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The Brazilian sectoral innovation system in the field of Tissue Engineering and Bioprinting: actors, challenges and perspectives

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Abstract: The objective of this work is to map the main actors within the Brazilian innovation system framework in the field of tissue engineering and bioprinting, and analyze the main conditioners related to entrepreneurship and innovation. While keeping as a backdrop, the history of 3D Biotechnology Solutions startup, its challenges and projects. Tissue engineering is a subcategory of regenerative medicine with the purpose of repairing or substituting, partially or completely, tissues or organs that have been affected by some disease or lesion. The conventional methods used for the production of these biomaterials via tissue engineering do not have the capacity to mimic the reality of native structures in the nano, micro and macro scales, while guaranteeing the reproducibility andscalability of the materials. Technologies such as 3D bioprinting or additive manufacturing could change the way that many diseases are treated in the medium term by replacing the damaged tissues with custom bio-similar constructs. Mapping and reflections based on the innovation systems framework contribute to organize stimulus policies, stimulate interaction between actors, identify gaps and technological demands and periodically organize the analysis and expansion of this system in Brazil.

Keywords: Bioprinting; Tissue engineering; Biofabrication; Sectoral Innovation systems.

Introduction

3D bioprinting has emerged as a technological platform with great potential to meet the growing demands of regenerative medicine. Tissue engineering (TE) as a subcategory within the field of regenerative medicine was defined by Langer and Vacanti [1] as a "an interdisciplinary field that applies the principles of engineering and life sciences to the development of replacements that restore, maintain or improve tissue function". TE develops alternatives to induce a tissue regeneration process, overcoming some disadvantages found in organ transplantation, such as the lack of donors nd the need for immunosuppressive therapy. TE applications also have potential for the conception of in vitro models of healthy or pathological tissues and organs, assisting in drug screening, evaluation of new therapies, as well as the investigation of complex phenomena that occur within the progression of a disease such as cancer [2].

In addition to their high scientific potential, these models run into ethical questions, the issue of using animals for drug testing is a practical example of how TE is a disruptive technology platform. In Brazil, as of this year (2019), comes into force the Normative Resolution of the National Council for the Control of Animal Experimentation (Concea) that obliges the mandatory substitution of the original method performed on animals by the alternative method for research activities. This resolution, which seeks to apply the replacement, reduction and refinement (3Rs) principle in the country [3]encourages the research community to recognize the importance of well-being for animals used in science, and was also officially endorsed by the National Health Surveillance Agency (ANVISA) so that these methods could be applied for regulatory purposes. The European Union has determined, since 2004, the transfer of tests for toxicity assessment to in vitro systems. In 2013, it also banned the import of animal-tested cosmetic products (Amendment 2003/15 / EC of Directive 76/768 EEC).

The potential use of bioprinters is high because repair of damaged or lost tissue is a worldwide concern, as well as the increase in the rates of obesity, diabetes and the elderly population. To give you an idea, Brazil today has 20.6 million elderly, a figure that represents 10.8% of the population. By 2060, the country is expected to have 58.4 million elderly (Brazilian Institute of Geography and Statistics-IBGE). A point to note is that the list of patients awaiting some type of transplant in Brazil is around 33,000. Even though there is an annual increase in the number of transplants performed, the demand for organs has been growing at a higher rate.

Hence, with the growing interest of the medical and pharmaceutical communities, the demand for these bioproducts has increased and a wide range of bioprinting equipment have been developed within the labs of research institutions and also by startups[4]. Therefore, although the number of technologies, design and applications have grown as research advances to create increasingly complex fabric, a series of scientific technical challenges need to be overcome such as equipment precision, aseptic conditions, amongst others.

From a market perspective, the BCC Research report[5] predicts that by 2021 this field will reach US$ 1.8 billion. This growth is estimated at a compound annual growth rate of 4.3% from 2016 to 2021. Another report from the consultancy Grand View Research [6] estimated the global bioprint market at US$ 682 million in 2016 expected to reach US$ 2.6 billion by 2024. Growth should be driven by new printing technologies as well as by the expansion of new applications within the medical field such as vascularized tissues, vascular grafts, cartilage, bone, skin and other applications.

