Bioprinting Regulatory Oversight
Ethics, Law and Intellectual Property

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Special Topics in 3D Bioprinting
Overview

- Potential uses of bioprinting
- Ethics
- Regulatory: The FDA
- The legal landscape: Case law
- Intellectual property
- International scene: UK/EU, Wales
- Discussion
1. What does “public opinion” drive?
2. Where do regulations come from?
3. Who owns the IP?
Potential Uses of Bioprinting

- Biopharmaceutical Research and Development
- Disease modeling generally
- Solid organs and other tissue replacement.
- Prosthetics and other implants.
- Models for pre-surgical training.
Laid the foundation for current guidelines on informed consent and human experimentation.
Ethical considerations in the translation of regenerative biofabrication technologies into clinic and society

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“In translational medicine, dynamic interactions between scientists, clinicians, ethicists, patients, and other members of society are instrumental in enabling effective scientific progress.”

“Ethics is sometimes regarded as a brake on science, yet in our perspective, ethics provides moral guidance and the incentive to continuously refocus on the scientific direction and its impact.”


Positive ethical consequences, for example, creating alternatives to animal testing (e.g. drug testing), filling a therapeutic need for minors and avoiding species boundary crossing.

Needed disease modeling.

3D bioprinting remains an untested clinical paradigm and is based on the use of living cells placed into a human body; there are risks including teratoma and cancer, dislodgement and migrations of implant.

Ethical Considerations

- Protecting personal data.
- Inappropriately extending the human lifespan.
- Inappropriate cosmetic use.
- Managing public expectations.
- Avoiding scientific research exploitation.
- Conflict of interest of the experts.
- Transparency of the entire process.
- Making it affordable.
- Meeting supply and demand of human or non-human animal transplants.
Organ Waiting List as of 9/2017

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<tr>
<th>Type</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>All</td>
<td>116,533</td>
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<tr>
<td>Kidney</td>
<td>96,648</td>
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<tr>
<td>Pancreas</td>
<td>902</td>
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<tr>
<td>Kidney/Pancreas</td>
<td>1,679</td>
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<td>Intestine</td>
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<tr>
<td>Heart</td>
<td>3,953</td>
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<tr>
<td>Lung</td>
<td>1,337</td>
</tr>
<tr>
<td>Heat/Lung</td>
<td>40</td>
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</table>
Induced Pluripotent Stem Cells

- Researchers may now pursue the more recently developed “Induced Pluripotent Stem Cells” (iPSC) technologies, or collect multipotent stem cells (adult/somatic stem cells) for producing pluripotent stem cells for 3D tissue engineering in order to bypass the destruction of human embryos.
  - In 2006, Shinya Yamanaka described successful reprogramming of human somatic cells into a pluripotent state that was similar to ESCs in both its phenotype and transcriptome.
    - This was accomplished by using retroviral transduction of what have become known as the Yamanaka factors (Oct3/4, c-MYC, Klf4, Sox-2).


FDA’s perspective on additively manufactured medical products:

- **Center for Devices and Radiological Health (CDRH).**
  - Cleared additively manufactured devices for over a decade within the existing medical device regulations.

- **Center for Drug Evaluation and Research (CDER).**
  - Approved the first 3D printed drug within the existing chemistry, manufacturing and control standards that all other drug products are regulated by.

- **Center for Biologics Evaluation and Research (CBER).**
  - Following the literature and interacting with stakeholders.

3D bioprinting is regulated by existing laws, mainly those concerning medicinal products and medical devices.

Part 1271: Human Cells, Tissues and Cellular and Tissue-Based Products.
- An electronic registration and listing system for establishments that manufacture human cells, tissues, and cellular and tissue-based products.
- To establish donor-eligibility, current good tissue practice, and other procedures to prevent the introduction, transmission, and spread of communicable diseases. (Safety and quality control.)
Currently, products that use stem cells or are derived from stem cells are treated by the FDA as somatic cellular therapies and are regulated as “biologics” under Section 351 of the Public Health Act.

Bioprinted tissues typically used in research do not require FDA approval during animal and in vitro testing because they are not intended for use on humans.

