Review Article

Prospects of emerging 3D bioprinting technologies: major startup companies and regulatory issues for human use—part II

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Abstract

In its highly developed form, the evolving three-dimensional (3D) bioprinting technology aims to create 3D structures with living cells to mimic real tissue and organ functions. It would offer significant benefits across research, personalized medicine, and multiple other applications when adequately developed for human medicine. Presently, more technological activities are witnessed in North America, followed by Europe, Asia Pacific countries, Israel among the Middle East countries, and some South American countries. Around 75 commercial companies are active in 3D bioprinting, with only about a dozen making significant commercial progress. This number is expected to rise phenomenally as breakthroughs in manufacturing and the safe use of 3D bioprinted tissues and organs emerge. Legal frameworks for 3D bioprinting will likely be established, incorporating additions to existing drug laws once countries like the United States of America authorize using 3D bioprinted products in personalized medicine. The demand for 3D bioprinting products is rising based on expectations of future benefits. Therefore, intense research and development activities are ongoing, resulting in demands for the supply of research materials. The legal framework still needs to be put in place for the commercial use of 3D bioprinted tissues and organs in personalized medicine; therefore, laws are to be created for their safe use. This review provides a flavor of the evolution of 3D bioprinting startup companies globally using these technologies.

Keywords: Biofabrication, bioinks, bioprinters, bioprinting startups, 3D bioprinting, tissue engineering

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INTRODUCTION

The global 3D bioprinting market is experiencing growth within various regions, contributing to its expansion. Part I of my review[1] provided a flavor of the potential benefits of using three-dimensional (3D) bioprinting technology across various usage areas, including research and development (R&D) and applications in a wide spectrum, including personalized medicine. Promising potential applications of 3D bioprinting technology in personalized medicine include the creation of complex functional organs, such as ears, liver, heart, kidney, and other vital ones. To effectively treat burn cases and other skin disorders, 3D bioprinted skins are immensely valuable.

This review provides a flavor of the evolution of 3D bioprinting startup companies globally using these

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technologies. Based on the analysis of crucial papers selected from over 31,000 publications that appeared in print from 1998 to the present time on bioprinting and its potential applications, a research group[2] found that based on the number of publications, most brisk activities are being pursued in the United States of America, followed by China, Germany, UK, the Netherlands, South Korea, Japan, India, Israel, Beirut, South Africa, Canada, Qatar, Russia, Australia, Sweden, Belgium, France, Ireland, Italy, Thailand, Taiwan, Latvia, Turkey, and Iran. The research publications also provided a flavor of the technological advancements in the total reconstruction of damaged tissues and organs.

Over the last two decades, more than 1000 3D bioprinting companies, including startups, have been founded in different countries and regions.[3] However, only about 100[4] are presently operating, and among these companies, only about a dozen have made significant progress. Most startups could not sustain their business for long. Even though only about 100 are operating, the author's search up to June 2024 revealed that about 75 companies are currently in active business. Even among these companies, only about a dozen have made significant progress. This number is anticipated to flare up as noteworthy outstanding[5] breakthroughs in science and technology are achieved in manufacturing and safely using 3D bioprinted tissues and organs in human subjects, thereby enabling the cure of specific tissue and organ defects and promoting increased longevity. The demand for 3D bioprinting products is rising based on expectations of future benefits. Therefore, intense R&D activities are ongoing, resulting in demands for the supply of different research materials and 3D bioprinted cell-based diagnostic devices. This review provides a flavor of the evolution of 3D bioprinting startup companies globally using these technologies. It also touches upon the need to develop new laws within the framework of existing laws of the Drugs Act to enable safe and effective manufacture and use of the products and technologies in human medicine.

MAJOR 3D BIOPRINTING COMPANIES BY REGION

Here, is an attempt to profile the present major 3D bioprinting companies, region-wise, worldwide.

NORTH AMERICA

United States of America

A maximum number of 3D bioprinting companies are presently operating in the United States of America.

A 3D Bio Therapeutics,[6] USA, is a clinical-stage biotechnology company specializing in manufacturing and supplying therapeutic-grade 3D bioprinters, bioinks, and other allied materials. They have developed infrastructure that complies with the Food and Drug Administration (FDA)'s requirements for therapeutic manufacturing. The company was founded in 2014. The company focuses on designing personalized living tissue implants for patients.

A 3D System, in South Carolina, USA, has engaged itself in developing inputs in various aspects of regenerative medicine and bioprinting solutions. Originally a 3D printing company, they are venturing to enter the personalized healthcare area.[7,8]

Advanced Solutions Life Sciences, USA, is a 3D bioprinting technology company.[9] It markets various bioprinters for studying living organisms, molecular biology, and biotechnology. The company is dedicated to designing, discovering, and developing integrated software, hardware, and biological solutions for 3D bioprinting technologies.

Allevi Inc., Philadelphia, PA, USA, is a company[10] specializing in printing devices, including bioprinting machines. The company produces a wide spectrum of bioinks for working on organs, such as the liver, heart, bones, kidney, skin, lungs, brain, and cartilage. It also provides 3D bioprinters, biomaterials, and specialized laboratory software.

Axol Bioscience,[11] North Grafton, MA, USA, specializes in patient-derived induced pluripotent stem cells (iPSCs) required in drug discovery research using 3D bioprinting scaffolds containing such stem cells. They have developed their library of iPSCs from donated cells from patients. Using the iPSCs, they develop physiologically relevant *in vitro* models useful for drug discovery research. Axol Bioscience was founded in 2013. After the merger with Censo Biotechnologies in 2021, they have expanded their activities in-house and provided services to customers in iPSCs-linked 3D bioprinting technologies for drug discovery research.

Bio Bots, USA, is a startup biotech company that offers 3D bioprinters[12] to researchers, pharmaceutical companies, and others who work on bioprinting technologies where 3Dbioprinted materials are used for working on problems and issues concerning bones, lung, liver, heart, brain, skin, and cartilage.

Brinter Inc., USA, is a startup biotech company[13] specializing in bioprinters and bioprinted products. They offer 3D bioprinting solutions and services.

Frontier Bio, Oakland, CA, USA, is another startup 3D bioprinting company[14] that was founded in 2018. The company aims to build blood vessels, nerves, and muscle tissues through implants to serve the clinical needs of bioprinted organs.

Greiner Bio-One,[15] Monroe, NC, USA, is an old company engaged in business in developing, producing, and distributing high-quality plastic laboratory products, which are also used in biological and biotechnological research and applications. The company was incorporated in 1963 as a division of the Greiner Group. Greiner Bio-One acquired[16] the assets of 3D Cell Culture Technology from Nano3D Biosciences Inc. in 2018. The company provides clients with magnetic 3D (M3D) cell culture technology. M3D cell culture enables the magnetization of cells.M3D bioprinting combined with cell-repellent surfaces has several advantages in high-throughput screening.

Nano3D Biosciences, Houston, TX, USA, is a startup biotechnology company[17] focused on activities like 3D cell culture solutions for biomedical research, drug discovery, toxicology studies, developments of precision medicine, and regenerative medicine. Their M3D bioprinting technology magnetizes cells and aggregates them with magnetic forces.

