Chapter 7: Patenting Bioprinting-Technologies in the US and Europe– The 5th Element in the 3rd Dimension

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"Me fifth element- supreme being. Me protect you"
-LeeLoo in "The Fifth Element" (Columbia Pictures 1997)-

Introduction**

When entering the headquarters of the US Bioprinting company "Organovo" at 6275 Nancy Ridge Drive in San Diego, California,[1] you might meet *Bruce Willis*. The famous actor stares at researchers from a machine in a sterile room, where several bioprinters carry labels with the names of characters from the 1997 sci-fi motion picture *The Fifth Element*.[2] In the movie, which is set in the 23rd century, a robotic machine uses cells from a severed human hand to print and reanimate the "Fifth Element".[3] The creature turns out to be a highly enhanced and very capable "supreme being" named *LeeLoo*.

Today's science is still far from achieving anything resembling such sci-fi wonders, but scientists have made fascinating advances in developing sophisticated tools that enable us to better visualize and model such processes.[4] Moreover, they have made promising advances in starting to address one of the major challenges: to make printed tissue behave like real tissue in a biological organism. In 2016, for example, *Hyun-Wook Kangsee* and his co-authors published their paper entitled "A 3D bioprinting system to produce human-scale tissue constructs with structural integrity" in *Nature Biotech* and announced:

> We present an integrated tissue–organ printer (ITOP) that can fabricate stable, human-scale tissue constructs of any shape. Mechanical stability is achieved by printing cell-laden hydrogels together with biodegradable polymers in integrated patterns and anchored on sacrificial hydrogels. The correct shape of the tissue construct is achieved by representing clinical imaging data as a computer model of the anatomical defect and translating the model into a program that controls the motions of the printer nozzles, which dispense cells to discrete locations.[5]

While producing three-dimensional, vascularized cellular constructs of clinically relevant size, shape and structural integrity certainly remains a major challenge for tissue engineering, *Hyun-Wook Kangsee* and his colleagues succeeded in incorporating microchannels into tissue-constructs, which enhances the diffusion of nutrients to printed

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[1] See the homepage of Organovo, available at: http://organovo.com/about/contact/ (accessed 10 December 2016).

[2] Steven Leckart, *How 3-D Printing Body Parts Will Revolutionize Medicine, Popular Science*, available at: http://www.popsci.com/science/article/2013-07/how-3-d-printing-body-parts-will-revolutionize-medicine (accessed 5 December 2016).

[3] *Ibid.*

[4] *Ibid.*

[5] Hyun-Wook, Kang et al., *A 3D bioprinting system to produce human-scale tissue constructs with structural integrity* , 34 Nature Biotechnology, 312–319 (2016).

cells.[6] In addition to increasing the chances of cell survival in engineered tissues by this achievement, they further demonstrated the capabilities of their 3 D bioprinter to produce "mandible and calvarial bone, cartilage and skeletal muscle".[7] Moreover, they announced that the future development of their bioprinting research is being directed to "the production of tissues for human applications and to the building of more complex tissues and solid organs".[8]

Building upon such fascinating research results, today's state-of-the art 3 D bioprinting companies, such as *Organovo*, aim at designing, creating and ultimately selling living human tissues that with increasing accuracy represent human biology and function, like native tissues and organs. Their vision and mission is to use 3 D bioprinting technologies in order to develop groundbreaking therapies and to bridge the gap between pre-clinical testing and clinical trials.[9] To achieve these ambitious goals, they team up with biopharmaceutical companies, hospitals and academics to design, build, and validate more predictive in vitro tissues for disease modelling and toxicology. This entails the opportunity to test drugs on functional human tissues before ever administering the drug to a living person or to create functional, three-dimensional tissues that can be implanted or delivered into the human body to improve, repair or replace damaged or diseased tissues.[10]

These enormous opportunities and the broader implications of bioprinting raise a wide variety of crucial legal issues. These may range from regulation of the science, its societal effects and wider ethical implications to questions regarding commercialization, innovation policy and governance of the technology. A broader analysis of all these important issues falls outside the limited scope of this paper. Rather, we will concentrate on selected commercialization aspects and in particular the question of what types of products and uses should be regarded as protectable subject matter under the relevant intellectual property right (IPR) frameworks. Considering that the availability of IPRs might have a great impact on where the greatest investments and scientific efforts in this technology will be made, this is a significant question. In addition to trade secrets, copyrights, trademarks and other IPR-related rights, patents will certainly play a major role in that respect and will thus be the primary focus of this paper.

In the following, we examine what sorts of bioprinting inventions are being patented or would be protectable under European and US patent laws. Rather than focusing on the highly relevant questions that 3D printing poses for patent infringement doctrines and research exemptions[11], this paper concentrates on the question of patentable subject matter and patentability. To this end, we start out by (1) briefly describing the relevant state of the art in bioprinting. This allows us to better describe and understand the current bioprinting patent landscape (2), and to examine how far any future inventions stemming from such technology would meet the most basic US and European patent requirements (3). A related question is, of course, whether some bioprinting technologies should be categorically excluded from

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[6] *Ibid.*
[7] *Ibid.*, 312.
[8] *Ibid.*,312.
[9] See the homepage of Organovo, available at: http://organovo.com/about/about-organovo/ (accessed 18 November 2016).
[10] *Ibid.*
[11] A good overview of US infringement issues relating to 3D printing is provided by Timothy R. Holbrook, and Lucas Osborn, *Digital Patent Infringement in an Era of 3D Printing*. 48 UC Davis Law Review, 1319-1385 (2015). Regarding the situation in Australia and Europe, cf. Johnathon E Liddicoat, Jane L. Nielsen, & Dianne Nicol, *Three Dimensions of Patent Infringement: Liability for Creation and Distribution of CAD Files*, Australian Intellectual Property Journal (2016), available at SSRN: https://ssrn.com/abstract=2792601; Rosa Maria Ballardini, Marcus Norrgård, and Timo Minssen, *Enforcing Patents in the Era of 3D Printing*, 10(11), Journal of Intellectual Property Law and Practice, 850 (2015); Marc Mimler, *3D Printing, the Internet and Patent Law – A History repeating?*, 62 (6) La Rivista di Diritto Industriale, 352 – 370 (2013).

patentability, i.e. even when meeting the most basic patent criteria, or whether they are barred from patenting because they are perceived to be immoral. We address this specific issue by discussing patent limitations and morality exclusions from patent law (4), which will allow us to complete the paper with some concluding remarks (5).

1. Bioprinting: A brief scientific preface

Bioprinting is an emerging field of technology that is part of the wider field of tissue engineering and uses 3D printing technology.[12] Bioprinting is used to fabricate three-dimensional structures of biological materials, generally cells and biochemicals, through layer-by-layer precise positioning.[13] The printing process is controlled by a computer according to a predetermined instruction, usually a computer-aided design (CAD) file of the respective tissues or object. The ultimate goal of the technology is to replicate functioning tissue and material, up to full organs which then can be transplanted into human beings.[14]

In order to be able to print complex tissues and organs, a model of the object to be printed needs to be produced and which is able to instruct the 3D printer. This is a complex task as the objects that are aimed to be reproduced are complex and heterogeneous.[15] In order to provide a printing template, medical imaging is used to create a virtual image of the construct by using computed tomography (CT) scans or magnetic resonance imaging.[16] After these images are created, further processing leads to the creation of a CAD file which can be used to instruct the printer. Where an exact copy of the patient's organ is not required or desirable, computer modelling can be applied to design the desired structure.[17]

A further component of the bioprinting process is the "ink" the printer uses. Such "bioink" can, for instance, consist of autologous cells, i.e. cells that have been taken from a patient through biopsy.[18] Bioink can also be made of cells from different individuals from the same species (allogenic cells) and also from cells from different species (xenogenic cells).[19] After isolation of the cells, these are then cultivated and multiplied *in vitro.*

Aside from cells, bioink consists of a hydrogel pre-polymer-solution.[20] Such hydrogels are crucial for the success of bioprinting and need to possess certain properties.[21] It has to be borne in mind that 3D printing was originally developed for non-biological applications, such as rapid prototyping, which operate in conditions that are not suitable for use of biomaterials,

[12] Jasper L. Tran, *To Bioprint or not to Bioprint,* 17 (1) N.C. J.L. & TECH., 123, 132 (2015), refers to bioprinting as "the stepchild of 3D Printing and synthetic biology".
[13] Sean V Murphy & Anthony Atala, *3D bioprinting of tissues and organs*, 32 (8) Nature Biotechnology, 773 (2014).
[14] Chee Kai Chua and Wai Yee Yeong, *Bioprinting : Principles and Applications*, 53 World Scientific Publishing Company (2015); Mathew Varkey and Anthony Atala, *Organ bioprinting: A closer look at ethics and policies,* 5 Wake Forest Journal of Law & Policy 275, 277 (2015).
[15] Dhakshinamoorthy Sundaramurthi, Sakander Raud and Charlotte A. E. Hauser, *3D bioprinting for regenerative medicine applications* (2) International Journal of Bioprinting, 9, 21 (2016).
[16] Soumen Jana and Amir Lerman, *Bioprinting a cardiac valve*, 33 (8) Biotechnology Advances 1503-1521, 1505 (2015); Murphy & Atala, *supra* n. 13, 775; Shuai Wang, Jia Min Lee & Wai Yee Yeong, *Smart hydrogels for 3D bioprinting*, 1 (1) International Journal of Bioprinting, 3, 4 (2015); Christian Mandrycky, Zongjie Wang, Keekyoung Kim and Deok-Ho Kim, *3D bioprinting for engineering complex tissues,* 34 (4) Biotechnology Advances 422-434, 426 (2016).
[17] Murphy & Atala, *supra* n. 13, 775.
[18] Chua & Yeong, *supra* n. 14, 165.
[19] *Ibid*., 166.
[20] Mandrycky, Wang, Kim & Kim, *supra* n. 16, 427.
[21] Wang, Lee & Yeong, *supra* n. 16, 5.

such as heat and pressure during the printing process.[22] These conditions may negatively affect the viability of cells.