Title 21 of the Federal Code of Regulations defines certain restrictions with regard to shipping and disposal of these products.
In May 2016, the US Food and Drug Administration (FDA) released draft guidance for medical device manufacturers working with additive manufacturing.

- Technical considerations.
- Characterizing and validating devices.
- Type of information to be submitted – premarket submissions.
- Does not address the use or incorporation of biological, cellular, or tissue-based products.

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**Technical Considerations for Additive Manufactured Devices**

**Draft Guidance for Industry and Food and Drug Administration Staff**

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.


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FDA: Combination Product

- Biological products are defined as combination products under 21 CFR 3.2(e) if they are produced as a single entity but are physically or chemically combined with at least one integral constituent, independently regulated part.
  - The FDA classifies these combination products according to the claimed primary mode of action (MoA), the characteristics of the active substance, and the way in which it is combined in the finished product.
  - This includes medical devices that consist of biological materials, medical technologies, and drugs of different compositions.

Definition of a Combination Product...

1) “A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;”

2) “Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;”
Combination Product...

3) “A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose.”
Combination Product…

4) “Any *investigational* drug, device, or biological product packaged separately that according to its proposed labeling is for use *only with another individually specified investigational* drug, device, or biological product where both are required to achieve the intended use, indication, or effect.”
Combination Product…

- A combination product will command a high level of regulatory scrutiny, particularly for the manufacturer that makes multiple constituent parts.

- Major regulatory concerns are in the process from design to manufacture, software system chain control and validation, and potential variation in critical quality attributes (CQAs) of the final manufactured product.

Legal Landscape

Case law
- Henrietta Lacks and the HeLa Cell Line
- Moore v. Regents of University of California
- Bayh–Dole Act 1980
- The Myriad Decision

In 1951 a patient named Henrietta Lacks went to Johns Hopkins Medical School for a biopsy of a lesion on her cervix.
Dr. George Gey received a portion of the tissue, and his successful proliferation of the cells in vitro gave rise to the popular HeLa cell line.
Dr. Gey freely distributed the cell line without patenting.
The scientific community viewed the cell line as an extension of Lacks.
  - If the HeLa cells could exist apart from Lacks, their validity as a human analog and as a living organism would be questioned.
In the 1980 thinking changed, and cell lines were patented.
  - Lockean labor view of property – “people own the fruits of their labor.”
  - Redefinition of “living” as the ability to “retain . . . biochemical integrity and . . . replicate.”
Supreme Court of California considered an argument for an absolute property right in tissues and organs that have been abandoned by a patient.

Plaintiff John Moore was treated for hairy-cell leukemia, and underwent a splenectomy.

- The University attending physician and the researcher filed a patent that entitled them to a share of the university’s royalties and profits from the “potentially lucrative” cell line developed from the spleen.

Moore’s claims was a claim for conversion, under the theory that Moore had ownership and possessory rights to the cell line and he did not extend authorization for the use of his spleen.

- The court disagreed, Moore could not have a possessory interest in the spleen after its removal. Conversion theory could not be extended to this case.
- The public has a strong interest in encouraging socially important medical research.

The federal government would no longer retain title to inventions supported by government funding.

- Cut down on bureaucracy and encourage private industry to utilize government financed inventions through the commitment of the risk capital necessary to develop such invention to the point of commercial application.
- Gene research was influenced the most; approximately 33,000 patents related to DNA were granted by 2006.

Myriad Genetics, Inc. ("Myriad") made a medical breakthrough in discovering the location of the BRCA1 and BRCA2 gene sequences.

- Myriad used this knowledge to develop tests for the detection of BRCA1 and BRCA2 mutations that would signal an increased risk for breast and ovarian cancer.
- They proceeded to obtain broad patents that claimed the DNA sequences for BRCA1 and BRCA2, the cDNA sequences that code for BRCA1 and BRCA2, and subsets of these sequences.

The Supreme Court held that the mere isolation of a naturally occurring DNA segment is not patent-eligible under 35 U.S.C. § 101, but a distinguishable cDNA segment is patent-eligible.

- The latter did pass the test of having “markedly different characteristics from any found in nature,” whereas the former did not.
- In creating the cDNA, the court determined Myriad had created or altered genetic information, which was patentable.
Patents: bioprinters, bioprinting materials, and fabrication and postproduction maturation processes.