Nanofiber Solutions, Columbus, OH, USA, manufactures[18] 3D nanofiber scaffolds made up of electrospun polycaprolactone (PCL)-based nanofiber substrates. Some of their products are Nanofiber Plates (nanofiber matrix = 700 nm diameter electrospun PCL), aligned fiber matrix (mimics white matter of the brain), nanofiber chamber slides (eight chamber slide coated with nanofiber matrix for microscopic imaging), nanofiber dishes nanofiber plate inserts; and some others. Their products can be used in various research works in regenerative medicine and cancer.

Organovo Inc., San Diego, CA, USA, is a clinical-stage biotechnology company developing drugs using 3D human tissues created by 3D bioprinting technologies. They are working on developing drugs for inflammatory bowel disease using 3D tissue technologies. They have made considerable advancements in their research activities[19] and have developed certain lead molecules.

Prellis Biologics, USA, is a bioprinting startup company[20] that was founded in 2016. The research focuses on building human tissues for drug development and designing human organs for transplantation. Prellis works with CELLINK, Sweden, to develop a high-resolution holographic laser-based bioprinter. CELLINK is a premier bioprinting company for 3D cell culturing, bioprinting, tissue engineering, and fabrication applications.

TeVido BioDevices, Austin, TX, USA, a biotech company founded in 2011 specializing in regenerative medicine,[21] announced close-down as it could not generate enough revenue to sustain its operations. The company used 3D printing technology in breast reconstructive surgery by taking a woman's cell and fat tissue to rebuild the nipple.

Volumetric Biotechnologies, USA, is a bio-fabrication company,[22] which was founded in 2018. The company has marketed its own Lumen X Bioprinter. It has collaborated with CELLINK, Sweden, providing its bioprinter with 3D bioprinting work that combines microfluidics, lab-on-a-chip, and living tissue. 3D Systems, USA acquired Volumetric in 2021.

A few more companies exist in the United States of America, which are too tiny and have not yet come up to business significance in 3D bioprinting technologies.

Bioprinting companies in the United States of America are anticipated to hold the global leadership role in various aspects of 3D bioprinting technologies faster than companies elsewhere. The US government is spending more on R&D to develop novel organic living cell-based prosthetics. As this technology offers promising applications, especially in treating cardiovascular diseases, much hope is bestowed upon using 3D bioprinted products in human medicine. The United States (US)FDA regulates the medical products emanating from this technology to ensure patient safety.

Canada

The Canadian government is trying to promote R&D in 3D bioprinting technologies through its various arms, such as the National Research Council of Canada. There are some developments in the industry toward 3D bioprinting technologies.

Aspect Biosystems Ltd., Vancouver, BC, Canada, specializes in 3D bioprinting and tissue engineering.[23] They specialize in developing custom-made bioprinted human tissues for use in the life sciences. The company aims to develop human tissues that would become biologically functional, immune-protective, and suitable for surgical implantation.

Axolotl Biosciences,[24] Victoria, BC, Canada, was founded in 2020. The company initially engaged itself in producing bioinks, which were in demand by academic researchers and

biotechnology companies. The bioink developed by then is sold by the trade name "Tissue Print" and can be used with hiPSC-derived neural cells, where cell viability can be maintained for over a month. "Tissue Print" bioink can be used for bioprinting, utilizing a range of patient-derived cell lines.

VoxCell BioInnovation, Victoria, BC, Canada,[25] is a startup tissue engineering company established in 2020. They manufacture bioinks, 3D bioprinters, and engineered tissue models manufactured by 3D bioprinting technology. Their engineered tissue models are expected to increase the confidence of new drug development researchers.

EUROPE

Europe is wholeheartedly trying to promote the development of 3D bioprinting technologies across countries. The Tissue Engineering and Regenerative Medicine International Society (TERMIS) European Chapter concluded a conference, known as the TERMIS-EU 2022 conference, held in Poland from June 28, 2022, to July 1, 2022. The conference proceedings[26] provide multiple R&D work across Europe in tissue engineering and regenerative medicine. Regionwide, several 3D bioprinting technology-based companies are operating in Europe. There are several countries in Europe. Therefore, the information is provided country-wise in alphabetical order. More important companies have been described here.

Armenia

FoldInk[27] Yerevan, Armenia, is a 3D bioprinting technology-based startup company. It is marketing its bioinks for 3D printing 3D bioprinting machines and can provide advanced tissue engineering to the collaborating partners. The company was founded in 2018 as a research project and has made considerable progress. In 2019, FoldInk became a full-fledged company. Several Yerevan State Medical University researchers had come together to develop the products and technologies.

Bulgaria

Printivo Ltd., Sofia, Bulgaria, is a 3D bioprinting startup company[28] that was founded in 2016. Their 3D bioprinting efforts are on bone tissue. They are engaged in creating micro-architecture of bone tissue with great accuracy. The company provides bone tissue grafts to pharmaceutical companies that can be used for drug testing in pre-clinical trials.

Finland

Brinter, Finland, is a startup 3D bioprinting technology company[29] with an office in the USA. It was founded in 2018. It is currently working on bioprinting scaffolds, which will be used for differentiation, using stem cells obtained from patients. They aim to develop 3D-printed implants to restore damaged body parts.

France

CIbiotech,[30] Lionel Terray Meyzieu, France, is a 3D bioprinting technology-based company founded in 2009, specializing in multiple aspects of regenerative medicine and cancer. The company created artificial liver-like tissue by using embryonic-like adult stem cells. The company's expertise is in cell manipulation, drug testing, biobanking, and development of pre-clinical trials.

Healshape,[31] Lyon, France, is working on problems with soft tissue reconstruction. They specialize in 3D bioprinting, unique and implantable biological inks, human tissue engineering, and related subjects. They have generated their own IPR on certain aspects of regenerative medicine and can develop bioprosthesis for women who have undergone mastectomy following breast cancer. Their bioprosthesis is based on a 100% natural scaffold made from bio-sourced materials. It is 3D bioprinted, re-absorbable, and can be combined with lipofilling to regenerate women's tissues for a natural and esthetic look. The company was founded in January 2020.

Poietis, France, is a biotech company[32] specializing in the laser-assisted bioprinting of living tissue. They claim to be in four-dimensional (4D) bioprinting in the technology arena. The dynamic structures that can change shape or function over time through proper stimuli belong to 4D bioprinting technology. In 4D bioprinting technology, time is added as the fourth dimension to 3D printing. Poietis has developed a next-generation bioprinting platform to overcome current tissue manufacturing limitations by integrating automation and robotics technologies with numerous online sensors, including cell microscopy and cell processing by Artificial Intelligence. Their bioprinters are used to manufacture tissue, which has multiple clinical applications.

Germany

Black Drop Biodrucker[33] GmbH, Gasborn, Aachen, Germany, is a 3D bioprinting technology-based company that manufactures and sells bioprinters and bioinks. They also provide a range of bioprinting technology-linked services. The company was founded in 2017.

Cellbricks,[34] Berlin, Germany, is another 3D bioprinting-based company created to bio-fabricate organs and human tissue. The company aims at replicating human tissue by combining synthetic biology with 3D bioprinting

technologies. They have developed proprietary bioinks and can produce and supply multiple cell types and matrices arranged in a complex 3D structure produced by their proprietary 3D bioprinting technology. The company has published several high-class works of literature using its technology. Their 3D-printed tissue has multiple applications in 3D research.