Hence, the materials used for bioink need to be capable of sustaining these conditions while being able to enhance cell viability during and after the printing process.[23] The material should also be printable and capable of being deposited accurately. Additionally, the material would need to be biocompatible, i.e. able to provide a favourable environment for the cells.[24] After the printing process, the bioinks should be able to provide structural and mechanical support.[25] Finally, the material uses should be biodegradable.[26] This means that the scaffolding function initially provided by the hydrogel should be taken over by growing cells.[27] Commonly, materials such as collagen, gelatine, fibrin, and other natural polymers are used for bioink.[28] But synthetic polymers are also applied due to their particular characteristics, i.e. "their biocompatibility, strong mechanical properties [and] degradation profile".[29]

Currently in use are three common bioprinting techniques[30]: inkjet, laser assisted and extrusion bioprinting – all of which have strengths and shortcomings.[31] Inkjet printing was the first method applied in this context. It resembles two-dimensional inkjet printing[32] and is a widely used method of bioprinting.[33] The printer head generates droplets by thermal or acoustic force[34] to eject the bioink[35] and prints the bioink according to a prescribed way.[36] This technology, however, has its drawbacks as it is not able to print bioink of high viscosity.[37] The lower level of cell concentrations that are used make it difficult to create cell densities which are relevant.[38] The advantages of this technology, on the other side, are its low costs and the fact that many tissues can be reproduced with it.[39] Additionally, the high speed of the technology makes it possible to reproduce biological material, such as skin and cartilage, in situ.[40]

Micro-extrusion printing, or bioplotting,[41] is another method commonly used for bioprinting. In comparison to inkjet printing, this method prints the bioink as a continuous stream or beads of material rather than as individual droplets.[42] This technology uses either pneumatic or mechanical means to control the flow.[43] Micro-extrusion constitutes an

[22] Sundaramurthi et al., *supra* n. 15, 16.
[23] *Ibid*., 16.
[24] *Ibid*., 16.
[25] Wang, Lee & Yeong, *supra* n. 16, 5.
[26] Murphy & Atala, *supra* n. 13, 779.
[27] Chua & Yeong, *supra* n. 14, 88; Mandrycky, Wang, Kim & Kim, *supra* n. 16, 427; Sundaramurthi et al., *supra* n. 15, 16.
[28] Sundaramurthi et al, *supra* n. 15, 16; Wang, Lee & Yeong, *supra* n. 16, 4.
[29] Sundaramurthi et al, *supra* n. 15, 17.
[30] Wang, Lee & Yeong, *supra* n. 16, 4.
[31] Mandrycky, Wang, Kim & Kim, *supra* n. 16, 423.
[32] *Ibid*. 422-434, 423.
[33] Murphy & Atala, *supra* n. 13, 775.
[34] *Ibid*., 775 – 776.
[35]Mandrycky, Wang, Kim & Kim, *supra* n. 16, 423.
[36] Chua and Yeong, *supra* n. 14, 67.
[37] Generally, the more cells that are included in the bioink the higher its viscosity - Jana & Lerman, *supra* n. 16 , 1505.
[38] Murphy & Atala, *supra* n. 13, 776; Chua & Yeong, *supra* n. 14, 71.
[39] Murphy & Atala, *supra* n. 13, 776.
[40] *Ibid*, 773, 776.
[41] Jana & Lerman, *supra* n. 16, 1507.
[42] *Ibid.*, 1503-1521, 1507. *See also* Murphy & Atala, *supra* n. 13, 777.
[43] Murphy & Atala, *supra* n. 13, 773, 777; Jana & Lerman, *supra* n. 16, 1507.

elaboration of the inkjet technology without its pitfalls[44] because bioinks with a higher viscosity can be used.[45] Additionally, this technology allows more materials to be used as it could be applied at room temperature, which promotes the cross-linking of material. A negative element of micro-extrusion is the lesser degree of cell viability in comparison to inkjet printing.[46] This is based on the pressure used, which affects cell membrane damage and can cause cell lysing.[47] This problem can be addressed by applying less pressure but this would lead to loss of speed and printing resolution.[48]

Finally, laser-assisted printing is another, but less common, method applied in bioprinting. However, it is gradually becoming more widely used.[49] The technology uses "a pulsed laser source, a laser-focussing tool, a laser-energy-absorbing metallic ribbon film and a receiving substrate."[50] Printing is conducted by the laser, which pushes the bioink toward a collector substrate.[51] Laser-assisted printing does not suffer from the pitfalls of inkjet printing. The lack of a nozzle means that clogging is not an issue[52] and the technology is precise enough to print single cells in a row.[53] In addition, this method allows for a large variety of material to be printed.[54]

The applications that advances in the field of bioprinting may provide are mind-boggling – to say the least. The most obvious field where this technology can be applied is regenerative medicine.[55] Engineering of artificial organs would first and foremost alleviate the shortage of donor organs that are required.[56] It could also put an end to the illegal trade with human organs.[57] Additionally, the technology allows the use of autologous material, i.e. material that derives from the patient: the immune system would not reject an organ created from the patient's own cells.[58] Regeneration of functional skin and cartilage by using inkjet bioprinting is already possible.[59] The skin could be used for severely burned victims.[60] Inkjet and laser-assisted bioprinters have also been used to fabricate bone tissues.[61] Bioprinting of nerve cells could be applied to treat diseases of the central nervous system such as Alzheimer's and Parkinson's disease.[62] *Jana* and *Lerman* provide an overview of current research in relation to bioprinting.[63] The table shows that the printing of blood vessels, bones, breast implants, cardiac valves, cartilage, but also more complex objects such as complete organs (ear, heart, kidney, liver, nerves and skin) are currently being researched on.

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[44] Mandrycky, Wang, Kim & Kim, *supra* n. 16, 425.
[45] *Ibid*., 422-434, 425; Murphy & Atala, *supra* n. 13, 777.
[46] Murphy & Atala, *supra* n.13, 777.
[47] Jana & Lerman, *supra* n. 16, 1508.
[48] Murphy & Atala, *supra* n. 13, 777.
[49] Sundaramurthi et al., *supra* n. 15, 13.
[50] Jana & Lerman, *supra* n. 16, 1507.
[51] Murphy & Atala, *supra* n. 13,778.
[52] *Ibid*. 773, 778.
[53] Jana & Lerman, *supra* n. 16, 1507.
[54] *Ibid*., 1503-1521, 1507 (adding that the coated film used for the printing process must be biologically individualized).
[55] Sundaramurthi et al., *supra* n. 15, 9.
[56] Ravi Birla, *Introduction to Tissue Engineering: Applications and Challenges*, 3 (1st ed., Wiley 2014).
[57] Katherine A. Smith, *"Transplanting" Organ Donors with Printers: The legal and ethical implications of manufacturing organs*, 49 (3) Akron Law Review 739, 767-768 (2016).
[58] Chua & Yeong, *supra* n. 14, 168.
[59] Murphy & Atala, *supra* n. 13, 776.
[60] This technology has also been conducted *in vivo*, i.e. by bioprinting skin directly into a wound or burned tissue – Murphy & Atala, *supra* n. 13, 782.
[61] Chua & Yeong, *supra* n. 14, 165.
[62] Sundaramurthi et al., *supra* n. 15, 19.
[63] Jana & Lerman,*supra* n. 16, 1510.

The applications, however, go further than direct applications within or on the human body. Such tissues can also be used in basic research and drug discovery[64] or for pre-surgery planning on realistic bioprinted organs.[65] Reproducing human tissue by bioprinting could end animal testing for regulatory approval.[66] Additionally, meat and leather could be produced by using bioprinting.[67] The technology promises to be exciting, with a wide array of applications. The current challenges that the technology faces are based on specific technical, material and cellular aspects.[68] One challenge that bioprinting complex organs needs to tackle is the vasculature of such 3D constructs to create a viable organ.[69] Nutrients and oxygen have to be supplied to create a viable organ.[70] Once a certain degree of thickness of a tissue is reached then a vascular system is required.[71] Aside from these technical challenges, the high costs of bioprinters will be likely to prohibit wider application of this technology.[72]

2. A basic overview of the current patent landscape in bioprinting

In the context of a growing field of technology, the question of patenting becomes increasingly relevant for the emerging bioprinting industry. While sharing elements of conventional 3D printing[73], 3D bioprinting encompasses an entirely new and distinctive range of applications that may individually attract patent protection, such as new forms or improved versions of bioink[74], or new and innovative bioprinting apparatuses.[75] While patenting appears to be the intuitive intellectual property right used to exploit these new and research-heavy applications[76], it must be borne in mind that other intellectual property and related rights may be similarly relevant: Trademarks, copyright and database protection along with trade secret law and unfair competition could be equally important measures for bioprinting entrepreneurs[77] and will be addressed by other contributions. In the following section we focus on 1) main patent actors, stakeholders and activities; 2) most relevant fields of technologies and typical patent claim categories, and 3) the most likely future developments in the patent landscape.

2.1 Main patent actors, stakeholders and activities

[64] Murphy & Atala, *supra* n. 13, 782; Varkey & Atala, *supra* n.14, 278.
[65] Varkey & Atala, *supra* n. 14, 280.
[66] Chua & Yeong, *supra* n. 14, 166.
[67] Carolyn Mattick and Brad Allenby, *The future of meat*, 30 (1) Issues in Science and Technology 64, 65 (2013).
[68] Murphy & Atala, *supra* n. 13, 773, 781; Mandrycky, Wang, Kim & Kim, *supra* n. 16, 431; Lijie Grace Zhang, John Fisher and Kam Leong, *3D Bioprinting and Nanotechnology in Tissue Engineering and Regenerative Medicine*, 73-74 (1st ed., Academic Press 2015).
[69] Chua & Yeong, *supra* n. 14, 164; Varkey & Atala, *supra* n.14, 295.
[70] Sundaramurthi et al., *supra* n. 15, 19.
[71] Xiaofeng Cui, Thomas Boland, *Human microvasculature fabrication using thermal inkjet printing technology* 30 (31): 6221-7 Biomaterials (2009).
[72] Chua & Yeong, *supra* n. 14, 164.
[73] Tran, *supra* n. 12, 123, 137.
[74] Zhang, Fisher and Leong, *supra* n. 68, 356.
[75] John F. Hornick and Kai Rajan, *The 3D Bioprinting Patent Landscape Takes Shape as IP Leaders Emerge* (July 2016) available at: https://3dprintingindustry.com/news/3d-bioprinting-patent-landscape-takes-shape-ip-leaders-emerge-84541 (accessed: 06 January 2017).
[76] Zhang, Fisher and Leong, *supra* n.68, 354.
[77] Robert W Esmond, *Bioprinting: The patent landscape*, available at: https://www.pharmafocusasia.com/strategy/bioprinting (accessed 6 January 2017).

Due to enormous and risky investments in this complex new technology, the bioprinting industry and researchers are increasingly relying on patent protection, with the number of patent applications expected to rise steadily.[78] This is highlighted in a study by *Hornick* and *Rajan*, who have conducted a worldwide search for patents in the field of bioprinting.[79] The search revealed a steady rise in patents and pending applications from 700 in April 2015 to almost 900 in June 2016; an increase of 36% in patent activity.[80] *Hornick* and *Rajan* also demonstrated that while more than 100 companies from different countries around the globe are currently showing patent activity in the field of bioprinting, a few companies are clearly lying ahead of the others. The aforementioned market leader Organovo, which doubled their portfolio in the period investigated, as well as Wake Forest University and Philips, are the three top companies on *Hornick* and *Rajan's* list.[81] Generally, the patents investigated are owned by companies while some are held by the original inventor.[82] But advances in technology along with regulatory approval of the medical applications of bioprinting are likely to shift the dynamics between the players in the field of bioprinting.[83]

Another investigation into current patent activity by *Robert W. Esmond* showed that the majority of patent filings originate from the United States.[84] The findings of this search pooled the patents granted into three main areas of relevant technologies with particularly vibrant patent activity. The following section provides a brief summary of these categories and the typical patent claims.