Copyrights would protect the CAD–CAM files for scanning, manufacturing, and bioprinter control.

The U.S. Code permits patents on "any new and useful process, machine, manufacture or composition of matter."
- Products of nature are not patent-permissible; however, variations of naturally occurring organisms may be patented.
Raw *digital blueprints* from an organ scan will unlikely receive the benefit of patent protection.*

Less clear is the patentability of a *scanned organ that retains its form but has been transformed* into a mesh structure with structural improvements in order to function as a scaffold.*

Bioprinted constructs *integrating imaging data, cells and other materials may be patentable.*

Additional consideration must be given if proprietary cell lines and materials are used.

Bioprinted *in-vitro* devices for drug testing and other applications may be patentable.

Newly developed software will require copyright rather than patent protection.**

- Copyright protects the means of expression of an idea and can be useful to protect software, code, digital drawings, sculptures, and 3D models.

Rivalry and exclusivity of patient, physician, university, and biotechnology company.

- **Rivalry** is the degree that the use or consumption of a good reduces its availability for a subsequent user.
- **Exclusivity** is the ability to prevent others from enjoying the good.

The three main components of bioprinted organs—the blueprints, the biomaterials, and the cells—can generally be characterized as being nonrivalrous and noncompetitive.

- However, arguments for broader property rights and increased regulation could be supported even if bioprinted organs are conclusively determined to be public or private goods by nature.

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## Potential Patenting Areas

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<th>Areas of potential IP</th>
<th>Examples of possible IP contents</th>
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- Novel methods on how to derive/synthesize such materials.                                                                 |
| Isolation and growth/differentiation of cells in the context of bioprinting           | - Novel methods on how to derive cells, either primary or pluripotent, that can be used as sources for bioprinting.  
- Methods to prepare the cells for printing, with or without the combination of scaffold materials.                                                                                                                                   |
| Bioreactor/method to grow printed organ precursors                                   | - Methods of integration and coupling of printed organ precursors with the external bioreactors.  
- Development of modular bioreactor/bioreactor components that sub-serve different culture conditions.  
- Novel methods that enable automated organ growth after printing.                                                                                                             |
| Methods of dispensing/printing techniques                                            | - Single-cell precision loading and dispensing of various types of cells  
- Method to improve speed of printing, for example, deployment of multiple dispensing arrays.  
- Novel methods to dispense liquid materials with higher viscosities, in form of droplets, which may broaden the choices of printable materials.                                                                                          |
| Methods of novel 3D fabrication techniques                                            | - Hybrid approaches to constructively enhance the current 3D printing principles.                                                                                                                                                                                                                     |
“Stem-cell researchers in Europe are reeling after the court of Justice of the European Communities issued an opinion questioning the ethics of their work and threatening to ban them from patenting stem-cell lines.”
Human Tissue Act 2004:
- Only a licensed person is allowed to remove a living person’s transplantable material.
- Such removal would need to be non-commercial.
- A full informed consent process should minimize the risk of harm and possible violation of ethical considerations.
- Express consent from the donor is required to remove, store, and use his or her tissues.

Legislation relevant to 3D printing:
- ATMP Regulation
- EC Tissues and Cells Directive
- Pharmaceutical Regulation
- Medical Device Regulation

Wales

- **The Human Transplantation (Wales) Act 2013**
  - The Act aims to increase deceased donor organ and tissue donation in Wales by introducing a ‘soft opt-out’ system to replace the previous requirement of express ‘appropriate’ consent under the Human Tissue Act 2004.
  - Adults dying in Wales (with certain exceptions) will be ‘deemed’ to consent to donation, unless evidence of their objection is produced, and a duty is imposed on Ministers to promote transplantation and inform the public through awareness campaigns about how to choose the deemed status or opt out.

Discussion

- Will regulations based on non-biological additive printing suffice?
  - In contrast to bioprinters, other types of 3D printers, including those used for medical devices, should probably not be directly regulated.*

- Will software and hardware setups for bioprinting be regarded as “medical devices?”

- How do we classify bioprinted constructs – are they to be regulated as “products”, medical devices, drugs, or a new category? Presently they are considered “biologics.”