Envision TEC Inc. is a privately held global company with its office located in Dearborn, I, USA, and its International headquarters in Gladbeck, Germany. The company was founded in 2002 by Hendrik John, a German inventor. Al Siblani, a Lebanese immigrant who studied in the United States of America, became the owner. Envision TEC sells multiple products, including 3D printers, print materials, and replacement parts. Envision TEC is also in the bioprinting and bio-fabrication business.[35,36] The company[37] was acquired by Desktop Metal Inc., USA in 2021. It has focused more on products that serve health care, dental, and medical customers with multiple 3D printed products, including 3D bioprinted substances. Envision has been included among the bioprinting companies in Germany.

GeSiM,[38] Radeberg, Germany, is a bioinstrumentation company. It was founded in 1995. GeSiM specializes in microfluidics, microarrays, piezoelectric dispensing, and other low-volume liquid handling. They specialize in 3D bioprinting.

I&L Biosystems S.A.S.,[39,40] Königswinter, Germany, is involved in the sales and distribution of high-quality laboratory equipment to customers and researchers in the microbiology, cell biology, and biotechnology markets in Europe and other parts of the world. They have several materials for 3D bioprinting technology appliances, including bioprinters and others. The company was founded in 1991.

Greece

PhosPrint,[41] Neapoleos, Athens, Greece, is a 3D bioprinting technology-based startup company developing laser bioprinting systems for regenerative medicine applications. They are devoted to developing tools and procedures to battle diseases and medical conditions. The company is a spin-off of the Institute of Communication and Computer Systems of the National Technical University of Athens, Athens, Greece. It was founded in 2019. The group has created the Dual Beam I (PhosDB. I) bioprinter, which is valuable in regenerative medicine research. The company is pursuing a couple of R&D projects for product development using their bioprinter.

The Netherlands

Ourobionics,[42] Amsterdam, Noord-Holland, The Netherlands, is involved in developing human tissues and organs to transform regenerative medicine. Their mission is to speed up drug discovery, replace animal testing, and lower the costs of R&D in the pharmaceutical arena. They have developed several human-derived biomaterials for use in tissue engineering and regenerative medicine research, such as human skin collagen type I (lyophilized and in solution); Huma Osteo Gelatin Type A, Lyophilized (Medium Bloom and High Bloom); and Huma Matrix, Native Human-Derived E.C.M., (Solution and lyophilized). Ourobionics was founded in June 2020.

Norway

ClexBio,[43,44] Oslo, Norway, is a startup pre-clinical-stage regenerative medicine company developing microfluidic chips for laboratory purposes using 3D bioprinting technology, using hydrogel bioinks. They have developed 3D implants that grow with the body. The 3D implants can be cast into chosen geometric shapes, including tubes, sheets, and more complex constructs that can recreate real human anatomies. Their expertise is useful in research and new medicine development. The company was founded in 2020.

Poland

Sygnis Bio Technologies[45,46] (legal name Sygnis New Technologies sp. z o.o.), Warsaw, Mazowieckie, Poland, is a Polish 3D bioprinting technology company that sells 3D bioprinting equipment, specialized microscopes, living cell isolation and imaging techniques, supply of lab equipment, exosome isolation, and others. They are also the distributor of CELLINK, 3D bioprinting products in Poland. Furthermore, they provide consultancy services in various aspects of 3D bioprinting technologies. The company was founded in 2019.

Russia

A 3D Bioprinting Solutions,[47] Moscow, Russia, was established as a private company on September 6, 2013. They created the first Russian bioprinter of an original construction and design in 2014. In 2015, they created an organ construct of a mouse thyroid gland. In 2016, they created a printhead for their bioprinter—FABION 2. In 2017, they assembled their first model of a magnetic bioprinter. The scientific and technological progress was fast and high in 3D bioprinting technologies. The company is the largest 3D bioprinting technology-based establishment in Russia and has a multi-disciplinary team of researchers, scientists, engineers, and a management team.

Spain

EBERS Medical Technology[48] SL, Zaragoza, Spain, is developing devices for research in 3D-based cell culture, bioreactors, and culture chambers for tissue engineering research. The company is a spin-off of research conducted at the University of Zaragoza, Spain. It has rich publications in various aspects of tissue engineering. The company was founded in 2009. The company is focused on developing and commercializing tissue engineering equipment and providing consultancy services in the area.

Regemat[49] 3D, Spain, is a 3D bioprinting technology-based company that manufactures and supplies 3D bioprinters, bioreactors for cell growth, biomaterials required for running the bioreactors and the 3D bioprinters, and allied accessories. The company was founded in 2015 to design and develop innovative solutions in bioprinting and regenerative medicines.

Sweden

BICO Group, Sweden, was founded initially as Cellink in 2016. The company was started based on the technologies developed at Chalmers University, Sweden. It was a startup company that provided design, R&D services, and supplies relating to bioprinting technologies, mainly for research purposes. They initially started by selling bioprinters, bioinks, and other research products. Presently, BICO Group is an established international company. Cellink's name remains maintained for their bioprinting business,[50] and collaborations are being made using this name. Cellink was one of the earliest bioprinting companies to introduce branded products in bioprinters, bioinks, other biomaterials, and consumables required for pursuing 3D bioprinting R&D.

BioLamina[51,52] Sundbyberg, Stockholms Lan, Sweden, is a 3D bioprinting technology-based company offering cell culture matrices for primary cells. They market laminins, which are large cell-adhesive glycoproteins. These proteins are required to form and function in basement membranes in all animals. These are heterotrimeric proteins composed of one α, one β, and one γ chain. These proteins have 16 human isoforms, formed from 5 α chains, 3 β chains, and 3 γ chains. The laminins they market are recombinant products. Laminins are important components of the extracellular matrix.

Bico Group, Sweden, acquired SCIENION GmbH, a German company. Cellenion,[53] Lyon, France, is a spin-off company of SCIENION GmbH, Berlin, Germany. Cellenion was founded in 2016. Cellenion developed technology for working on single-cell workflow windows under protection from extraneous disturbances and contamination. In 3D bioprinting technologies, the isolation of single cells plays an important role in certain aspects of investigation. Cellenion technology can be utilized to work with different kinds of cells. Different machines are available to work on different kinds of single cells. Their expertise is particularly important in dealing with the isolation of and working with single-cell omics technologies. In 2020, SCIENION GmbH was acquired by Bico Group, Sweden, and thereby they became the owner of Cellenion.

Fluicell,[54] Gothenburg, Sweden, specializes in multiple areas of regenerative medicine, focused on changing how diseases are treated. The company was founded in 2012. Their platform areas of research are single-cell technology and microfluidic bioprinting technology. They are working to find a curative solution to type 1 diabetes based on bioprinted tissue therapeutics and chronic disorders arising from tissue damage in multiple life-threatening body parts, such as cardiac, pulmonary, kidney, and metabolic disorders.

Switzerland

Auregen Biotherapeutics[55] SA, Zurich, Switzerland, is a 3D bioprinting technology-based human tissue origination company devoted to producing human body parts from cells and tissues. They have developed their lead product, AUR-201, produced from an autologous cell line and are about to enter clinical trials. They also have their "Bio Foundry" to bioprint tissues to work on regenerative tissue origination technologies. The company was founded in 2016.