From a business strategy perspective it is only natural that companies offering products for bioprinting will gradually come to provide bioprinting products, given the different business possibilities that open up with this technological platform. A representative case is of the American company Organovo, founded in 2007 it initially focused in products for bioprinting (bioprinters, bioinks, etc.) and today is a leader in the co-development of bioprinting products, with patent requests for different therapeutic applications. It is also natural that important ethical, moral and social questions have to be analyzed so that an appropriate regulatory framework can be put in practice and make possible for bioprinting products to find their way to the market and improve patients' quality of life, as discussed by Li [7].

In this regard, it is important to highlight that other countries for some years now have been working toward providing an adequate regulatory environment to foster the development of therapeutic applications with cells using TE and bioprinting. The creation of an environment conducive to research and development can provide companies and institutions an advantage in these countries, demanding a robust strategy so that Brazil does not lag behind and positions itself as a protagonist in this type

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of vanguard technology. In this sense, mapping actors can support the organization of policies and funding mechanisms, stimulate cooperation and interaction, identify demands and provide a systemic platform for periodically analyzing the evolution of this system.

The article is organized into four items other than this introduction. In the next two items, the analysis referential based on the innovation systems and the characterization of the Brazilian sectoral system will be analyzed. Next, we will present the case of 3D Biotechnology solutions startup, its history and projects. Finally, we will present some reflections regarding the entrepreneurship in this emerging sector. It is noteworthy to highlight right away, that the mapping exercise carried out was not exhaustive and should not be complete, and that we encourage the constant addition of new actors.

The Innovation Systems Approach to Characterize Leveraging of Skills in Research Development and Innovation

Innovation system (IS) models have traditionally been applied on a national innovation system (NIS) approach. This approach has also been applied to analyze industry sectors and specific enabling of sectoral technologies. This approach has also been applied to analyze industry sectors and sector specific technology capabilities. These approaches share the view that the innovative process can best be explained by characterizing system components and how they interact. Specifically, its actors, networks and institutions, including regulatory norms.

The IS approach makes explicit the importance of systemic interactions between various components of an invention, of the research, technical change, learning, and innovation. Such interactions have multiple internal and external sources of information and knowledge coming from different classes of actors and institutions. These interactions have created an informal systemic interdependence in the production systems of the respective actors, giving rise to what is now called the "Innovation System". The central idea of the IS approach is the notion that what appears as innovation at the aggregate level is in fact the result of an interactive process that involves several actors at the micro level, and that alongside market forces many of these interactions are governed by non-market institutions. The efficiency of this process observed at the macro level thus depends on the behavior of individual actors, in addition to the institutions that govern their interaction.

It is no surprise that economists in the institutional tradition of innovation studies [8, 9] and scholars of evolutionary theories [10] , became the strongest supporters of the notion of innovation systems as this point of view refers to a continuous process in which institutions (habits, practices and rules) coevolve through learning processes, while playing a central role in generating innovation and technological change.

From an analytical perspective, the Sectorial Innovation Systems (SIS) [11] approach takes a multidimensional and dynamic cut of a given industrial sector, composed of the following elements:

(i) its products, (ii) agents, such as companies, universities, financial institutions, central and regional governments, (iii) knowledge and learning systems (group courses and research lines) (iv) interrelationships and complementarities of basic technologies, supplies and demands, (v) mechanisms of interaction between external and within the sector companies, involved in both market and non-market processes, (vi) competition and selection processes, (vii) institutions, understood as productions standards, regulations and the job market. This framework serves as a practical tool for the design and implementation of innovation policies.

In this sense, Chaminade and Edquist [12] affirm that the innovation policies based on the Innovation Systems perspective aim to solve systemic problems or failures, which are not automatically resolved by private actors. The authors highlight some possible systemic failures, such as (i) the provisioning of infrastructure and investment failures, (ii) failures in the technological paradigm transition (iii) lock-in problems, (iv) failures in "hard" and "soft" institutions, (v) networking failures, (vi) learning and competency failures and (vii) complementarity failures. In practice, this approach allows the analysis of blocking and induction mechanisms and to delimit the main functions which this system should provide to develop virtuously. Table 1 summarizes induction and blocking mechanisms and functions of these systems.