2.2 Most relevant fields of technologies and typical patent claim categories

Considering the different stages of development in bioprinting, the most relevant fields of technologies and typical patent claims can be distinguished into (1) a *preprocessing or design phase*, (2) a *production phase*, and (3) a *post-production maturation* phase.[85]

In the *preprocessing or design phase* patent claims are typically directed to machines, methods and techniques used in bioimaging and computer aided design (CAD). One example that falls into this category is US patent No. 8579620 "Single-action three-dimensional model printing methods" (Exp. Date: May 30, 2031), which is assigned to the inventor Andy Wu.[86] This patent claims systems and methods for single-action printing of 3D physical models from a three or n-dimensional image data set. It describes geometric representations of different physical models and discloses complex data conversion processes that convert input image data into geometric representations compatible with third party 3D printers. The patented technology uses printing templates to encapsulate complex geometric representations and complicated data conversion processes from users for fast and simple 3D physical model printing applications.[87]

In the *production phase* some of the most important patents issued are directed to bioinks, in particular hydrogels, biopaper and bioprinting apparatuses as such. One example is

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[78] Seung-Schik Yoo, *3D-printed biological organs: medical potential and patenting opportunity*, 25 (5) Expert Opinion on Therapeutic Patents, 507, 510 (2015).
[79] Hornick and Rajan, *supra* n. *75*.
[80] This value relates to the observable, i.e. published patents and application while the actual value could be higher due to unpublished patent applications - Hornick and Rajan, *supra* n. 75.
[81] Hornick and Rajan, *supra* n. 75.
[82] *Ibid*.
[83] *Ibid*.
[84] Esmond, *supra* n. 77.
[85] *Ibid*.
[86] Andy Wu, *Single-action three-dimensional model printing methods*, US 8579620 B2, http://www.google.com/patents/US8579620 (2013).
[87] *Ibid*.

US patent No. 8143055 "Self-assembling multicellular bodies and methods of producing a three-dimensional biological structure using the same".[88] The patent claims appear to cover bioprinted tissues and organs containing patterned discrete filler bodies that resist migration and ingrowth of patterned multicellular bodies containing living cells. These filler bodies may include sacrificial hydrogels that form tubular engineered blood vessels inside tissues and organs.[89] This patent, which was also filed at the European Patent Office and in Australia, Canada, China, Japan and South Korea, was originally assigned to *The Curators Of The University Of Missouri* and expires on June 24, 2029. However, the University of Missouri had entered into an agreement with *Organovo*, which now holds the exclusive license in all fields to multiple patent families, including this issued patent and future continuation patents derived from the same application.[90]

Another example is British patent GB2478801 directed to "Multilayered Vascular Tubes" (Expiration date March 16, 2031) which was also filed in Canada, China, European Patent Office, Israel, Japan, South Korea, Russia, and the United States.[91] It is assigned to *Organovo Inc*. and claims *inter alia* "an engineered multilayered vascular tube comprising an outer layer of differentiated adult fibroblasts, at least one inner layer of differentiated adult smooth muscle cells and differentiated adult endothelial cells, which have particular features."[92] This patent describes in detail how the engineered multilayered vascular tube is constructed and produced by laying manually elongate cellular bodies and elongate bodies of gel matrix. The patent also describes the use of a bioprinter to make the same structure.[93]

In the *post-production and maturation phase***,** additional patenting prospects might emerge in advanced organ production. These include so-called *maturongens*, i.e. biochemical and physical factors that accelerate tissue maturation[94], or so-called *bioreactors*, i.e. new technologies, materials and machines that provide nutrients to cells in the post-print phase.[95] The aforementioned *Esmond* study, however, only identified pending patent applications that

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[88] Gabor Forgacs, Francoise Suzanne Marga, Cyrille Norotte, *Self-assembling multicellular bodies and methods of producing a three-dimensional biological structure using the same*, US 8143055 B2, http://www.google.com/patents/US8143055 (2012).

[89] Cf. Esmond, *supra* n. 77. What is claimed is: 1. A three-dimensional structure comprising: a plurality of multicellular bodies, each multicellular body comprising a plurality of living cells cohered to one another; and a plurality of discrete filler bodies, each filler body comprising a biocompatible material that resists migration and ingrowth of cells from the multicellular bodies into the filler bodies and resists adherence of cells in the multicellular bodies to the filler bodies, wherein the multicellular bodies and filler bodies are arranged in a pattern in which each multicellular body contacts at least one other multicellular body or at least one filler body.

[90] Press Release of 9 July 2012, *Organovo Announces Two Issued Patents, First Company Patent and Key Founder Patent*, https://www.sec.gov/Archives/edgar/data/1497253/000119312512297696/d379308dex992.htm (accessed 10 December 2016).

[91] *See* Covalent Data, *Multilayered vascular tubes*, GB 2478801 B, https://covalentdata.com/patent/GB2478801B, referring also to patents: AU2011227282B2, CA2793205C, CN102883680B, CN105749349A, EP02547288A2, GB2489081B, HK1159682A1, mJP2016052527A, JP5950899B2 and KR20130007610A.

[92] Claim 1 reads: "1. An engineered multilayered vascular tube comprising an outer layer of differentiated adult fibroblasts, at least one inner layer of differentiated adult smooth muscle cells and differentiated adult endothelial cells, and having the following features: (a) a ratio of endothelial cells to smooth muscle cells of 1:99 to 45:55; (b) the engineered multilayered vascular tube is compliant; (c) the internal diameter of the engineered multilayered vascular tube is 6 mm or smaller; (d) the length of the tube is up to 30 cm; and (e) the thickness of the engineered multilayered vascular tube is substantially uniform along a region of the tube; provided that the multilayered vascular tube is non-innervated and free of any pre-formed scaffold".

[93] Lens.org, *Multilayered vascular tubes*, https://www.lens.org/lens/patent/GB_2478801_B.

[94] *See* the definition provided in Paulo Jorge da Silva Bartolo, *Innovative Developments in Virtual and Physical Prototyping: Proceedings of the 5th International Conference on Advanced Research in Virtual and Rapid Prototyping, Leiria, Portugal, 28 September - 1 October, 2011*, 127 (CRC Press 2011); *See also* Ibrahim Tarik Ozbolat, *3D Bioprinting: Fundamentals, Principles and Applications*, 319 (Academic Press 2016).

[95] Yoo, *supra* n. 78, 507, 509; 510.

cover these types of technologies.[96] Instead of covering fully functioning organs or more advanced maturation systems, current patents rather cover the production of organ cells, such as 9,442,105 " Engineered liver tissues, arrays thereof, and methods of making the same"[97] assigned to *Organovo* Inc. in 2014, or technology that might one day provide the foundation for the transplantation of bioprinted organs. One example is US *8747880* "Engineered Biological Nerve Graft, Fabrication and Application Thereof". Once again the patent, which expires on May 28, 2031, has been originally assigned to *The Curators Of The University Of Missouri* with *Organovo* being the most likely licensee. It covers an engineered three-dimensional nerve graft that may be made using bioprinting techniques. The structure is suitably a graft that facilitates restorative axon growth when the graft is implanted between the proximal and distal stubs of a severed nerve in a living organism. [98]

2.3 What lies ahead in the patenting landscape

As described above, the foundational technology for bioprinting has already resulted in many, partially overlapping, patents that are predominantly assigned to a few market-leaders, such as *Organovo Inc.* Yet several missing engineering components for the ultimate creation of printed biological organs indicate that much room remains for further patentable improvements.[99] After all, the production of complete organs is still in a state of infancy. The complicated nature of human organs, in addition to the legal and ethical requirements for safe implantation into the human body, would require significant research and development to produce marketable bioprinted organs.[100] As is further pointed out by *Seung-Schik Yoo,* this also suggests the possibility for further patenting and licensing opportunities from different sectors of the economy. In particular, Yoo asserts that so many technical aspects of organ printing remain unresolved that it is unrealistic to expect intellectual property in this area to be dominated by a monopolist or an oligarchy. He fully expects biotechnological advances to result in human organ production in a wider context of multiple uses of printed organs and tissue, in turn associated with an ever-growing volume of patent applications. [101]

However, a caveat needs to be added: Based on the current state of the art, it would take many years, probably even decades, of research and development to have marketable bioprinted organs with high-order functionality that fulfill the ethical and legal requirements for ultimate use in humans.[102] Some researchers have even questioned whether it will be technically possible to create a functioning bioprinted organ:

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[96] 1. A multicellular construct consisting essentially of: a multicellular region comprising: a plurality of living cells cohered to one another to form an elongate graft for restoring neural connection between the ends of a severed nerve; a plurality of a cellular channels extending axially through the multicellular region; and wherein the multicellular construct does not comprise any scaffold material at the time of implantation into a living organism having a nervous system.

[97] Benjamin R. Shepherd, *Engineered liver tissues, arrays thereof, and methods of making the same*, US 20140274802 A1, http://patents.com/us-9442105.html.

[98] Gabor Forgacs et al., *Engineered biological nerve graft, fabrication and application thereof,* US 8747880 B2 http://www.google.com/patents/US8747880.

[99] Mohsan Alvi, Matthew Duckett & Robert Gleave, *3D Bioprinting of human transpant organs – A patent landscape*, 15, http://www.collerip.com/userfiles/739.pdf.

[100] Yoo, *supra* n.78, at 507.

[101] *Ibid*., 510

[102] *Ibid.*, (adding that 3D bioprinting could nevertheless "be used to exploit a few niche applications, with less stringent FDA-related regulations, which can be readily put to practical use. These include, but are not limited to, applications to create: i) the artificial skin constructs as testing beds for cosmetic industries (3D bioprinting can readily be adapted to create skin layers with different phenotypes, along with skin blemishes and colors); ii) the 3D tissue structures/mini-organs, replicating major key components of liver/kidney tissues that have relevance to

> For example, Dr. Darryl D'Lima, a researcher at the University of Manchester in Britain, has been quoted as saying that "Nobody who has any credibility claims they can print organs, or believes in their heart of hearts that will happen in the next 20 years." And, there have been reports that Dr. Gabor Forgacs, inventor of the Missouri patents and Scientific Founder at Organovo, has questioned whether the days of printing organs will ever come.[103]

Before the first fully functional bioprinted organ can be made and approved by regulatory authorities, such as the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA), it is thus highly likely that many basic patents will have expired. Moreover, many countries have codified various exceptions to patent infringement, such as research *and/or* experimental use exemptions.[104] In both Europe and the United States, the law provides, for example, for an exemption to patent infringement when the patented item or material is tested for obtaining market approval from the EMA or the FDA.[105] Thus, in many countries, some research and clinical testing of a patented bioprinted organ or tissue could be carried out without infringing patents. However, due to rather vague wording in the legislation and different interpretations in national case law, the precise scope of such exemptions varies and is hence rather unclear. Unsurprisingly, this provides rich fodder for debates in academia and jurisprudence, which often call for harmonized approaches with regard to such types of exemptions.

Be that as it may, overall it can assumed that if the technical and regulatory challenges to making and using bioprinted tissues and organs are overcome, the future of innovation in bioprinting technology will be very bright and patenting activities will continue.[106] Another question is of course how far future advances in bioprinting technology would comply with the regulatory framework for technological uses and if they would meet the basic patent criteria or fall under the exceptions and exclusions from patentability.

