses gel bioinks that are extruded (pushed out) by the printer using pressure. They handle the highest cell concentrations due to their increased print nozzle diameter but have the lowest resolution. Most commercial bioprinters use this technology as it is the cheapest and most accessible bioprinting method.[34]

There is ongoing research into the above methods as each is likely to be suited to different applications. However, they all have two main limitations. First, the natural density of cells present within body tissues is high, and these methods can struggle to print to this concentration.[46] Second, current limitations on resolution means that it may be difficult to produce the more intricate structures found in the human body, such as blood capillaries.[45] Research is underway to develop new bioprinting methods to address these limitations (Box 2).

Box 3: Examples of current biofabrication research
The following cases are examples of recent research in 3D bioprinting. They are still proof-of-concept studies and as such are a long way from human clinical trials.

- Lung (alveoli). The core functional unit of the lung is the alveolus, where gases (such as oxygen) enter small blood vessels. A group of universities in the US has developed a hydrogel that can form channels mimicking vessels (header image, page 1). When red blood cells are pumped through the channels, they are able to take up oxygen..[47,48]
- Ovary. Researchers at Northwestern University in the US have printed a gelatin structure capable of sustaining ovarian follicles. When implanted into sterilised female mice, the ovaries develop blood vessels and follicles mature naturally. These were capable of being fertilised and mice were able to carry pups to full term with live births. Mothers were also able to nurse, showing normal hormonal functions.[49]
- Cornea (stroma). Researchers at Newcastle University have printed a part of the cornea (the transparent front area of the eye) using microextrusion printing. They created a collagen and alginate bioink that contained human corneal cells, and printed it into a bespoke corneal mould, which, when removed, left clear corneal tissue.[50]

Following the printing stage, the printed 3D constructs undergo a period of maturation.[51] This maturation period allows the cells that were in the bioink (or were added to the biofabricated construct after printing)[52] to adhere and adapt to the structure. Once adapted, cells may begin self-assembly of the biological features that could not be printed due to technological limitations (see below). Following maturation, the construct would be clinically evaluated for accurate functionality, and, if approved, used for clinical applications.

Biological challenges

3D bioprinting is a rapidly developing field, resulting in several proof-of-concept studies (Box 3). The overall aim of such research is to produce organs and tissues for use in regenerative medicine, but there are challenges to be overcome before this is possible. These include:

- **Tissue heterogeneity**. Tissues and organs consist of a variety of different cell types. Isolating and then printing each type, ensuring they occupy anatomically relevant positions and they fully function remains a challenge.[53]
- **Vascularisation**. Blood supply is a key feature of almost all tissues and without it most tissues die rapidly. Recreating this network is difficult, but work is ongoing to explore the printing of blood vessel (endothelial) cells or promoting their growth using hormones.[54,55]
- **Organ and tissue rejection**. The biomaterials used to print constructs may elicit an immune rejection response from the patient. This may be especially the case if the construct contains cells from a donor (see below).[56]

When printing with a bioink that contains cells, there is ongoing debate over the pros and cons of using the patient's own (autologous) cells within the ink, or those from a donor (allogeneic cells).[57] A key benefit of autologous cells is the low risk of immune rejection, but if the patient has a genetic disease then their cells may need to be genetically edited to repair them before use.[58] Furthermore, sourcing the large number of cells required for printing a tissue or organ is difficult if the cells are derived from each patient individually.[67] The use of allogeneic cells could overcome this, as large standardised batches of cells could be pre-prepared and stored in a cell bank to be made available when required. The cells could also be produced in such numbers that they could be used to treat several patients.[68] A disadvantage is that, as these cells come from a donor, patients would still have to take drugs to manage the risk of immune rejection (potentially for their lifetime).[69]

Box 4: Regulatory bodies in biofabrication
UK and EU regulatory bodies that oversee the stages of the biofabrication process and the use of its products include:

- The Human Tissue Authority (HTA) regulates the removal, storage and use of human tissue for research and medical treatment under the Human Tissue Act 2004[59] and EU Tissue and Cells Directives[60–62]
- The Medicines and Healthcare products Regulatory Agency (MHRA) regulates the safety, quality and efficacy of medicines, medical devices and blood components used in the UK.[63] It has also set up a cross-agency Brexit task force to manage the regulatory implications on the sector as the UK leaves the EU.[64]
- The European Medicines Agency (EMA) regulates applications to market medicines and classifies advanced therapy medicinal products in the EU.[65,66]

Regulatory issues

As biofabrication is a new technology, there is no exact regulatory definition of what a biofabricated construct is. Depending on the nature of the construct and the process used to make it, a range of EU and UK regulations may apply. These include regulations on medicinal products and biomaterials,[70] chemical components,[71] or animal derived components.[72] However, the UK's alignment to the EU regulations post-Brexit is uncertain. The most relevant EU regulations that are likely to apply to biofabricated products are those that regulate:

- advanced therapy medicinal products (ATMPs)[73]
- medical devices. The Medical Device Regulation (MDR)[74] is due to be implemented by May 2020, and replaces the current medical device directives.[75,76]

ATMP Regulation

Given that biofabrication represents an advanced therapeutic process, it is widely assumed that biofabricated constructs would fall within the scope of the EU ATMP Regulation. This regulation defines four classes of ATMPs:

- gene therapy products (GTMPs) that contain genes that lead to a therapeutic, prophylactic or diagnostic effect.
- cell therapy products (CTMPs) that use cells or tissues to cure, diagnose or prevent diseases.
- tissue-engineered products (TEPs) that contain modified cells or tissues that can be used to repair, regenerate or replace human tissue.
- combined ATMPs (cATMPs) that contain one or more medical devices (jointly regulated by the MDR, see below) as an integral part of the medicine, for example, cells embedded in a matrix or scaffold.