Induction Mechanisms	Functions	Blocking mechanisms
• Governmental R&D Programs • Investments Subsidies • Measures that affect relative prices • Public purchase notices	• Knowledge creation and propagation • Influences in the direction of R&D • Business experimentation • Market development • Resource Mobilization • Legitimation of new technologies • Development of positive externalities	• Features of the new technology • Weak institutional power • Lack of customer competence • Weak links within the collaboration network • Established Lock-in Technology • Lack of long-term goverment vision

Adapted from Jacobsson e Bergek [13]

Table 1 – Characteristics of Technological Innovation Systems.

The sectoral system of innovation in Brazilian Bioprinting and tissue engineering

The sectoral system of innovation in the Brazilian field of bioprinting is in an emerging phase, that is, innovative applications based on this technological platform begin to be explored economically. This system is made up mostly by: university research groups, research institutes, companies and startups. In addition, the regulatory agency ANVISA. The analysis performed based on the data available from the group research Directory of the Lattes[2] platform identified 60 research groups and 71 threads of research hosted in 30 universities, 2 hospitals and 3 research institutes.

Search Query:
Date: 07/31/2019
Terms: Bioprinting, Tissue engineering and Biofabrication – Exact search: Group name, research field name, research field keyword

Actors	
Universities	Federal Center of Technological Education of Minas Gerais Brazilian Agricultural Research Company Porto Alegre Clinical Hospital Little Prince Children's Hospital Paraíba Federal Institute of Education, Science and Technology Federal Institute of Ceará – Rectory Pontifical Catholic University of Rio Grande do Sul Brazil University Araraquara University University of Brasilia University of Pernambuco University of Sao Paulo State University of Minas Gerais Campinas State University Paulista State University Julio de Mesquita Filho Federal University of Southern Frontier Federal University of Campina Grande Federal University of Itajubá Federal University of Mato Grosso do Sul Federal University of Minas Gerais Federal University of Pernambuco Federal University of Santa Catarina Federal University of São Carlos Federal University of Sao Paulo Federal University of Sergipe Federal University of Viçosa Federal University of ABC Federal University of Espirito Santo Federal University of Piaui Universidade Federal do Rio de Janeiro Universidade Federal do Rio Grande do Sul Universidade Federal do Vale do São Francisco Universidade Federal dos Vales do Jequitinhonha e Mucuri – Campus JK Universidade Federal Fluminense Universidade Ibirapuera

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		Bioprinting areas of practice
Research Institutes	CTI Renato Archer	Biofabrication, prosthesis, software applications and systems
	IPEN	Applications
	CNPEM LNBio	Organoids
	INCT Biofabris	Development of biomaterials
	Dante Pazzanese Institute	Cardiovascular therapeutic applications
	The Heart Institute (Incor)	Cardiovascular therapeutic applications
Startups	InSitu Cellular Therapy (2016),	Bioprinting Products: Biocuratives
	3D Biotechnlogy Solutions (2017),	Products for Bioprinting: equipment and supplies Bioprinting Products: InVitro Models
	BioCellTiss (2017),	Bioprinting Products: InVitro Models
	BioEdTech (2018),	Products for Bioprinting: Low cost equipment and educational area
	TissueLab (2018),	Products for Bioprinting: Bioinks
	Bioprint3D (2019),	Products for Bioprinting: Low cost equipment
	GCell (2019)	Spheroids
Companies	Embrapa Genetic Resources	Bioprinting applications: biomaterials, nanopigments, and applications in agriculture
	Natura Cosmetics	InVitro Skin models
	AC Camargo Câncer Hospital	In Vitro models to fight Cancer
Government Agencies	ANVISA	Advanced Therapy Regulation

Source: Self Developed

Table 2 – Main actors of the Sectoral System of Bioprinting Innovation

Among the main research centers in Brazil we can highlight the pioneering work of the Biofabrication Research Group of the Information Technology Center CTI Renato Archer, which has been using additive manufacturing technologies for the creation of prostheses since 1994. Also, the research lines by the Embrapa Nanobiotechnology Laboratory, in the development of biomaterials originating from agriculture. Finally, the cutting edge research by the National Center for Materials Research CNPEM on organoid development, amongst others. Moreover, the essential role of universities in providing the appropriate environment that allows connection with this cutting edge area under different lines of research.