3. Basic US and European patentability criteria and bioprinting

The above concise overview on the current patent landscape and the typical claims provide the very first understanding of what categories of patents are typically being granted or applied for. Patent landscaping may also reveal useful information about the main stakeholders in the field and where the area is heading. At the same time, it also became clear that there are many unknowns with regard to pending applications and that the landscape might be rapidly shifting due to new technological developments, new collaborations and strategic alliances. Moreover, the patentability of future developments and applications, involving cloned organs, stem cells and other biologically engineered tissues, remains problematic and raises many questions and uncertainties.

It is evident that the interplay between patent law and technological development is two-fold. On the one hand, bioprinting application will challenge patent law and other legal frameworks, which might result in new court decisions or even legislative developments. On

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systemic toxicity/efficacy screening of pharmacological drugs in high-throughput fashion; and iii) the in vitro tumor tissue models that enable the examination of tumor infiltration, growth and metastasis".

[103] Cf. Esmond, *supra* n. 77.

[104] Cf. Hans Rainer Jaenichen & Johann Pitz, *Research exemption/experimental use in the European Union: patents do not block the progress of science*, 5(2):a020941 Cold Spring Harb Perspect Med. (2014); *see also* Alicia A. Russo and Jason Johnson, *Research Use Exemptions to Patent Infringement for Drug Discovery and Development in the United States*, 5(2):a020933 Cold Spring Harb Perspect Med. (2015).

[105] See András Kupecz et al., *Safe harbors in Europe: an update on the research and Bolar exemptions to patent infringement*, 33 Nature Biotechnology, 710–715 (2015).

[106] *Ibid.*

the other hand, the applicable rules on patentability and regulations will certainly have an impact on the financing of research and might accordingly direct research focus into particular lucrative areas.

This illustrates the importance of understanding how current patent law applies to bioprinting technologies. Hence, this section will briefly describe the current legal frameworks and requirements for patentability that we consider to be most relevant for bioprinting technology. The patent landscape discussed above showed that bioprinting contains an array of different stages which encompass different fields of technology such as biochemistry, biotechnology, computer sciences and mechanics. We will focus our analysis on selected aspects regarding the "biological" material and processes involved in bioprinting relating to the production and post-production phase of bioprinting, rather than dealing with "mechanical" inventions stemming from this technology. This is because biological material poses more issues for patenting than mechanical devices. Furthermore, our analysis will concentrate on US patent law and the European Patent Convention (EPC). We will also touch upon relevant stipulations in the EU Biotech Directive. However, the analysis will concentrate on the legal framework applicable at the European Patent Office (EPO), rather than national patent laws. Section 3 will focus on basic patent criteria for product and method claims. Section 4 will deal with the particularly important questions of *morality* and *ordre public* in patent law and will analyse whether bioprinting technologies will pose new challenges to the existing legal framework.

3.1 Product claims

As indicated above, product claims on bioprinting technologies might encompass the machines and mechanical parts that are being used in the bioprinting process itself. But they might also be directed to innovative biological printing material, such as bioink, or the end-product made from biological material and resulting from the bioprinting process. As mentioned, strictly "mechanical innovation" relating to bioprinting machines and mechanical processes might not lead to any extraordinary issues in the assessment of the basic patentability criteria, such as patent eligibility, novelty, inventive step/nonobviousness, industrial application/utility and sufficient disclosure. The patent system has dealt with these types of inventions for hundreds of years. This is why our brief analysis will focus on the biotechnological aspects of bioprinting innovation, where patentability issues are far more complex.

3.1.1 US[107]

Unlike European patent legislation,[108] US patent statutes have traditionally not defined what sorts of inventions or discoveries fall outside the scope of patentability.[109] It has thus been the province of the courts to establish limits for subject matter that may not be granted patent protection. The generally accepted explanation is that these are Constitutional limitations

[107] As for the introduction to section 3.1.1, cf. Robert M. Schwartz & Timo Minssen, *Life after Myriad: The Uncertain Future of Patenting Biomedical Innovation & Personalized Medicine in an International Context*, 2015 (3) Intellectual Property Quarterly, 189-241, 190.

[108] *See* e.g. the exceptions to patentability of Art. 52(2)–53 EPC. However, the interpretation of these ambiguously phrased exceptions is also highly controversial. European debates are further complicated by the contentious definition of the term "invention" in i.a. Art. 52 (1) EPC and the stipulations in the Biotech Directive 98/44/EC.

[109] Until recently nuclear weapons were the only invention-category completely excluded from patent eligibility (albeit not from a prize-system). However, this exclusion is not codified in the Patent Act, but in the Atomic Energy Act. 42 U.S.C. § 2181(a) (2000).

based upon the framers' intent in enacting the Patent Clause.[110] Although several bills had attempted to exclude genes and proteins from patent protection,[111] the *2011 America Invents Act (AIA)*[112] only introduced very few exceptions, which will be considered in section 4. [113] Hence, fundamental questions of patent eligibility are principally still left relatively open and for the courts to decide.

Until a few years ago, US Courts kept this threshold rather low as exemplified by the decision in *Diamond v. Chakrabarty* (1980)[114] which held that any *man-made* product or process could be patented if it did not claim "principles of nature, natural phenomena, abstract ideas or mental processes." *Chakrabarty* thus identified "human intervention" as the key to patentability. For many years, the "human intervention" standard was interpreted in a rather patent-friendly way. Human genes and proteins, for example, were held to be principally patent-eligible, as long as some human inventive activity was involved, such as new identification and isolation of a naturally occurring gene from its natural environment.

On June 13, 2013, however, the threshold was raised considerably when the US Supreme Court decided the *Myriad gene* patent case[115]. In a unanimous judgment, the Court held that patent claims directed to isolated genomic DNA are identical to the naturally occurring sequence and thus unpatentable "products of nature". Because its genetic information was neither created nor altered, DNA did not qualify as a product of human ingenuity and because isolating DNA from its surrounding genetic material did not significantly add to DNA's natural state, it did not qualify as non-naturally occurring.[116] This decision affects all isolated "products of nature", including genes, gene fragments, and other naturally occurring nucleotide sequences, as well as naturally occurring amino acid sequences, including peptides, ligands, and proteins. Consequently, *Myriad* may have an impact on bioprinting patent portfolios, although it is still not entirely clear how much modification is required to render a molecule sufficiently distinct from naturally occurring counterparts.

It is clear, however, that *Myriad* does not directly affect the patentability of cDNA or sufficiently modified compounds, such as synthetic DNA and other synthetically produced biological material. Moreover, the most recent USPTO guidance and new Federal Circuit decisions provide hints on how the new eligibility standard can be met.[117] To avoid a "product of nature" rejection, a claim must satisfy a two-prong test:

(1) *a product of human ingenuity*, and
(2) *nonnaturally occurring*.

Accordingly, the patentability of bioprinting depends on whether a bioprinted product is a product of human ingenuity and nonnaturally occurring. While some of the base materials used in printing may be naturally produced, in the same way as nucleotides in cDNA can be

[110] E.g. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) at 315.
[111] In 2007, for example Michael Crichton teamed up with Lori B. Andrews, from the Chicago-Kent College of Law, and found support by Representatives Xavier Becerra and Dave Weldon, who unsuccessfully introduced a Bipartisan Bill (HR 977) in the 110th Congress to restrict future patenting of genes and proteins.
[112] The HR 1249 Leahy-Smith America Invents Act (2011).
[113] The HR 1249 introduced an immediately effective ban on patents covering tax strategies and/or claims "directed to or encompassing" human organisms (see section 33). These will apply to all pending applications (Dr. Frankenstein must now rely on trade secrets).
[114] *Diamond v. Chakrabarty*, *supra* n. 110 (holding that a genetically engineered bacterium created by the inventor's process was a patentable "manufacture" under §101 of the U.S. Patent Act).
[115] Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).
[116] Jasper L. Tran, *Patenting Bioprinting* Harvard Journal of Law and Technology Digest, 2015 symposium, 2, https://ssrn.com/abstract=2603693 (2015).
[117] The current 2016 USPTO patent eligibility guidelines are available at: https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility (accessed 10 December 2016).

naturally produced, technically, anything related to bioprinting is a result of human ingenuity: both bioprinting processes and bioprinted products are man-made. The more complex prong is proving that a bioprinted product is non-naturally occurring.[118]

State of the art bioprinting technology does not yet allow for perfect reproduction of human organs; marked differences exist between real organs and bioprinted ones.[119] Current bioprinted human living tissues are functionally similar to but structurally different from real human living tissues. Until scientists can bioprint structurally similar living tissues, bioprinted products are different enough from their naturally-occurring analogs to be patent-eligible subject matter.[120] However, should the technology develop in the future to allow for the perfect replication of human organs, the line between patentable and unpatentable subject matter could blur significantly.[121] Such perfectly replicated organs could be considered analogous to "very short series of DNA [that] have no intervening introns to remove when creating cDNA" which "may be indistinguishable from natural DNA" and thus not patent-eligible under § 101.[122] But what about the bioprinting of biological clones?

In this context, the Federal Circuit decision in *In re Roslin Institute* needs to be observed, where it was held that a clone which was an exact genetic copy of a naturally existing sheep was not patent-eligible subject matter.[123] Yet, according to some US commentators, this would not necessarily prevent the patentability of a clone-printed, man-made and non-human organism. As it is pointed out by Jasper L. Tran:

> There is no reason to expect that a clone made by any other process would be treated differently. However, in the wake of *Chakrabarty*, numerous patents have been filed on transgenic organisms. For example, U.S. Patent No. 8,088,968 claims a transgenic animal (e.g., a mouse) and its tissues.[124]Accordingly, cloneprinting of a naturally existing organism is likely not patentable, but cloneprinting of a man-made organism (i.e., a genetically engineered animal) could likely be patentable.[125]

The patenting of clones of entire human persons (including fetal, embryonic states and chimera), however, would not be possible due to section 33 AIA, which will be addressed in section 4.

3.1.2 Europe

The most essential patentability criteria in the European Patent Convention ("EPC")[126] are summarized in Article 52(1) EPC 2000, which provides:

> European patents shall be granted for any inventions, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application.

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[118] Tran, *supra* n. 116. 2.
[119] David Wang, *Are 3D Printed Tissues and Organs Patentable?* Columbia Science and Technology Law Review Blog, http://stlr.org/2015/10/07/are-3d-printed-tissues-and-organs-patentable/ (accessed 10 December 2016).
[120] Tran, *supra* n, 116, 2.
[121] Wang, *supra* n. 119
[122] *Ibid* (citing Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S.Ct. 2107, 2116 (2013), 2219).
[123] *In re Roslin Institute* 750 F.3d 1333 (Fed. Cir. 2014).
[124] Tran, *supra* n. 116, 2.
[125] *Ibid* (internal citation omitted).
[126] European Patent Convention of 5 October 1973 as revised by the Act revising Article 63 EPC of 17 December 1991 and the Act revising the EPC of 29 November 2000 ("EPC"). Text as adopted by decision of the Administrative Council of 28 June 2001. *See also* OF 4/2007 Revision of the European Patent Convention (EPC 2000).