CELLnTEC Advanced Cell Systems,[56] Bern, Switzerland, is a developer of corticosteroid-free epithelial cell culture technology,[57] which is essentially a range of cell culture media used in multiplying iPSCs and embryonic stem cells, required in developing cell scaffolds by 3D bioprinting technology and used as substitutes for animal models in drug discovery research and applications. CELLnTEC was founded in 2002.

MimiX Biotherapeutics,[58,59] Biel/Bienne, Switzerland, has developed a technology where sound-induced morphogenesis or structures are produced by using sound in conjunction with cells, stem cells, spheroids, organoids, and bioactive substances to create tissue-relevant architectures or biopatterns. They market a product called FastSkin, which is designed for complex wound care and produced using 3D bioprinting technology. This technology employs relevant cells and scaffolds to create bioprinted materials that resemble natural skin. The technology group Heraeus, based in Hanau, Germany, has invested in MimiX,

which has partnered with several worldwide companies interested in artificial skins.

REGENHU,[60] a Swiss company with an office in Cambridge, MA, USA, was founded in 2007 to develop bioprinting technologies. They introduced their eight-printhead bioprinter, "BioFactory," in 2009 and have since developed improved versions of their 3D bioprinters. Their other products include "SHAPER" (advanced bioprinting software), "R-GEN 100 BIOPRINTER," and "R-GEN 200 BIOPRINTER."The company continues to invest in engineering R&D, sourcing new technologies from across Europe and developing its innovations.

Turkey

Axolotl Biosystems,[61] Istanbul, is a 3D bioprinting technology-based company specializing in tissue engineering instruments. It manufactures melt electrowetting devices, bioreactors, bioprinters of various kinds, and bioprinting systems. The company was founded in 2016 and manufactures tissue engineering products and solutions.

United Kingdom

Arrayjet Ltd.,[62] Edinburgh, UK, is a 3D bioprinting company specializing in inkjet technology to print biological samples onto solid substrates and create microarrays. The company was established in 2000 with private equity from Archangel Investors Ltd., and the Scottish Government. They started commercializing their inkjet assembly from 2006 onwards. The company's microarray spotters are one of the fastest ultra-low-volume dispensers.

Biogelx Ltd.,[63] Bio City Scotland, Lanarkshire, UK, is a spin-out of the University of Strathclyde founded in 2012. The company developed 3D cell culture scaffolds in synthetic peptide hydrogels, which can act as an extracellular matrix to support cell growth. They also have designed several bioink products.

Cell Guidance Systems[64,65] Cambridge, UK, having an office in the United States of America, is also a biotechnology company that is, devoted to developing technologies that enable the delivery of bioactive molecules and for controlling the fate of cells in areas of medical, research, and biomanufacturing applications. The company was founded in 2010. Their product range includes a protein depot formulation technology through which the flexibility and utility of proteins, such as growth factors, can be expanded; exosome research products; self-assembling peptide hydrogels and hydrogel production services; and others used in stem cell research. They also collaborate with researchers and companies in the UK, the USA, Italy, and Japan.

Censo Biotechnologies[66,67] Cambridge, UK, is a stem cell technology company providing clients with various human cells. It also undertakes contract research services for drug discovery and toxicity testing. In 3D bioprinting technology-based work, the need arises for access to various kinds of cell lines. Censo Biotechnologies has created a pool of patient-derived iPSCs authenticated by whole genome sequencing and tested for suitability for drug development research. Their collection of iPSCs especially supports neurodegenerative, neuro-inflammation, and rare disease-focused research. Censo Biotechnologies was founded in 2016. Later, in March 2021, Censo Biotechnologies merged with Axol Bioscience. Axol specializes in iPSCs.

FABRX[68,69] Ashford, Kent, UK, is a 3D bioprinting technology-based company that is, engaged in the manufacture of pharmaceutical 3D printers for personalized medicine, sold under the trade name of M3DIMAKER1 and M3DIMAKER2, available with exchangeable printhead system. The company also collaborates with hospitals, universities, and pharmaceutical companies from all over the world. The company was founded in 2014, and over the years with progress, they have launched their subsidiary company in Spain, FABRX·AI, which is focused on advanced software solutions for pharmaceutical 3D printing technologies.

Jellagen,[70] UK, is a biotechnology company specializing in developing and manufacturing medical-grade collagens. Such collagens are used in tissue engineering and regenerative medicine and can be used in orthopedics (ligaments and cartilage) in formulations of scaffolds, resorbable membranes, hydrogels, and bone fillers. Formulations utilizing their collagens can be developed for various applications, including cardiovascular research, bone formation, cell and gene therapy, brain and central nervous system research, and general surgery. The company was founded in 2015.

Nuclera[71,72] (formerly known as Nuclera Nucleics), Impington, Cambridge, UK, specializes in constructing designer proteins required in new drug discovery research by using their novel automated protein synthesis technology platform, where the designer protein can be synthesized in less than 48 h, using their reagents, comprising a complementary deoxyribose nucleic acid (cDNA; conceptualized and constructed based on the requirement of the drug discovery scientists, and tagged with an identifier protein DNA) and using the benchtop

eProtein Discovery platform of Nuclera. The protein discovery platform reagents comprise cell-extract-derived products, co-factors, polymerase, urease, substrates, and energy systems required for synthesis (consisting of magnesium, ammonium ions, ammonium paratungstate, and others). The eProtein Discovery platform is a cell-free protein synthesis system in smart cartridges using digital microfluidics principles. The company was founded in 2013 by PhD students at the University of Cambridge, UK. It also has an office in the United States of America.

Oxford MEStar Limited,[73] Oxford, UK, is a spin-off 3D bioprinting-technology-based startup company in the UK, which was started in 2013. The company can provide consultancy services in bioengineering products and solutions, particularly translational and regenerative medicine. Their expertise is in bioprocessing, bioengineering, and bio-manufacture. They have developed simplified diagnostic kits, lab reagents, kits for DNA/ribonucleic acid (RNA) extraction, real-time polymerase chain reaction kits, and precision pipet-tips. The company welcomes partnership and collaboration activities.

ProColl[74] Wales, UK, is a synthetic biology company specializing in manufacturing recombinant human collagen and other high-value proteins. These substances have been used in 3D bioprinting technologies. The company is spun out of Swansea University's Faculty of Science and Engineering, UK. The company was founded in 2018.

ASIA PACIFIC COUNTRIES

Among the Asia Pacific countries, China, Japan, South Korea, India, Australia, Taiwan, and Malaysia are seen to have made progress in adopting 3D bioprinting technologies compared with other countries in the region.

Advances in tissue engineering are driving significant progress in regenerative medicine, including developing novel life-saving drugs. These foundational scientific breakthroughs primarily occur in academic institutions at the early stages. Consequently, various countries are funding academic institutions to advance tissue engineering, particularly through 3D bioprinting applications. The fundamental knowledge generated in academic settings often leads to the establishment of biotech startups, many of which evolve into successful biotech enterprises over time.

China

China is thought to be leading in 3D bioprinting technology advancements, with several publicly funded institutions working on tissue engineering and regenerative medicines among Asia Pacific countries. The number of startups and 3D bioprinting companies is increasing, although only a few are currently.