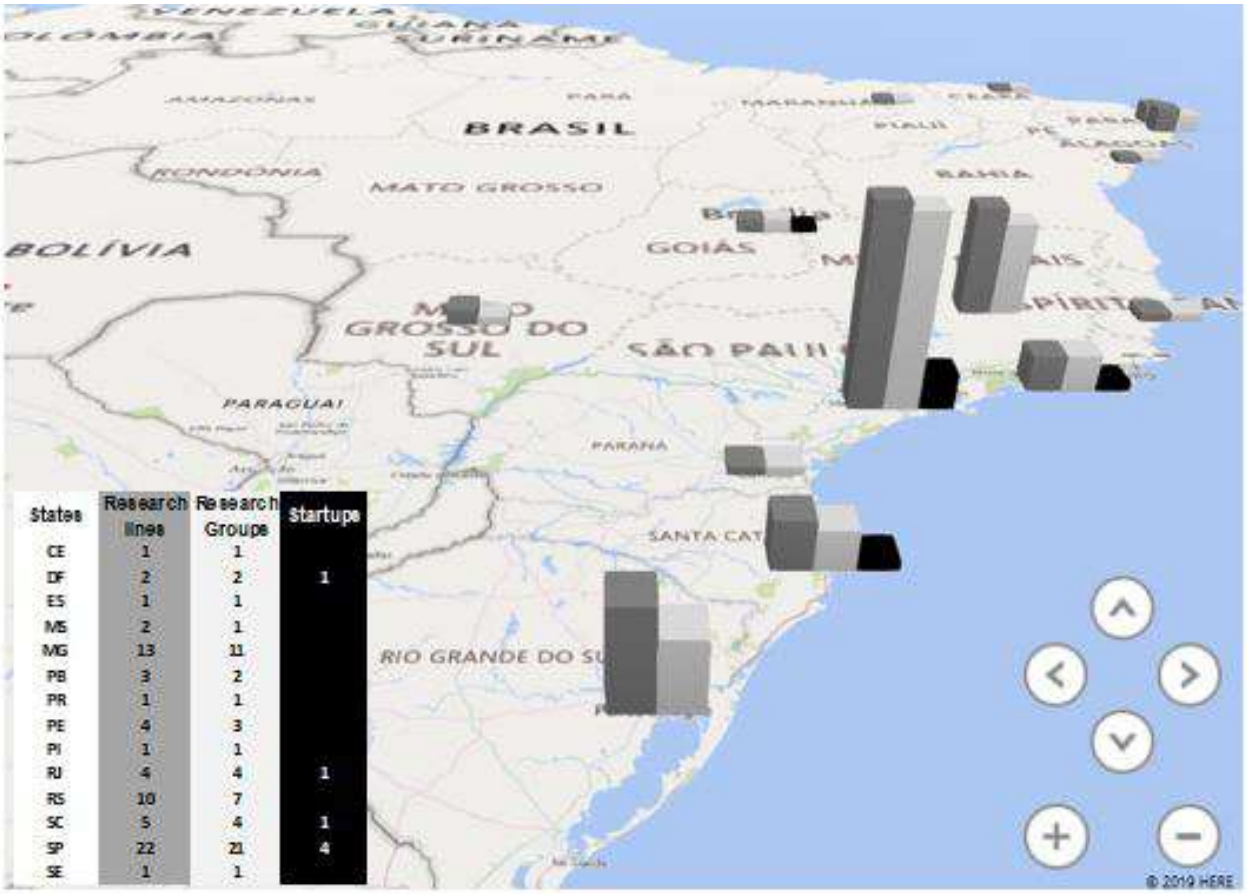
An example of a large Brazilian company that comes to view applications in the field of bioprinting is Natura Cosmetics. One of its ongoing projects aims to develop a dermo skin equivalent from the 3D bioprint technique to serve as an in vitro platform for cosmetic product evaluation. Fibroblasts, keratinocytes and melanocytes will be co-cultured on layer-by-layer polymeric support, following the trend of alternative in vitro models, which serve as an alternative to the use of animals for effectiveness and safety for the testing of cosmetics. The arrangement for the execution of this project includes leading researcher at startup 3D Biotechnology Solutions, Dr. Ana Luiza Millás under the supervision of Prof. Silvya Maria--Engler Stucchi, from the School of Pharmaceutical Sciences, University of São Paulo / USP. Figure 1 below shows the geographical distribution of groups, research lines and startups in Brazil.