Considering the wording of the article, it is clear that despite having to meet the most basic patent criteria, such as novelty, inventive step and industrial application, patents and patent applications in bioprinting must be based on a "technical invention". This is also confirmed by the implementing regulations to the EPC, which emphasize that the invention must have *technical features* (Rule 43(1)), which relate to a technical field (Rule 42(1)(a)) and are concerned with a technical problem (Rule 42(1)(c)). Although the EPC does not explicitly define the concept of "inventions" as such, it is evident from these provisions that the "technicality" of inventions is a crucial prerequisite for meeting European patent eligibility standards. Hence it comes as no surprise that several court decisions in EPC contracting states have elaborated on the issue.[127]

However, and in contrast to most of the codified US patent law, Articles 52(2) and 52(3) of the EPC explicitly codify exclusions, which are not considered to be inventions, i.e. at least if they are claimed "as such" . These exclusions are used to reject claims that are abstract in nature (discoveries) or non-technical in nature (scientific theories or methods for performing mental acts).

Most bioprinting processes and bioprinted products are the result of a technical man-made process with the help of man-made machinery and would thus fulfill the European technicality requirement. But what about the naturally occurring compounds in bioink and other bioprinted products?

With respect to isolated biological compounds, such as DNA sequences and proteins, the main provisions of the EU's Biotechnology Directive 98/44/EC were quickly incorporated into the Implementing Regulations ("IR") to the EPC by a decision of the Administrative Council of the European Patent Organization ("EPOrg") of June 16, 1999.[128] Thus, the patentability of biotechnological inventions is assessed by the EPO based on a one-to-one implementation of the EU Biotech Directive, i.e. although the EPO is not formally bound by European Community law. Rule 23(e)(2) (now Rule 29 (2) EPC 2000) of the Implementing Regulations now defines which biological material originating from the human body may be patented. Like Article 5 (2) of the Biotech Directive it states that:

> (2) An element isolated from the human body or otherwise produced by means of a technical process including the sequence or partial sequence of a gene may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

But even before the relevant stipulations of the Biotech Directive were incorporated into the EPC, the patent-eligibility of isolated biological material had already been unambiguously and clearly confirmed by earlier EPO case law. For example, in decision T 272/95 *Relaxin/HOWARD FLOREY INSTITUTE*[129] concerning a DNA fragment encoding human H2-preprorelaxin with a specific amino-acid sequence useful during the child birth-process, the EPO appeared to lay the issue to rest. The opponent had argued that the essence of the invention was no more than elucidation of the genetic sequence of the H2-relaxin gene. In the view of the opponent this was no more than a discovery of the characteristics of a substance which had existed in nature probably for many thousands of years. In granting the patent the EPO rejected *inter alia* these specific arguments based on the understanding that an isolated gene contains technical information, in the sense that the aspect of "isolation" is considered to be the result of technical processes used to identify, purify and classify it, techniques which

[127] *See* e.g. Biogen Inc. v. Medeva Plc. Hepatitis-B-virus, 1997: R.P.C. 1 (41–42); Red Dove (Rote Taube), X ZB 15/67: Federal Supreme Court, 1969. 1 I.I.C. 136, 1970 ("Lehre zum planmässigen Handeln" = "methodological teaching").
[128] OJ EPO 1999, p. 437-440 and 573 ff.
[129] *See* T0272/95 Relaxin/Howard Florey Institute (Unreported, Boards of Appeal, European Patent Office), 23 October 2002), [4], [6]–[7].

human beings alone are capable of carrying out in a methodological manner and which nature is incapable of accomplishing by itself. [130]

The same reasoning, now codified in Rule 29 (2) of the Implementing Regulations to the EPC 2000, has also been applied in various EPO decisions on Myriad's BRCA1 patents related to claims for diagnosing a predisposition for breast and ovarian cancer in a human subject.[131] In addition it should be noted that the EPC – apart from certain specific exceptions[132] – does not contain any categorical use restrictions for product protection. There are thus no technology-specific provisions in the EPC that categorically limit the protective scope of gene- or protein-related patent applications to the uses specified in the claims – in contrast to some national European jurisdictions.[133] Under Rule 42(1) (f) EPC 2000,[134] it is sufficient if the applicant provides the industrial applicability in the description of the invention, and must only do so explicitly when it is not obvious from the description or nature of the invention. This basic condition is now specified particularly for gene sequences and partial gene sequences in Rule 29(3) EPC 2000, which fully corresponds to Article 5(3) of the Directive.

Isolated genomic DNA *per se* is thus, in contrast to the current US approach, principally patentable both before the EPO and national patent offices as no office distinguishes between naturally occurring genomic DNA and corresponding cDNA. Accordingly, it may be concluded that, although the patentability of isolated biological material remains controversial in Europe, the decision by the US Supreme Court to exclude naturally occurring biological compounds from patent-eligibility appears to be in conflict with current European practice.

Hence, most bioprinting products would in principle be patent-eligible in Europe, unless they fall under the exemptions from patentability, which will be dealt with in sections 3.2 and 4. In particular the morality clauses in European Patent Law could turn out to be a major obstacle for the patentability of organs and clones.

3.2 Method claims

Even when bioprinting products might not pass the US and European patent eligibility requirements, applicants could still consider seeking patent protection for process claims rather than product claims. Instead of covering ineligible products, a bioprinting process claim could be limited to printing activities and thus pass the bar. Provided that ineligible products are not mentioned in process claims, and the relevant claims do not depend on bioprinted ineligible products, such claims can be patentable.[135] Or, in other words: the 3D printing process itself does not necessarily violate the principle of no patent for human organisms *per*

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[130] *Ibid*. *See also* Article 5 (2), as well as Recitals 20 and 21 in the Biotech Directive. Cf. Howard Florey/Relaxin [1995] EPOR 541.

[131] Cf. *T 1213/05 Breast and ovarian cancer/UNIVERSITY OF UTAH* (EPO 27 September 2007); *T 0666/05 Mutation/UNIVERSITY OF UTAH* (EPO 13 November 2008 & *T 0080/05 Method of diagnosis/UNIVERSITY OF UTAH* (EPO 19 November 2008).

[132] For instance, patent applications in respect of medicinal indications pursuant to Article 54(4) and (5) EPC, and product claims that can be defined solely through their function. *See* for more: Timo Minssen, *KliFoRe*, Heft Nr. 3 and 4 (2008), p. 93 ff, available at: http://jura.ku.dk/english/staff/research/?pure=en%2Fpublications%2Fes-bleibet-dabei-eine-schwedische-stellungnahme-zur-europaischen-debatte-uber-den-absoluten-erzeugnisschutz-bei-der-dnapatentierung--teil-1(35c50066-1f9c-4757-8b52-17a18e7922e5).html (accessed 30 January 2017).

[133] Cf. Rainer Moufang's contribution to the 15th European Patent Judges' Symposium, Lisbon, 14-18 September 2010: *Use and purpose limitations in patent claims*, OJ EPO Special edition 1 (2011).

[134] Rule 42(1)(f) "[The description] shall indicate explicitly, when it is not obvious from the description or nature of the invention, the way in which the invention is industrially applicable."

[135] Cf. Tran, *supra* n. 116, 2.

se notwithstanding the mere possibility that 3D-printed human tissue could theoretically be used in unpatentable products later in the process."[136]

3.2.1 US

At first sight, two recent US Supreme Court cases addressing the patent-eligibility of method claims appear to be relevant for bioprinting:

In 2012, the US Supreme Court issued a unanimous decision in *Mayo v. Prometheus*[137] invalidating patent claims for diagnostic methods under the "laws of nature, natural phenomena, and abstract ideas" exception to 35 U.S.C. § 101's standards for patent-eligibility. Writing for the Court, Justice Breyer invalidated the relevant claims[138] because they "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm."[139] The Court further held that the steps of "administering" the drugs, telling the physician to take the laws of nature into account, and "determining" the metabolite level, in a specific order of steps were "well-understood, routine, conventional activit[ies]…" adding that they comprised "nothing beyond the sum of their parts...".[140] While the additional steps recited in the processes claimed in the case were not to be considered natural laws as such, a patent applicant would have been required to add more in order to transform them into patent-eligible claims. Thus, the Supreme Court held that in order to transform an unpatentable law of nature into a patent-eligible application of such a law, it is not sufficient to simply state the law of nature and add the phrase "apply it". The Court held that appending conventional steps, specified at a high level of generality, to laws of nature, natural phenomena and abstract ideas could not render those laws, phenomena, and ideas patent-eligible.

Yet, since bioprinting processes are created by scientists and are carried out by machines that are not found in nature, most bioprinting processes would normally not qualify as a "law of nature" under the *Prometheus* approach. Therefore, *Mayo* usually does not apply to bioprinting process claims.[141] But what about claims concerning the software that is used in bioprinting machines?

In 2014, the Supreme Court considered the patentability of software patents in *Alice Corp. v. CLS Bank*[142]. In *Alice*, the Supreme Court set forth a two-step process for assessing patent-eligible subject matter in the context of computer-related inventions:

1) Initially, determine whether the patent claim at issue is directed to an abstract idea.
2) If so, consider whether the claim elements individually or in combination "transform" the claim into a patent-eligible invention.

The Court described the test as a quest for an "inventive concept" to ensure that the patent amounts to "significantly more" than an abstract idea. For the second step, the Supreme Court

[136] *Ibid.* (Providing examples of this approach by referring to U.S. Patent No. 7051654 B2 claiming a method of "forming an array of viable cells" & U.S. Patent No. 8691974 B2 claiming a method of "producing 3-D nano-cellulose based structures.)
[137] *Mayo v. Prometheus*, 132 S.Ct. 1289, 1291–92 (2012).
[138] The claims at issue in the patents were directed to three essential steps in a process by which a doctor (1) administered the drug, (2) determined the metabolite levels in the blood, and (3) a 'wherein' step which described the likely effects of a dose and respectively indicated a need to increase or decrease the dosage. *See* e.g. Prometheus Laboratories' US Patent No. 6355623 B2 and US Patent No. 6680302 B2.
[139] *Mayo v. Prometheus*, *supra* at 137, 1296.
[140] *Ibid.*, 1297-1298.
[141] Tran, *supra* n. 116, 2 (adding: "Unfortunately, besides Mayo, there is no closer case where the process was patentable despite being closer to a law of nature than bioprinting is.").
[142] *Alice Corp. v. CLS Bank*, 134 S.Ct. 2347, 2357–59 (2014).

in *Alice* clarified that "the mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention." Moreover, the Court decided that claiming well-understood, routine, and conventional features specified at a high level of generality does not suffice for an "inventive concept." However, the Court gave little guidance beyond those rather extreme patterns and did not specify the precise delimitations of the 'abstract ideas' category.

Be that as it may, 3D printing and bioprinting do not fundamentally depend on software, but print using an electronic blueprint—i.e., a CAD file. Thus, at the current state of the art neither *Prometheus* nor *Alice* necessarily affects the patentability of 3D printing and bioprinting.[143]

Yet this might change. So far, most bioprinting technologies lacked biologically sophisticated software and other bioinformatics tools.[144] But in the future the patentability of more sophisticated software mimicking biological processes and correlations might become more important for bioprinting technologies. Rapid advances in systems biology and synthetic biology in combination with the evolution of data-based applications are now providing increasingly powerful tools. It can be assumed that the combined use of Big Data in bioinformatics will enable the field's next wave of breakthroughs. While a more detailed analysis of these developments falls outside the scope of this paper, these technological developments will certainly have to be observed very carefully. It might therefore make sense to have a look at the European approach in this area.