Regenovo Biotechnology Company Limited,[75] Hangzhou, Zhejiang, China, is a 3D bioprinting technology company manufacturer and supplier of platform-level high-fidelity biological 3D printers. They also manufacture and sell more than 20 types of bioinks, which can be used in tissue engineering research in skin, bone, cartilage, nerves, tendons, blood vessels, and stem cells. They supply bioprinting nozzles of various kinds. The company specializes in 3D bioprinters, materials, and software. The company was started in 2013.

Medprin Regenerative Medical Technologies Co. Ltd.,[76] Guangzhou, Guangdong, China, manufactures and distributes medical equipment, including 3D-generated equipment. They also offer biotechnology-based development, consulting, and other related services. They sell biological 3D printing machines.

Revotek Co., Ltd., Chengdu, Sichuan, China,[77,78] is a 3D bioprinting company established in 2014. They have their 3D Bioprinters and claim to have fabricated artificial organs and artificial blood vessels.

Japan

In Japan, certain universities like Kyoto University, Osaka University, and Saga University have profound 3D bioprinting research interests.[79] Kyoto University has teamed up with Cellink, Sweden. Osaka University, Shimadzu Corporation, and SIGMAXYZ, all Japanese establishments, have collaborated in 2022 to develop 3D bioprinted products in food, people's health, drug discovery, and new medicines.[80] Saga University is set to begin clinical research on generating printed blood vessels from patients' cells using a 3D bioprinting technology.[81]

On the industry front, Cyfuse Biomedical K.K., Mita, Minato-ku, Tokyo, Japan, is an established 3D bioprinting company[82] that sells 3D bioprinters. Their Bio 3D Printing Platform combines biology and engineering. It can work on a diverse array of cells to develop 3D bioprinted products, including cartilage and bone, blood vessels, nerves, and many more, which are useful research products in regenerative medicine. Cyfuse works on novel methods to generate steric tissues and organs solely from cells without using artificial materials through 3D bioprinting technologies. Such materials shall be used to restore innate functions in patients.

MICROJET Corporation,[83] Nagano, Japan, works in the inkjet technology-related field. It can provide R&D assistance for inkjet technology in bio-industry applications. Technology can be useful in drug delivery, microarrays, micro-dispensing, biosensors, and diagnostic chips. Inkjet technology can be applied to bioprinting enzymes, proteins, antibodies, cells, and other biological materials of nanosize, thereby developing biochips and biosensors. The company was founded in 1997.

In time, more companies will be visible in 3D bioprinting technology in Japan.

Australia

Australia has initiated 3D bioprinting technology development through government-funded initiatives. A Training Centre for Medical Implant Technologies[84] has been set up by the Australian Research Council, where 24 organizations across hospital clinicians, academics, and industry have been brought together to develop an integrated framework for 3D printed prostheses, implants, and personalized surgical devices. The core focus of the Training Centre, with leadership inputs from Queensland University of Technology, is to develop the next generation of multi-material and multi-functional platforms with 3D bioprinting inputs for excelling in tissue engineering technologies and regenerative medicine areas. The Translational Research Initiative for Cellular Engineering and Printing (TRICEP),[85] Wollongong, New South Wales, Australia, is involved in developing 3D bioprinting technologies. TRICEP works with research institutions and industry. University of Wollongong, Australia, and the Australian National Fabrication Facility have supported TRICEP. They are involved in developing bioinks, biomaterial formulations for research use, and customized technologies required for clinical research. While there are a few private initiatives for the manufacture of 3D implants and the use of 3D technologies, private industries based on 3D bioprinting technologies are still in tiny numbers.

One company by the name Inventia Life Science Pty Ltd.,[86] Alexandria, New South Wales, Sydney, Australia, was found to have made substantial progress in 3D bioprinting technology. Inventia was established in 2013. The company develops and sells equipment and reagents for advanced medical research assays through 3D bioprinting technologies. They manufacture and sell 3D Bioprinters, sold by the trade name "RASTRUM" bioprinters, "RASTRUM" cartridges (single-use medical-grade plastic), "RASTRUM" Matrices (synthetic matrix scaffold), Standard well plates (6-, 24-, 48-, 96-, and 384-well plates), and others.

South Korea

The Republic of South Korea (also known as South Korea) has realized that the additive manufacturing industry based on bioprinting technologies has great potential. However, the industry is presently in its developmental stages. The South Korean government's Ministry of Science and Information and Communication Technology had decided to invest $70 million in 2023 to encourage 3D technology development,[87] which included 3D bioprinting technology too.

Several startup biotech companies[88] in the South Korean Republic are interested in some aspects of 3D bioprinting technologies. ROKIT Healthcare Inc.,[89] Geumcheon-gu, Seoul, Republic of Korea, is a biotechnology company that has a profound interest in 3D bioprinting technologies and is involved in multiple high-tech modern biology platforms such as organ regeneration comprising providing autologous cells-enriched bioinks with bioprinters, which platform is suitable for supporting research in skin regeneration, cartilage regeneration, and kidney regeneration. The bioprinting platform provides bioprinters (sold as Dr. INVIVO 4D2, Dr. INVIVO 4D6, and Dr. INVIVO EDU) with bioinks and other connected materials for research in multiple areas of bioprinting technology. They also have an anti-aging platform suitable for providing medical devices, tissue banks, and other health supplements related to anti-aging research. Furthermore, ROKIT also has a next-generation sequencing-genome-research platform. ROKIT was established in 2012. The company teamed up[90] with the Korean Institute of Science and Technology, Seoul National University Bundang Hospital, Hanyang University, and Korea Institute of Machinery and Materials in a government-supported project in 2015 to develop 3D bioprinters and the collaboration was beneficial towards the development of their 3D bioprinters.

T&R Biofab,[91] Gangnam-gu, Seoul, Republic of Korea, is involved in 3D Bioprinting System research and product development. T&R Biofab was established in 2014. The company has developed bioinks, 3D organoid models, artificial organs, and cytotherapeutic agents. They have developed a 3D printed biodegradable scaffold for microtia; 3D bioprinted liver organoids; 3D bioprinted skin model composed of epidermis and dermis close to human skin; and phenotypically relevant analogs of human liver lobules.

There are brisk activities in South Korea for developing 3D bioprinting technology-based industries.

India

In the Indian context, following the amendment in Indian New Drugs and Clinical Trial Rules[92] in March 2023 vide notification GSR 175(E) dated March 9, 2023, where the

non-clinical testing methods to assess the safety and efficacy of a new drug or investigational new drug can be carried out by any one of the methods, namely the cell-based assay; organ-on chips and micro physiological systems assay; sophisticated computer modeling; other human biology-based test methods; animal studies, the 3D bioprinting R&D as well as the development of startup bioprinting industry got a shot in the arm. A mini-view write-up[93] depicted the proliferation in labs and startup bioprinting companies to explore the development of 3D bioprinted tissues for drug testing and transplantation. A few of these are described here.

Avay Biosciences, Bangalore, an Indian startup biotech company, was established in 2021. The company has developed an indigenous 3D bioprinter (MITO bioprinters) that can print human tissues.[94] They also supply multiple biomaterials, including bioinks. The company is collaborating with multiple Indian Research Institutes to further their knowledge base in 3D printing, including 3D bioprinting.