While they are still being developed, biofabricated products are yet to be classified, but it is envisaged that they are most likely to be TEPs or cATMPs. Classifications are decided by the

European Medicine Agency's (EMA, Box 4) Committee for Advanced Therapies (CAT) or by the relevant country's Competent Authority on a case-by-case basis.[77,78] In the UK, the Competent Authority is the Medicines and Healthcare products Regulatory Agency (MHRA, Box 4). Once approved and classified, ATMPs can be used clinically in one of two main ways.[77] First, developers can apply through the EMA's centralised system for market authorisation to commercialise the product across all EU member states. Applications must be backed up with evidence from clinical trials of the product's safety, quality and efficacy.[77] Otherwise, ATMPs may be delivered to clinic via a 'hospital exemption' route. This circumvents market authorisation on the basis that they are one-of' customised products that address an unmet need, and are not derived from an industrial source.[79,80] This route is intended to allow for bespoke treatments in a single member state.

Medical Devices Regulation

If biofabricated constructs are classified as cATMPs, then these are co-regulated by the new MDR. Compliance with the MDR brings extra regulatory challenges to biofabrication, and may add extra complexity and cost to production processes.[74,81]

Regulations on the use of human cells

The biofabrication process may also fall under regulations covering human cell use, and standards for the manufacture and distribution of cell-based medicines. The donation and use of human cells in the UK is regulated by the Human Tissue Authority (HTA, Box 4), which oversees cell and tissue storage, processing and sample traceability requirements.[59] The MHRA also produces standards for the manufacturing and distribution of cell-based medicines, which are known as the Good Practice (GxP) guidelines. Several GxP guidelines are relevant at different stages of biofabrication, such as during manufacture (Good Manufacturing Practice, GMP), and clinical trials (Good Clinical Practice, GCP).[82,83] Producers of bioprinted products would have to meet the GxP standards, regardless of facility size, location, or scale of production.

Manufacturing challenges

A key challenge in adopting biofabrication is deciding where and who will manufacture these products. While conventional medicines are manufactured at a centralised site, the bespoke and delicate nature of biofabricated products mean they may be better suited to local manufacturing by an approach known as redistributed manufacturing (RDM). This involves making products in local biofabrication hubs based in private facilities,[84] or existing healthcare settings, such as hospitals or NHS Blood and Transplant Centres.[85] Potential benefits of an RDM approach include reduced waiting times for products, lower burden on major hospitals, and more accessible treatments.

However, some stakeholders have questioned whether the routine use of biofabrication methods in such facilities would meet good quality assurance standards.[84] Others have also questioned whether sustained production under the hospital exemption pathway would be permitted, because these are intended to allow bespoke treatments for individual patients. There are also general concerns that some groups are using this route as a way of circumventing the clinical trial data requirements of market authorisation.[81] In response to this, the House of Commons Science and Technology Committee has recommended that the Government should review how hospital exemptions are used for ATMPs across the UK, and assess how they might be adapted for the UK post-Brexit to provide a balance between safety and accelerated access to cutting edge technologies.[5]

Establishing GMP-compliant hubs

RDM requires the creation of a series of local production centres equipped with advanced facilities that adhere to GMP standards, however, establishing these centres would likely be expensive. The UK currently has 26 GMP-compliant facilities that are operating at close to full capacity (~73%).[86] One of these centres, based at the Royal Free Hospital in London, was opened in 2015 and cost £2.1 million to establish - this total excludes costs associated with bioprinting equipment or staff training.[87] Expanding the GMP network to enable UK-wide RDM for biofabrication would thus require significant investment.[88,5]

Ethical and legal issues

Risks of early adoption

Some stakeholders have concerns about the high expectations[88] of 3D bioprinting and the potential for bioprinted constructs to be deployed in a medical setting without full knowledge of their long-term impacts on human health. This may be exacerbated in cases where the bioprinted organ would be serving as a replacement (due to the likely irreversible nature of the procedure)[89] or where products are used within a hospital exemption capacity, where the requirement for clinical trials evidence may be lower than for ATMP market authorisation. There are reports of historical cases where tissue engineering constructs used in patients without being tested rigorously in animals may have contributed to patient deaths.[90,91]

Accessibility of treatment and enhancement

The clinical application of biofabrication is potentially highly bespoke, tailored to individual patients' needs. This means that biofabrication procedures are likely to be costly, which raises questions regarding accessibility and affordability.[92] Furthermore, biofabrication represents a potential route to human enhancement. For example, it has been suggested that biofabricated materials could include the integration of sensor technologies, which could be used to detect diseases earlier.[93] This raises a number of ethical questions on whether it is appropriate to modify organs in this way.

Patentability and confidentiality

There is ongoing debate over whether certain parts of the bioprinting process are patentable.[94,95] It is also not clear who might be the patent holder of the various components of a bioprinted organ, given the numerous players in the biofabrication process and the difficulty in identifying novel invention.[96] These difficulties have implications for product liability should the constructs malfunction, and for organ ownership. In addition, the distribution of CAD files for biofabrication requires sensitive patient data in order to design the construct. It is unclear how this stage of biofabrication would be compatible with current data protection legislation.[81]

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