3.2.2 Europe[145]

As mentioned in section 3.1.2 most bioprinting processes are the result of – or part of – a technical man-made process with the help of man-made made machinery and would thus fulfill the European requirements in Article 52 (1) - (3) . But what about software used in bioprinting?

In comparison, the European eligibility doctrine with regard to software, data-related inventions and diagnostic methods appears to be more flexible than in the US, i.e. despite the existence of an express provision on their excludability. Article 52 (2) of the EPC[146] famously recites a list of 'non-inventions', including abstract ideas, scientific theories, mathematical methods and computer programs, that are excluded 'as such'. The reading of this last condition has led to a de-minimis application of the provision.

"Technical character" is synonymous with invention in EPO Board of Appeals (BoA) case law; any demonstration and degree of 'technical character' passes the patent eligibility threshold. The role of the technical feature is irrelevant; to the point that the mere use of technical means, such as a computer, may render a patent claim eligible. Accordingly, the question asked for computer-based methods that could be used in bioprinting is: does the method achieve a technical effect, or has it only non-technical aspects, e.g. aesthetic or economic?[147]

Mere games or business methods, for example, are not patentable[148], but a method to analyse DNA in silico is.[149] This also applies to simulations or modelling as long as the result

[143] Tran, *supra* n. 116, 2.
[144] Leckart, *supra* n. 2.
[145] *See also* T. Minssen & J. Pierce, *Big Data and Intellectual Property Rights in the Health and Life Sciences*, in: G. Cohen, H. Fernandez Lynch, E. Vayena & U. Gasser (red.), *Big Data, Health Law, and Bioethics*, (Cambridge University Press (forthcoming in 2017)).
[146] Convention on the grant of European Patents (European Patent Convention), (5 October 1973),1065 UNTS 199 ('EPC').
[147] *T 208/84 Computer-related invention* (EPO 15 July 1986) (VICOM).
[148] *T 931/95 Control of a pension fund system* (EPO 8 September 2000) (PBS).

is a teaching which can be used to achieve technical effects in the real world. For instance, a method of encoding audio information in a communication system may aim to reduce distortion induced by channel noise. Although the idea underlying such a method may be considered to reside in a mathematical method, the encoding method as a whole is not a mathematical method "as such", and hence is not excluded from patentability by Article 52(2)(a) and (3) EPC.[150] Similarly, a method of encrypting/ decrypting or signing electronic communications may be regarded as a technical method, even if it is essentially based on a mathematical method.[151]

Similar reasoning applies to medical diagnostic methods and methods of treatment by surgery or therapy which are excepted from patentabilty under Article 53(c) EPC, but only if practiced on the human body. Caselaw has interpreted this requirement very narrowly to allow the patentability of specific genetic diagnostic methods.[152] Likewise it can be assumed that surgical methods conducted on bioprinted tissue and future bioprinted organs would prior to implantation not be considered to be practiced on the human body and would thus not fall under the surgical methods exception as interpreted by EPO case law.[153] Moreover, Article 53(c) EPC explicitly states that these exceptions shall not apply to products, in particular substances or compositions, for use in any of these methods.

In sum**,** the formalistic European approach has, in contrast to the more substantive US approach in *Prometheus* and *Alice*, made patent-eligibility a rather low threshold. In Europe, the patent-eligibility standard has become primarily a question of drafting, where many mixed bioprinting claims and Big Data techniques could with clever drafting pass the patent eligibility threshold. Hence, many bioinformatics programs and increasingly sophisticated applications of these will remain patentable if fulfilling the other patentability requirements such as novelty, inventive step, industrial applicability and sufficient disclosure.

4. Bioprinting and morality exclusions in patent law

While the applications that bioprinting may provide are astonishing, many questions emerge, not just in relation to what applications *are* technically possible, but also whether they *should* actually be achieved. As with many other advances in science, such as nuclear power or biotechnology, issues arise with regard to the morality of new applications. Bioprinting may bring previously fictitious applications closer to reality. Furthermore, it was mooted that the ability to produce new organs may provide mankind with the key to extend the human lifespan[154] or even enable immortality. These may be considerations that regulators and wider society may have to respond to.[155] The ethical aspects created by advances in bioprinting revolve, *inter alia*, around issues surrounding the "cells" used for bioprinting, ownership of the bioprinted organ and the religious and socio-cultural acceptance of this technology.[156] Additionally, the future accessibility of this technology, in other words its cost, can be added

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[149] *See T 0146/07 Prenatal diagnosis/ISIS* (EPO 13 December 2011).
[150] Cf. Guidelines for Examination in the European Patent Office, Part G, Chapter II at 3.3, (November 2016), OJ EPO 2016, A76.
[151] *T-1326/06 RSA Schlüsselpaarberechnung/GIESECKE & DEVRIENT* (EPO 30 November 2010). *See also T 1227/05 Schaltkreissimulation I/Infineon Technologies* (EPO 13 December 2006).
[152] Opinion G-1/04 (Diagnostic methods) (16 December 2005) OJ EPO 2006, 334 ("Opinion G-1/04"). *See also T 0146/07 Prenatal diagnosis/ISIS*, *supra* n. 149, where patent eligibility was not even an issue.
[153] *G 0001/07 Treatment by surgery/MEDI-PHYSICS* (EPO 15 February 2010).
[154] Varkey & Atala, *supra* n.14, 291.
[155] S. Vijayavenkataraman, W.F. Lu and J.Y.H. Fuh, *3D bioprinting – An Ethical, Legal and Social Aspects (ELSA) framework*, 1-2 Bioprinting, 18 (2016).
[156] Sanjairaj Vijayavenkataraman, *A Perspective on Bioprinting Ethics*, 40(11) Artificial Organs 1033, 1034-1035 (2016).

here. While bioprinting could provide individualised medicine with all its benefits, conversely it could mean that it may only be available for certain people that can afford it.[157]

Aside from these more general moral questions, this section will focus on the narrower question that arises in the context of the patentability of inventions involving bioprinting. In this regard, the TRIPS Agreement permits WTO Member States to exclude inventions "within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law."[158]

4.1 Morality considerations under US law

The United States has not included a broader and generally applicable *morality* provision within its patent law.[159] Instead the "moral utility" doctrine was developed by case law and was applied to invalidate frivolous or scandalous patents, usually gambling machines and fraudulent articles.[160] This doctrine provided a legal fiction that such inventions would not be "useful" according to the patent-eligibility provision of 35 U.S.C. § 101 of the US Patent Statute.[161] But this doctrine stands in contrast to the US Supreme Court decision in *Diamond v. Chakrabarty*[162] which declared that 'anything under the sun that is made by man' would generally be patentable. Additionally, the Courts of Appeal for the Federal Circuit have questioned the doctrine since section 101 would not mandate an assessment of morality.[163] Hence, questions surrounding morality do not normally constitute a significant bar as such to patenting in the United States. The patentability of stem cells is rather discussed within a technical debate over patent-eligibility and in the context of the so-called "natural phenomena" and "product of nature" doctrines. [164] As mentioned before, these debates have recently been invigorated by the Supreme Court decisions in *Prometheus, Myriad, and Alice*, but the focus appears to be on utilitarian considerations rather than on arguments based on *morality* or *ordre public*.

However, one exception exists under US law, which potentially might have further implications for bioprinting: Section 33 of the America Invents Act[165] states that "[n]otwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism." This provision aims to ban the patenting of human beings at any stage of development, including embryos, fetuses, human/non-human chimeras, and

[157] Varkey & Atala, *supra* n.14, 287.
[158] Article 27(2) TRIPS.
[159] With the minor exception that HR 1249 (the America Invents Act) introduced an immediately effective ban on patents covering tax strategies and/or claims 'directed to or encompassing' human organisms. These will apply to all pending applications. Moreover, the USPTO had previously refused to grant patents on human chimera, cf. Ana Nordberg and Timo Minssen, *A "ray of hope" for European stem cell patents or "out of the smog into the fog"? An analysis of recent European case law and how it compares to the US*, 47 (2) International Review of Intellectual Property and Competition Law, 138, 169 (2016) [adding in FN. 182 "Until recently nuclear weapons were the only invention category completely excluded from patent eligibility (albeit not from a prize system). Yet this exclusion was not codified in the Patent Act, but in the Atomic Energy Act. 42 U.S.C. § 2181(a) (2000)"].
[160] Joshua Whitehill, *Patenting Human Embryonic Stem Cells: What is so Immoral?* 34 (3) Brooklyn Journal of International Law, 1045, 1075-1075 (2009); Margo A. Bagley, *Patent first, ask questions later: morality and biotechnology in patent law*, 45 (2) William and Mary Law Review, 469, 489 (2003).
[161] Bagley, *supra* n. 160, 476.
[162] 447 U.S. 303 (1980).
[163] *Juicy Whip, Inc. v. Orange Bang, Inc.*, 185 F.3d 1364 (Fed. Cir. 1999).
[164] Nordberg & Minssen, *supra* n. 159, 171.
[165] Leahy-Smith America Invents Act, HR 1249.

clones. Under current case law this would normally not comprise human embryonic stem cells and organs. But some commentators, such as *Ava Caffarini*, note that the vague wording of section 33 and the lack of definitions for "directed to" and "human organism," give courts wide latitude when construing section 33, which could in the future lead to a construction that would invalidate several biotechnology inventions.[166] This view is also shared by *Jasper L. Tran* who notes:

> Courts could potentially construe § 33(a) broadly to derail patent eligibility of many inventions, including bioprinting.[16]But until the legislature or courts interpret "directed to or encompassing a human organism," the Patent Office can reject any bioprinting claim "directed to" or "encompassing" human under the broadest reasonable interpretation.[17] Patent prosecutors must carefully draft bioprinting claims to avoid falling into this pothole. One possible way is to couch bioprinted human living tissues as implants or medical devices to use in a human body. For example, U.S. Patent No. 8,394,141 claims an implant formed from "fibers of defatted, shredded, allogeneic human tissue" including a "tendon, fascia, ligament, or dermis" and a "growth factor" (to induce cell growth).[167]

4.2. Morality considerations under European law

Within the European context, however, Article 53(a) of the EPC explicitly excludes patent protection for any invention "the publication or exploitation of which is contrary to *ordre public* or morality." National patent laws have also introduced similar bars to that of the EPC.[168][169]Additionally, the then European Communities legislated within the field of biotechnological inventions. After many years of discussion, the European legislator adopted Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions (Biotech Directive).[170] The Directive provided specific rules on this issue with regard to biotechnological inventions. Article 6(a) of the Biotech Directive mirrors that of Article 53(a) of the EPC to a great degree.[171] This provision reads:

> 1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.

Article 6, section 2 of the Biotech Directive (see also Rule 28 of the Implementing Regulations of the EPC) provides an additional non-exhaustive list[172] of specific case groups describing when inventions are deemed to be unpatentable in the context of subsection 1:

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166 Ava Caffarini, *Directed To or Encompassing a Human Organism: How Section 33 of the America Invents Act May Threaten the Future of Biotechnology*, 12 J. Marshall Rev. Intell. Prop. L. 768 (2013).