Next Big Innovation Labs,[95] Bangalore Bio Innovation Centre, Bengaluru, Karnataka, India, is a startup 3D bioprinting company founded in 2016. They have developed several bioprinting machines, such as Trivia Basic, Trima Advanced, and Trivima Pro. These bioprinting machines provide bioprints that are useful for applications in tissue engineering and tumor modeling research.

Pandorum Technologies Pvt. Ltd.,[96] Bio-Innovation Centre, Bangalore, Karnataka, India, was incorporated in 2011 as a biotech startup company in Tissue Engineering and Regenerative Medicine. They are involved in generating innovative biomaterials that enable control of the extracellular environment of target tissues, which would interact with cellular components and provide a biomimetic environment. In tissue engineering, they work with stem cells from different tissue sources. They are also working on optimizing the cell expression profile of stem cells so that the cells secrete therapeutically enriched exosomes, comprising lipid nanovesicles of the size range of ~30 to 150 nm, consisting of protein, messenger RNA, micro RNA molecules, and others. They are also developing 4D biological structures for tissue consortiums.

Kreator3D Printer and Solutions Pvt. Ltd.,[97] Chennai, India, founded in 2019, is a 3D bioprinting company fabricating living artificial tissues using bioprinting technology. The company claims to manufacture instruments that act as "Tools for Innovation" for various industries. Details are not available.

A team of scientists from the Department of Textile Technology, Indian Institute of Technology in Delhi, has been working on 3D bioprinting technology, and they succeeded in developing bioprinted cartilage.[98] They also developed bioink containing a high concentration of bone marrow (derived from cartilage stem cells) and silk proteins. The team has made considerable progress in research in 3D printing technology.[99,100]

Indian Institute of Science (IISc), Bangalore, has its Biomaterials & Tissue Engineering Laboratory,[101] where the researchers study various aspects of the technology components of 3D bioprinting besides other aspects of 3D printing technology. IISc has also established[102] a Centre of Excellence in Additive Manufacturing for high-performance metallic alloys where biomedical metallic implants and substances used in the aerospace industry shall be researched. This center was inaugurated in December 2019. Furthermore, IISc signed a Memorandum of Understanding (MoU) on August 18, 2022, with CELLiNK,[103] Sweeden, for the establishment of a Centre of Excellence for 3D bioprinting at the IISc premises. The MoU is anticipated to advance collaborative research in tissue engineering, regenerative medicine, and drug discovery.

Taiwan

In Taiwan, 3D bioprinting technology is relatively new. However, the country is highly interested in developing these technologies. A few institutes, including some publicly funded organizations, are involved in developing 3D bioprinting technologies. Taiwan's Industrial Technology Research Institute (ITRI), founded in 1973, has contributed enormously to transforming Taiwan's industries into innovation-driven ones. ITRI is reported to have developed technologies for 3D printing biomimetic materials[104] and structures for tissue integration (BioMS-Ti). These new materials can produce a microporous prosthetic bone material that would grow cells and blood vessels. A group of scientists from Taiwan,[105] in a collaborative research project with the scientists of China and the USA, had fabricated a polydopamine-modified calcium silicate/poly-caprolactone scaffold with Wharton's jelly mesenchymal stem cells incorporated with human umbilical vein endothelial cells-laden hydrogel. In the developed composites, higher levels of bone formation proteins were observed. It was thought that 3D bioprinting could improve bone tissue regeneration in numerous aspects. Such high-class scientific work indicates the profound interest of the scientists of Taiwan in developing 3D bioprinting technologies, thereby stimulating the industry's interest in investing in new technologies. However, the 3D bioprinting industry is still in the formation stage in Taiwan.

A company by the name 3D Global Biotech Inc.,[106] New Taipei City, Taiwan, incorporated in 2014, is involved in developing a 3D human organ through 3D bioprinting technology platform, using its 3D printing equipment, composite bioink, and a variety of cells to reconstruct tissues and organs. The company collaborates with leading domestic and international medical centers, research institutions, international companies, and others connected with 3D bioprinting technologies. The company's entrepreneurs anticipate that Taiwan will soon have domestic legislation, enabling the fast establishment of 3D bioprinting products and services in the country.

Cytena Bioprocess Solution Co. Ltd.,[107] Taipei City, Taiwan, is another 3D bioprinting company founded in 2018 and is a subsidiary of the Swedish 3D printing company Cellink AB. The company provides bioprocess solutions for other companies in the pharmaceuticals sector and research institutes interested in 3D technologies. They sell a high-throughput microbioreactor for parallel cultivations in 96-well plates by the trade name C. BIRD. The microbioreactor can replicate bioreactor production environments into 150 μL to 1,600 μL microbioreactor scale.

Malaysia

In Malaysia, local industries have not yet widely accepted additive manufacturing techniques. A scientific paper from the University Tun Hussein Onn Malaysia depicted[108] the challenges faced when using 3D printing to manufacture biomedical products in the country. In a recently published paper,[109] a study revealed that 3D bioprinting products and processes are patentable under the Patents Act 1983 of the country. Copyright can protect computer-aided bioprinting design software and programs under the Copyright Act 1987, and the marks and brand of 3D bioprinting products can be protected under the Trademark Act 2019. The work was to reinstate confidence among people, especially in the industry, to encourage the country to explore opportunities in 3D bioprinting technologies. In one review,[110] the prospect of 3D bioprinting in Malaysia was analyzed, and it was opined that the adoption of 3D bioprinting technologies was yet sluggish because of the deficiency of funding for conducting research and inadequate focus of the medical profession on the use of the technology. The potential of the technology to generate low-cost 3D bioprinting products is not yet adequately reinstated. In another review, six challenges were highlighted[111] for enabling technology dissemination in the Malaysian industry, which include workforce development, guidelines for developing the technologies, rationalization in product pricing, cyber-security issues, patents and copyright issues, and marketing factors.

Under the prevailing situation, there has been feeble investment in 3D bioprinting technologies in the country's industry. Lönge Medikal[112] Sdn Bhd, UPM Serdang, Selangor, Malaysia is a medical device company created by a team of doctors(Malaysian Radiologists) and clinical staff in 2016. It is presently working with the University of Putra Malaysia to pursue its research work. Details are not available.

SOUTH AMERICAN COUNTRIES

A few 3D printing companies are operating in Latin American countries. However, 3D bioprinting technology and industry have not yet taken significant roots in these regions. The information available on more significant companies country-wise is as follows.

Argentina

WeBio—Bioprinting[113,114] Buenos Aires, Argentina, a 3D bioprinting technology-based company, was founded in 2018 to serve pharmaceutical companies to improve their drug discovery and developmental processes through bioprinting technologies and to enable them to develop and add bioprinted human tissues for the pre-clinical tests of invented drugs. The present status of the company is not known.

Life SI[115] Córdoba, Argentina is a 3D Bioprinting technology-based company that sells its 3D Bioprinters, accessories, and consumables and assists in research and technology development using their 3D Bioprinting systems. They support tissue engineering research. The company aims to improve the quality of life by using and developing new 3D bioprinting technologies-based products and services. The company was founded in 2015.

Brazil

Tissue Labs,[116] Sao Paulo, Brazil, was conceived at the University of São Paulo out of its IPEN-Cietec Incubator. They manufacture and supply 3D bioprinters, sold as " Tissue Start" and " Tissue Ray." The first one is useful for beginners in biofabrication research. In contrast, the second can produce organ-on-chips, cell-laden constructs and scaffolds, and other microfluidic devices. Tissue Labs also manufacture " Matrix Xpec" hydrogels, which, they claim, can provide tissue-specific microenvironments for 3D cultures and can be used to generate and support tissues, such as adipose, bone, brain, cartilage, colon, kidney, liver, lung, muscle, myocardium, pancreas, spleen, stomach, skins, and vascular system. Tissue Labs also supplies different kinds of cell/ tissue culture devices. In February 2021, the company moved its headquarters to Lugano, Switzerland. Here, the company is included as one in Brazil.

Chile

Smart Tissues[117] Santiago, Chile, is a 3D bioprinting technology-based company that manufactures innovative bioinks for fabricating human-like tissues. They have high skills in polymer sciences and bioengineering. Their bioinks-derived 3D bioprinted materials find applications in drug and cosmetic testing, regenerative medicine, and cancer research. The company was founded in 2019.

MIDDLE EAST AND AFRICAN COUNTRIES

In the Middle East, in the Arab countries like other countries, there is a growing demand for human organs. It is anticipated that 3D bioprinting technology when adequately matured, will be able to develop and provide 3D bioprinted organs to bridge the shortage. This calls for experience in 3D bioprinting technologies. No 3D bioprinting startups could be located in these regions yet. Since there are several 3D printing technology companies in the region, it is anticipated that some of these companies and others may evince interest in developing 3D bioprinting technologies if the United Arab Emirates Government funding supports and if some of the universities in this region start courses in 3D bioprinting, tissue engineering, and regenerative medicine so that trained workforce is developed locally for handling such technologies.

Israel

Among the Middle Eastern countries, Israel is technologically ahead in certain industrial sectors of human needs. In the health sector, Israel has positioned[118] itself at the forefront of the high-tech industry. Israel realized very early that the 3D bioprinting technology would enable the living cells to rebuild their extracellular matrix spontaneously and would produce functional tissues under appropriate and precise physicochemical conditions requiring the use of the bioprinter's digital codes and digital data processing machinery, and accordingly planned their R&D projects. In a short period, Israel in this region made more technological advancements in 3D bioprinting technologies than others. Their thought process of extrapolating 3D bioprinting technology by imagining that personalized human organs can be printed using the patients' cells or stem cells as a base was extraordinary. By pursuing their R&D work through such future developmental scenario, as early as in 2019, a group of scientists in Israel under the leadership of Professor Tal Dvir, who is a Professor of the Department of Biotechnology and Head of the Nanotechnology Center in Tel Aviv University (TAU), the 3D bioprinted heart was invented.[119] They used reprogrammed cells and biological material from a donor. The size of the heart was that of the size of a rabbit's heart. The work demonstrated the human ability to bioprint functional, profoundly vascularized portions of the human body according to the patient's anatomy. However, the cardiac cells could not work together to pump blood like a normal heart, although the cells in this heart appeared to contract and expand. The establishment of adjacent cellular connections and communications through such connections and synchronization of layers of cells to communicate and perform a rhythmic expansion and contraction, and more such requirements as seen in the natural heart cells could not be established yet in the 3D bioprinted heart. Yet, this work is a significant advancement of 3D bioprinting technology, and it displayed great hope that with further scientific developments, a functional heart or any other functional organ shall be developed in the future. This work boosted research in 3D bioprinting endeavors in Israel and several other countries, including the Middle East. Earlier, scientists in the Wake Forest Institute for Regenerative Medicine, USA, produced and transplanted[120] a 3D bioprinted bladder into a human in 1999. The transplanted organ is stated to be fully functional a few decades later. The results reinstate the belief that the technology can be perfected to enable 3D bioprinted organs for human transplantation.

In Israel, to commercialize the technology related to the 3D bioprinted heart globally, a commercial company was founded in 2019 by the name Matricelf,[121] with its head office at Ness Ziona, Israel. Professor Tal Dvir formed the company. To commercialize the technology related to the 3D bioprinted heart globally, TAU and Matricelf signed an exclusive contract.[122] Matricelf is a pioneering biotechnology company specializing in technology development on regenerative medicine platforms. They are concentrating on developing methods to treat spinal cord injury patients, using the right types of patient cells, converting those into iPSCs, and forming patient-specific neural implants expected to bridge injured spinal tissue. They are also trying to develop other methods to treat various medical conditions through autologous regenerative therapy, including heart disease, Parkinson's disease, and age-related macular degeneration.

CollPlant Biotechnologies Ltd.,[123] Rehovot, Israel, is another 3D bioprinting technology-based startup company in Israel. It manufactures recombinant DNA technology-based human type I collagen and produces its bioinks based on its recombinant collagen. The company collaborates with various other companies and assists by providing their collagen and extending their recombinant-collagen technology platform for developing 3D bioprinted

materials, which have applications in regenerative medicine. CollPlant Biotechnologies Ltd. was founded in 2004.

Precise Bio,[124] Israel, manufactures and commercializes 4D bio-fabricated functional tissues and organs, which can be used in tissue engineering research and applications. Their expertise includes bio-ink preparation, tissue engineering, and transplantation experience, enabling them to create a scalable bio-fabrication platform to facilitate human organ transplantation research. Precise Bio was founded in 2016.

More 3D bioprinting technology-based companies are anticipated to be founded as more advancements in science and technology of 3D bioprinting technology emerge.

THE AFRICAN COUNTRIES

The African countries are interested in developing 3D bioprinting technology-based enterprises. A section of the academic sector, including certain universities, studies the emerging area's various scientific and technological aspects. University of the Witwatersrand, Johannesburg, South Africa, had assessed[125] certain aspects of the technology and came out with certain recommendations. The South African Government's Department of Science and Technology officially launched its Additive Manufacturing Strategy in 2015 and allocated funds for developing the area in their country. Certain South African universities started R&D work after that.[126] However, the advancement of research has not yet percolated adequately in terms of startups in the country. A similar situation exists in other African countries in so far as startup 3D bioprinting companies are concerned.

GLOBAL 3D BIOPRINTING COMPANIES INCLUDING START UPS IN SUMMARY

It can be observed from the above that although a large number of entrepreneurs have invested to benefit from the sale of products in multiple aspects of 3D bioprinting technologies, the technological developments presently hover around bioprinters, bioinks, isolation and use of appropriate cells in bioinks, and converting multiple types of somatic cells into iPSCs, and using such cells in bioinks for various research purposes. Research studies on exploring the development of living prosthetics and implants are intense in a small number of companies. The competition for success is fierce. To become successful, companies are seeking collaborations and partnerships. Many companies are looking for funds for sustenance; many others are adopting more such strategies to remain in the market. Concurrently, mergers, purchases, and acquisitions are happening too fast in this sector, where eventually, the successful key players are enhancing and strengthening their positions. Presently, only a handful of companies are performing with high success ratings.