167 Tran, *supra* n. 116, 2.

168 The Convention on the Unification of certain points of substantive law on patents for invention (Strasbourg Convention) from 1963, which served as a template for some of the substantive rules within the EPC, already provided a similar provision within its Article 2(a).

169 E.g. Section 1(3)(a) UK Patents Act 1977; Section 2 (1) German Patents Act; Section 2 (1)(1) Austrian Patent Act.

170 Directive on the legal protection of biotechnological inventions by the European Parliament & Council, pp. 13–21 (30 July 1998), OJ L 213 (Biotech Directive).

171 Åsa Hellstadius, *A Comparative Analysis of the national implementation of the Directive's morality clause*, in: Aurora Plomer and Paul Torremans (eds.) *Embryonic Stem Cell Patents - European Law and Ethics* (OUP 2009), 120. For a more detailed and wider discussion of morality exclusions in patent law, *see* also Åsa Hellstadius, *A Quest for Clarity: Reconstructing Standards for the Patent Law Morality Exclusion* (Stockholm University 2015).

172 Recital 38 Biotech Directive.

2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:
(a) processes for cloning human beings;
(b) processes for modifying the germ line genetic identity of human beings;
(c) uses of human embryos for industrial or commercial purposes;
(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

While questions surrounding morality and patentability did not arise for some time, advances in the field of biotechnology pushed these issues into the limelight.[173] After adoption of the Directive, the Administrative Council of the EPO added Rules 23(b) to 23(e) (now rule 26-34 EPC 2000) to the Implementing Regulations of the EPC.[174] Hence, the discourse was mainly led within the EPO by its examining, opposition divisions as well as their BoA. But with the implementation of the Biotech Directive, the Court of Justice of the European Union ("CJEU") also became a major forum in the debate, since it is the competent court to interpret EU legislation. Along with national laws and the emerging Unitary Patent System, this provides a diverse framework of different fora with different legal traditions which makes the debate on morality and patenting more complex.

As mentioned, advances in the field of biotechnology have heavily influenced application of the morality exclusion. The case law on this exclusion has largely been generated by the implications of biotechnological inventions. Furthermore, the adoption of the Biotech Directive with its specific elaborations of what is deemed to be unpatentable in its Article 6(2) underline that the EU legislator found it necessary to clarify certain aspects of patenting in the field of biotechnology.[175] While the patenting of bioprinting may pose similar challenges, especially with regard to use of human embryonic stem cells (hESC) in bioink, it is submitted that the new and distinct applications that bioprinting may offer in future, such as use of xenogenic cells or creation of enhanced organs, will require a new assessment as to their compatibility with *ordre public* and morality.

For the purposes of this analysis, it is useful to differentiate the provisions governing immoral patents at the outset. The terms "ordre public" or "morality" of Article 53 EPC provide indeterminate terms which necessarily require interpretation. In contrast, the provisions on morality within the Biotech Directive, while only providing a non-exhaustive list, provide more or less clear case groups or examples when an invention is deemed to be immoral.[176] Hence, these specific case groups are discussed initially as they may apply to applications of bioprinting. Where the *leges speciales* of these case groups do not apply, one can revert to the more general rules of Article 6(1) Biotech Directive/ Article 53(a) EPC.[177] Article 6(2)(a) of the Biotech Directive and Rule 28 (a) of the EPC's Implementing Regulations declare processes for the cloning of human beings unpatentable. Recital 40 of the Directive mentions that "there is a consensus within the Community that interventions in the human germ line and the cloning of human beings offends against *ordre public* and morality" which is why the Directive would "exclude unequivocally" such processes from patentability. Hence, where bioprinters could be used to replicate human beings in the future using cloning

[173] Lionel Bently and Brad Sherman, *Intellectual Property Law*, 515 (4th ed., Oxford University Press 2014).
[174] In 1999 the member states of the European Patent Organisation decided to implement the Directive by amending the Implementing Regulations to the EPC. The aim was to bring the EPC into line with the terms of the Directive, not only to reflect the obligations of EU member states belonging to the Organisation but above all to comply with the requirement for uniformity in harmonised European patent law. Cf. Administrative Council document CA/7/99 of 4 May 1999 and the notice dated 1 July 1999 concerning the amendment of the Implementing Regulations to the European Patent Convention, OJ EPO 1999, 573.
[175] Recital 38 Biotech Directive.
[176] Åsa Hellstadius, *supra* n. 171, 120.
[177] In this line - *T 315/03 Transgenic animals/HARVARD*, OJ EPO 15, 51 (EPO 6 July 2004).

technology,[178] a patent application containing such a process would fall within the ambit of the provision and be rejected.

Tissue engineering is one application that can already be achieved through bioprinting.[179] The technology allows for several cells to be used in bioink, including stem cells. The great medical potential that stem cells possess is based on their ability to develop into any cells of the body. It has been said that stem cells will have an important role to play in the development of bioprinting.[180] The question of morality is focused on the use of hESC whereby the treatment often leads to the destruction of the embryo.[181] Until alternative ways are found to create stem cells that have similar properties to hESC[182], uses of these cells will remain "the most dominant ethical question" for bioprinting.[183]

Article 6 (2)(c) of the Biotech Directive specifically considers such inventions unpatentable where they relate to "uses of human embryos for industrial or commercial purposes." This provision was discussed in the *Brüstle* decision of the CJEU.[184] The patent in suit concerned "isolated and purified neural precursor cells, processes for their production from embryonic stem cells and the use of neural precursor cells for the treatment of neural defects."[185] The stem cells within the process in question derived from blastocysts. The Court had, *inter alia*, to assess whether such blastocysts could be considered as embryos in the reading of the Directive.[186] The Court affirmed this and found that the patent would violate Article 6 (2)(c) Biotech Directive since its technical teaching "requires the prior destruction of human embryos or their use as base material, whatever the stage at which that takes place and even if the description of the technical teaching claimed does not refer to the use of human embryos."[187]

The CJEU's decision was criticised,[188] *inter alia*, because of its autonomous interpretation of what would constitute an embryo.[189] The Court's interpretation would consequently mean that a patent of a bioprinting process for tissue engineering that would include the destruction of human embryonic stem cells or their use as a base material would not be patentable. The *Brüstle* decision, however, needs to be contrasted with the subsequent decision in *ISCO*.[190] Here, the CJEU appeared to have narrowed its interpretation of Article 6(2)(c) of the Biotech Directive. It held that non-fertilised ova would only be considered to be human embryos if found ''capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do.''[191] Some commentators therefore conclude that the CJEU aimed at correcting its verdict on human embryonic stem cells: "[T]he CJEU recognised that in *Brüstle* it had relied on incorrect scientific data concerning parthenotes, but it did so only indirectly, and fell short of actually acknowledging

[178] Tran, *supra* n. 12, discusses this possibility at 153-154.
[179] *See supra* in Section 1 of this paper: "Bioprinting: A brief scientific preface."
[180] Vijayavenkataraman, Lu & Fuh, *supra* n. 155, 14; Sanjairaj Vijayavenkataraman, *supra* n. 156, 1035.
[181] Tran, *supra* n. 12, 141-142.
[182] To mention here is research into induced pluripotent stem cells which may make the use of hESC unnecessary in the future - Nordberg & Minssen, *supra* n. 159, 139 -140.
[183] Vijayavenkataraman, Lu & Fuh, *supra* n. 155, 14.
[184] *C-34/10 Oliver Brüstle v. Greenpeace e.V.*, 2011 I-09821 (18 October 2011).
[185] *Ibid.*, [15].
[186] *Ibid.*, [23].
[187] *Ibid*., para. 52.
[188] Aurora Plomer, *After Brüstle: EU accession to the ECHR and the future of European patent law*, 2 (2) Queen Mary Journal of Intellectual Property 110–135 (2012); Enrico Bonadio, *Stem cells industry and beyond: what is the aftermath of Brüstle?*, 3 (1) European Journal of Risk Regulation, 93–97 (2012).
[189] *Case C-34/10 Oliver Brüstle v. Greenpeace e.V.*, *supra* n. 183, paras. 24 – 38.
[190] *C-364/13 International Stem Cell Corporation v. Comptroller General of Patents (ISCO),* OJ C 65, 7 (18 December 2014).
[191] *Ibid*., para 36.

that there had been a technical failure or that the CJEU was misdirected or had misunderstood the science at issue".[192]

Currently, there is no general prohibition to use hESC in processes for bioprinting. The *ISCO* decision clarified that the creation of hESC from blastocyst-like structures created by stimulation of unfertilised ova through parthogenesis is possible since they are not considered as human embryos.[193] This means that patent protection for bioprinting processes is possible where the stem cells derive from such processes that avoid destroying fertilised ova.[194] But the range of possible medical applications is limited with these permissible stem cells[195] and developments surrounding induced pluripotent stem cells have not yet technically matured.[196]

Other applications enabled through bioprinting may have to be assessed by the more general rules of Article 53 EPC/Article 6(1) Biotech Directive or its respective national counterparts. The obvious difficulty that surrounds the application of these provisions relates to defining what is immoral or what would be contrary to the *ordre public*. Since these provisions constitute hurdles to the grant of a patent, the additional question arises as to whether patent examiners are qualified to assess questions of morality. The Examining Guidelines of the EPO mention that inventions are deemed to be contrary to morality or *ordre public* where they are outrageous and provide a patent application for anti-personnel mines as an example for an abhorrent invention deemed to be immoral.[197]

The Technical Board of Appeal (TBA) clarified that morality relates to the "belief that some behaviour is right and acceptable whereas other behaviour is wrong, this belief being founded on the totality of the accepted norms which are deeply rooted in a particular culture."[198] Importantly, the TBA added that "for the purposes of the EPC, the culture in question is the culture inherent in European society and civilisation."[199] However, the TBA discarded often referred-to bases for assessing morality such as economic or religious considerations as they would not represent a common standard in European Culture[200] and questioned the usefulness of opinion polls.[201] With regard to interpretation of Article 53(a) EPC, the TBA held that the provision would constitute an exception to the generally wide concept of patentability and should therefore be construed narrowly.[202]

In the *Onco Mouse* cases that relate to a mouse that has been genetically modified to be susceptible of generating cancer, the EPO applied a utilitarian calculus. The TBA suggested that the question of patentability of such an invention would depend on "weighing up of the suffering of animals and possible risks to the environment on the one hand, and the invention's usefulness to mankind on the other."[203] In applying this test, the Examining Division of the EPO concluded that a patent would not be rejected when its benefits would outweigh its negative impacts.[204] In the second *Onco Mouse* case, the TBA held that the utilitarian balancing test could be applied as a general test for morality or ordre public

[192] Nordberg & Minssen, *supra* n. 159, 161.
[193] *C-364/13 ISCO, supra* n. 190, para. 38.
[194] Paul G. Cole and Stephen F. Jones (eds.), *CIPA Guide to the Patent Act 1977*, 1.21 (8th ed., Sweet & Maxwell 2016).
[195] Stem cells created through the process of parthogenesis only create pluripotent but not totipotent cells, which reduces their potential applications – *C-364/13 International Stem Cell Corporation v. Comptroller General of Patents*, PB C 65, 7 (17 April 2013), para.18.
[196] Nordberg & Minssen, *supra* n. 159, 139.
[197] Part G II, 4.1.
[198] *T 356/93 Plant cells/PLANT GENETIC SYSTEMS*, OJ EPO 545, 557 (EPO 21 February 1995).
[199] *Ibid.*, 557.
[200] *T 315/03 Transgenic animals/HARVARD, supra* n. 176.
[201] *Ibid.*, 55.
[202] *T 356/93 Plant cells/PLANT GENETIC SYSTEMS, supra* n. 197.
[203] *T 19/90 Harvard/Onco Mouse*, OJ EPO 476, 490 (EPO 3 October 1990).
[204] *Ibid*.

cases.[205] In the bioprinting context, the question is then how this calculus would apply and which considerations would be weighed against each other. Bioprinting applications which are not aimed at curing diseases, but in creating new improved characteristics of organs for humans may become an issue in the future. It has been said that such applications would be possible and sought after by individuals wishing to acquire enhanced characteristics and abilities, in particular athletes.[206] The question would very much lie in how such artificial improvements would be seen by the wider society and will pose an area of discussion for the ethics of bioprinting. An analogy from doping could be applied in this context. But the question may need to be assessed whether artificial enhancement of human beings through bioprinting is a desirable achievement that outweighs the potential negative aspects.