3D BIOPRINTING MARKET OUTLOOK

A 3D bioprinting technology development is fueled by working together or collaborating among biotech companies, academic institutions, healthcare institutions, and organizations to research and find applications for 3D bioprinted materials in the medical field. According to one estimate,[127] the demand for 3D bioprinting products is anticipated to reach US$6.82 billion by 2034 from the anticipated 2024 market of United States dollars (USD) 2.24 billion, growing at a Compound Annual Growth Rate (CAGR) of 11.8% from 2024 to 2034. According to another estimate,[128] the 3D bioprinting market size was estimated at USD 2.13 billion in 2022 and is projected to reach around USD 8.3 billion by 2030, growing at a CAGR of 18.51% during the forecast period. According to a third projection,[129] the 3D bioprinting market size was valued at USD 2.0 billion in 2022 and was projected to reach USD 5.3 billion in 2030, with a CAGR of 12.5% from 2023 to 2030. These estimates show that the 3D bioprinting technology and the commercial products have a highly prospective global outlook. Indeed, this technology draws us into the unknown in the broad area of manufacturing, using living prosthetics and living implants, and therefore, intense research is bound to be pursued in academics. Successful research results will promote investment in biotech companies.

REGULATIONS AND REGULATORY AUTHORITIES

No 3D bioprinted material has been approved for therapeutic use in personalized human medicine. Globally, the Regulatory Agencies play a major role in overseeing the safety and efficacy of 3D bioprinting technologies and products. For this purpose, a legal framework has to be put in place.

In the meantime, the regulatory authorities are accepting pre-clinical data generation on organ-on-a-chip devices to investigate new drugs. Nonclinical testing methods of assessment of the safety and efficacy of a new drug or investigational new drug are carried out on an organ-on-a-chip device and the data generated are legally accepted by the regulatory authorities in many countries. This provision has boosted R&D activities in 3D bioprinting technology worldwide. Advances in microfabrication and tissue engineering have enabled the effective development

of organ-on-a-chip, where 3D bioprinting technology is deployed. The development of organ-on-a-chip devices has been widely reviewed.[130-132]

The 3D bioprinting technologies unfold customer-specific solutions, commonly referred to in other commercial areas as bespoke products and solutions. The conceivable 3D medical bioproducts include custom-made 3D printed medical devices, bioprinted chips for evaluating new drugs, and customer-specific cell therapies. These medical products are not yet designed as mass-manufactured therapeutics and therapies as the standards and the standardized operating procedures (SOPs) are not yet in place. Consequently, the already-established regulatory rules and laws applied to mass-manufactured therapies cannot be applied without their amendments. The technical issues relating to the 3D bioprinting technologies, including the manufacturing process, input materials standardization norms, the quality control process for ensuring delivery of safe products with minimum risks to the patients, and the efficacy standards of such products are to be spelled out, which requires a different set of regulations that need to be evolved, especially from the shop-floor experience. A 3D bioprinting technology is an intelligent integration of multiple technologies. Therefore, it is also known as an additive manufacturing platform, where regulatory standardization for each additive component of technologies is to be considered. The physical products are objects manufactured from a digital model through the automated addition of material, including living cells, where several steps of precise 3D printing processes are involved, all of which must be quality-controlled using SOPs per the evolved regulations. Perhaps because of such complications, no commercial product (as of June 2024) has emanated from the 3D bioprinted technology. Innovations are moving faster than the Regulatory Agencies in the governments that formulate and promulgate regulatory laws. However, the regulatory hurdles shall be resolved, and the currently used regulatory laws shall be broadened to enable such products to be manufactured for patient welfare. Various aspects of regulatory challenges regarding 3D bioprinting technologies, including standardization and establishment of quality control in the manufacturing process, use of materials including the living cells, and propound sound regulations for enabling the use of 3D bioprinting products and services for human use have been elaborately and excellently discussed in a recent review paper.[133]

Interestingly, in the meantime, the USFDA has allowed[134] the first human clinical trial of a 3D bioprinted product in 2022, where the 3D Bio Therapeutics, Long Island City, NY, USA (a clinical-stage biotechnology company in regenerative medicine) and the Microtia-Congenital Ear Deformity Institute, San Antonio, TX, USA are conducting the human ear reconstruction experiment using the former's novel 3D bioprinted AuriNovo living tissue implant. The 3D bioprinted outer ear implant is produced from the cartilage cells of a patient to improve the results of outer-ear surgical reconstruction. The US FDA had approved several 3D printed (not 3D bioprinted) medical devices for clinical use through their 510(k) regulatory pathway.[135] However, it is unclear what provisions of USFDA regulations were applied to approve the outer ear surgical reconstruction using 3D bioprinted tissues. The provisions of regulations requiring cell therapies, including autologous cells, must have been used in addition to many other regulatory provisions. More shall be known if the clinical trial results in a successful outcome. The world would benefit once such products get USFDA approval under their regulatory provisions to ensure the safety and efficacy of such 3D bioprinted products. It would become easier for other countries to frame their regulatory laws using the USFDA provisions as the basis.

Concluding remarks

Globally, there is significant momentum in the development of 3D bioprinting technologies, which is evident from the rise in the number of patents in 3D bioprinting-technology-based inventions and the emergence of a sizable number of startups, particularly in the USA, followed by China, Germany, UK, the Netherlands, South Korea, Japan, Israel, Canada, Russia, Australia, Sweden, France, Italy, India, Taiwan, Turkey, Brazil, Argentina, and Chile. However, much of the technological activities remain exploratory within R&D establishments. Successful industries focus on selling materials for 3D bioprinting research, with research material suppliers outpacing those offering finished goods for medical applications. When more profoundly developed, the technology may provide opportunities to manufacture new functional organs that are anticipated to be useful to expand our longevity with good health.

Current business components include bioprinters, categorized into droplet-based, extrusion-based, laser-assisted, and stereolithography techniques. The most common bioprinters in use are inkjet-based, laser-assisted, and extrusion-based. Bioinks, crucial for constructing living tissues, organs, and other structures, comprise hydrogels, biodegradable scaffolds, less toxic crosslinking agents, additives, and living cells. Market analysis indicates a promising global outlook for 3D bioprinting technology and its products.

Cellular reprogramming of aged somatic cells by resetting the aging clock of the somatic cells along with an increase in

their telomere lengths to enable transformed cells to behave like PSCs is one important component of the emerging technology for enabling the development of improved bioinks using such cells, and to ease the development of 3D bioprinted tissue for use, for replacing the worn out organs. Assessment of safety and efficacy from using such materials and others used in 3D bioprinting technology would be paramount for developing safety regulations for using such products. The regulations requiring cell therapies, including autologous cells, must have been used in addition to many other regulatory provisions by companies developing 3D bioprinted products. As one or more products come out from the successful clinical trial results, the modified regulatory provisions shall emerge to ensure the safe use of such products. Global attention is on the first USFDA-authorized human clinical trial of a 3D bioprinted product (bioprinted outer ear implant) since 2022. Successful results and USFDA authorization could pave the way for other countries to formulate regulatory laws based on emerging USFDA provisions for human clinical trials of 3D bioprinted multiple other products for human use.

As of the end of June 2024, approximately 75 companies are active in 3D bioprinting, with only a dozen making significant commercial progress. The anticipation is that this number will increase with breakthroughs in science and technology, especially by resolving the issues regarding the safe use of 3D bioprinted tissues and organs in human medicine.

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