Aside from the already discussed use of stem cells, other cell material and tissue taken from human beings is used in bioprinting. The aforementioned *Relaxin* case[207] before the EPO shed some additional light on the question whether patents on human DNA are against *morality* or *ordre public*. With regard to the morality clause the opponent argued, *inter alia*, that the patent would violate Article 53(a) EPC "insofar as it relates to a DNA fragment encoding human H2-relaxin and its precursors."[208] In this regard the opposition was founded on three points: *First*, that the human right of self-determination would be infringed because the patenting of human genes would constitute a form of slavery. This was because it would "involve [] the dismemberment of women and their piecemeal sale to commercial enterprises throughout the world."[209] Additionally, the argument was raised that it was offensive against human dignity to profit from pregnancy and that it as intrinsically offensive to patent human life. The Opposition division, however, found that these claims were not founded. It held that the samples taken from the women were provided with consent. Additionally, it emphasised the nature of patents as a negative right to exclude third parties from using the patent. It does not provide rights over human beings. It also rejected the claim that patents on life were immoral as the patent in suit would relate to "a chemical substance which carries genetic information."[210]

This case provides important ramifications for patents involving bioprinting, since it implies that the use of human tissue *as such* is not immoral or against *ordre public*. This is relevant where cells are taken through a biopsy from a patient or other donors[211] and used for bioink in a bioprinting process. Based on the reasoning of the *Relaxin* decision[212], the use of cells in the teaching of the patent is not considered to be immoral where their use is based on the informed consent of the respective patient or donors.[213] Then no violation of Article 53(a)/ Article 6(1) Biotech Directive would be found.

An issue that could constitute a violation of the morality exclusion may be the use of xenogeneic cells in bioprinting. This could, for instance, occur where enhanced tissue is being

[205] *T 315/03 Transgenic animals/HARVARD*, *supra* n. 177. The TBA held that this test is "useful in situations in which an actual damage and/or disadvantage" occurs, which means that it is not the only test that can be applied to assess the question of morality or ordre public – *T 356/93 Plant cells/PLANT GENETIC SYSTEMS*, *supra* n. 198.
[206] Howard Wolinsky, *Printing organs cell-by-cell,* 15 (8) EMBO reports 836, 838 (2014).
[207] *T 74/91 Howard Florey/Relaxin*, OJ EPO 388 (EPO 23 October 2002).
[208] *Ibid*., 6.1.a.
[209] *Ibid.*, 6.1.b.
[210] *Ibid*., 6.3.4.
[211] While it is derisible to use the patient's cells for the bioprinting process it may not be feasible at times - Sanjairaj Vijayavenkataraman, *supra* n. 156, 1035.
[212] *T 74/91 Howard Florey/Relaxin*, *supra* n. 207, 6.3.1.
[213] Varkey & Atala, *supra* n.14, 288.

produced by mixing human cells with those of animals.[214] Article 6 (2) (b) of the Biotech Directive only sanctions such "processes to produce chimeras from germ cells or totipotent cells of humans and animals."[215] The idea of creating such enhanced organs by using animal cells may be found abhorrent by many and would therefore constitute an obstacle to patenting. It can also be doubted that such applications may be subject to a positive finding on the utilitarian calculus that the EPO applies.

5. Conclusions

This contribution highlighted the current state of the art and future applications of bioprinting technologies, which are already attracting increasing patent activity. Most bioprinting technologies and printing machines, as well as synthetically produced biological material and technical processes would often meet basic patent eligibility criteria in both Europe and in the US. However, recent US case law developments have severely limited the patentability of naturally occurring biological material and natural phenomena and correlations. In contrast, European patent law still regards isolated biological material, as well as technical methods based on natural phenomena that are not claimed *as such*, as in principle patent-eligible. On the other hand, the scope of protection granted in Europe might be rather limited in Europe and moral concerns might pose a potentially higher bar to patentability for some applications than in the US. In Europe, patent challenges may be based on morality clauses enshrined in the EPC and national patent laws to bar particular patent applications covering bioprinting technology. In the US these concerns are more limited, but a wider interpretation of the AIA's section 33 may pose a bar to several bioprinting applications. As elaborated, the application of the morality exclusions is a difficult task that patent offices need to achieve. Some clarity has been provided with regard to use of human embryonic stem cells but the further bioprinting technologies develop the more morality issues may arise. For the sake of promoting this new field of technology, we believe that only utterly abhorrent patent applications should be barred on the basis of morality.

Notwithstanding the ongoing debates on the patentability of biotechnological innovations, the market leaders in bioprinting will certainly continue to press the boundaries of what is possible in bioprinting and will continue to seek patent protection for their innovations and scientific advances. As 3D bioprinted products become more sophisticated and approach widespread use in clinics and hospitals, it can further be assumed that the actors with the biggest and most relevant patent portfolios will team up to develop patient-specific products.[216] In recent years, fascinating advances have e.g. been made with liver and kidney cells, which may begin clinical testing in the near future.[217] For products that will interact or reside within the human body, FDA and EMA testing and approval is crucial for many bioprinting companies to profit.[218] The special expertise that is required to gain FDA or EMA approval will probably motivate more companies to enter into partnerships and to purchase

[214] Aside from the implications within patent law, the question also arises whether such treatment with particular animal cells, such as porcine for instance, would be accepted by patients of Jewish or Muslim belief - Sanjairaj Vijayavenkataraman, *supra* n. 156, 1035. Similarly; Varkey & Atala, *supra* n. 14, 288.
[215] Recital 38 Biotech Directive.
[216] Hornick & Rajan, *supra* n. 75.
[217] *See* e.g. D.G. Nguyen, J. Funk, J.B. Robbins, C. Crogan-Grundy, S.C. Presnell et al., *Bioprinted 3D Primary Liver Tissues Allow Assessment of Organ-Level Response to Clinical Drug Induced Toxicity In Vitro*, 11 (7) PLoS ONE (2016).
[218] Hornick & Rajan, *supra* n. 75.

patents and acquire companies.[219] The bioprinting IP power structure is thus in a state of flux and it can be expected that we will see many changes and consolidations in the sector.[220]

While patents will remain important in stimulating scientific progress in this area, the wide and diverse fields of patent activity in the field might also create problems. The great variety of patents and patent applications where few market-leaders with enormous patent portfolios, such as *Organovo Inc.,* hold many overlapping patents covering key technologies, could lead to patent thickets and other potential anticommons scenarios.[221] However, before the first fully functional bioprinted organs and more complex tissues can be made and approved by regulatory authorities, it is highly likely that many basic patents will have expired. Moreover, many countries have codified various exceptions to patent infringement, such as research and experimental use exemptions. Unfortunately, these exemptions have a rather unclear scope of application. We therefore believe that an international clarification and more harmonized approaches with regard to such types of exemptions would be very helpful for effectively stimulating research in bioprinting, and in many other cutting-edge areas of life science

Among the *technological* trends that will have to be observed is the use of Big Data in bioinformatics, since it will enable the field's next wave of breakthroughs. So far, most bioprinting technologies have lacked biologically sophisticated software and other bioinformatics tools.[222] However, rapid advances in systems biology and synthetic biology in combination with the evolution of Big Data applications are now providing increasingly powerful tools, and it is clear that the interface between Big Data, competition law, standardization and a broad plethora of applicable IPRs, needs to be studied very carefully within the bioprinting area.[223]

Last but not least, it remains important to recall that any IP and competition law-related issues are dwarfed by the enormous regulatory and public policy challenges that are ignited by bioprinting on a more general level. As personal 3 D printers become more powerful and common, as independent service providers open their doors and grant access to increasingly sophisticated printers, and as industrial or private customers realize that they can produce replacement parts and other potentially harmful products, the democratization of manufacturing will increase and move away from control.[224] It is clear that this will have broader implications in many areas of currently applicable laws, such as criminal law, regulatory law, environmental law, constitutional law and for safety regulations, which are likely to become increasingly irrelevant or outdated.[225] In the bioprinting area with its strong impact on sensitive goods and values such as human rights, health, integrity and dignity, this is a particularly challenging development. It is thus clear that 3D printing, and bioprinting in

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[219] *Ibid.*

[220] *Ibid* (adding in this regard that "portfolio size is not all that matters. A company with only a few patents could hold the secret sauce to a highly successful and FDA-approved product, so it is important not to count anyone out in this pioneering age for 3D bioprinting").

[221] For more details, *see* Chapter 10 of this book: Liguo Zhang, Inigo Flores Ituarte, Rosa Maria Ballardini, *Essential Patents and Technical Standards in Additive Manufacturing*.

[222] Leckart, *supra* n. 2

[223] E. van Zimmeren, B. Rutz & T. Minssen, *Standards, Data Exchange and Intellectual Property Rights in Systems Biology*, 11 (12) Biotechnology Journal, 1477-1480 (2016). *See also* Minssen & Pierce, *supra* n. 145.

[224] John F. Hornick, *3 D Printing and Public Policy*, LI (2) les Nouvelles-Journal of the Licensing Executives Society International, 94, 95 (2016) [referring to the Five I's: *Illegal activity* (when anyone can 3 D print things with virtually any functionality, illegal, uncontrolled activity will proliferate), *Identification* (activity that is away from control will be increasingly difficult to identify), *Impracticable & Impossible* (it will be increasingly impractical or impossible to enforce the law against such activity) & *Impotent* (such laws will become increasingly impotent; they will exist and be enforceable for 3 D printing within control, but will be largely irrelevant for 3D printing outside control).

[225] *Ibid.*

particular, is an enormous game-changer that needs to be monitored very carefully and might require forceful and concerted interventions. Only then will it be possible to meet public policy objectives and to find a reasonable balance between prevention of harmful misuses and realization of the enormous benefits that will certainly result from this fascinating technology