Most of the system is located in universities and research institutes that are concentrated in the states of São Paulo, Minas Gerais, Rio Grande do Sul, Santa Catarina, and Rio de Janeiro. Ingeneral it can be said that all startups come from centers of excellence in this field which demonstrates the important function of any innovation system that is the dissemination of knowledge. The emergence of startups is an indication that resource mobilization toward enterprise experimentation is also taking place.

It is also worth noting that the groups as well as lines of research predominantly have an area of activity classified as "Engineering" followed by "Health Sciences" and "Biological Sciences", as shown in Graph 1 below. This indicates the interdisciplinary character of the field as researchers are encountering TE and Bioprinting from different disciplines and under different approaches and lines of research.

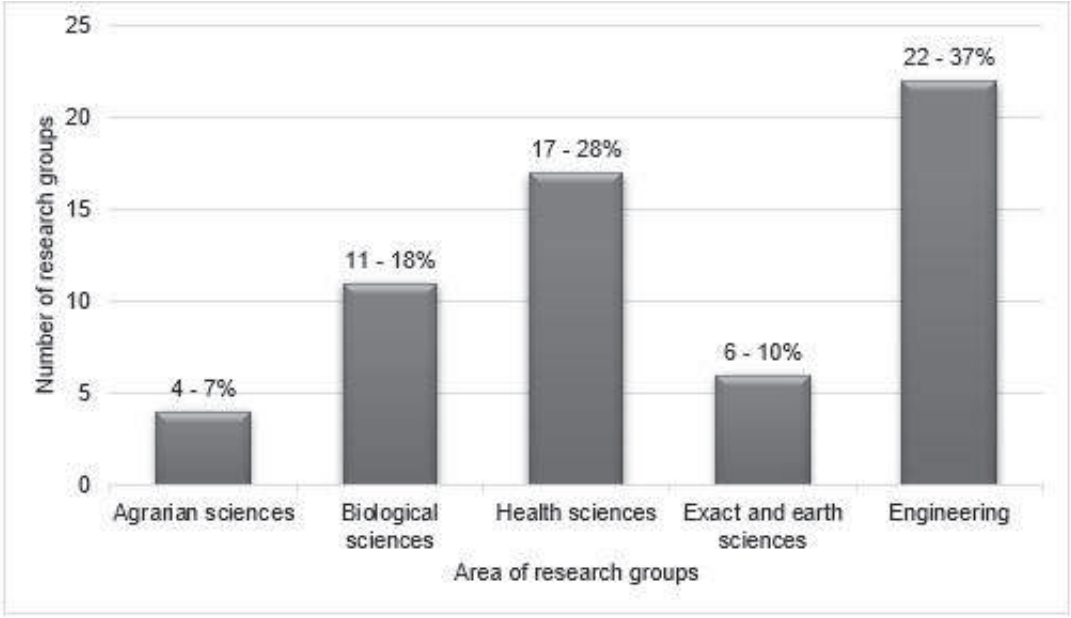
As for induction mechanisms and support for innovation, we did not identify any specific support line for the development of the field. The available support mechanisms are the same for other technology-based and innovation-promoting enterprises; however, an important point to highlight is the vital role of the São Paulo State Research Foundation – FAPESP, which through its PIPE program funded / funds projects in three of the four startups in this state.

From the regulatory point of view, it is worth highlighting the position of ANVISA, that approved the Resolution of the Collegiate Board (RDC 260/2018), which establishes specific criteria for studies with advanced therapy products, methods that consist of the use of genetic material (genes and cells) in various treatments. This resolution covers different application possibilities using stem cells for the field of bioprinting and tissue engineering.



States	Research lines	Research Groups	startupe
CE	1	1	
DF	2	2	1
ES	1	1	
MS	2	1	
MG	13	11	
PB	3	2	
PR	1	1	
PE	4	3	
PI	1	1	
RJ	4	4	1
RS	10	7	
SC	5	4	1
SP	22	21	4
SE	1	1	

Figure 1 – Distribution of groups, research lines and startups in the field of Bioprinting and tissue engineering.



Graph 1 – Predominant area of research groups.

Characteristics of innovation projects in the field of bioprinting from the perspective of a startup: The case of 3D Biotechnology Solutions – 3DBS

3DBS – 3D Biotechnology Solutions was established in December of 2017, registered with the National Register of Legal Entities (CNPJ): 29.150.401/0001–00, as the first Brazilian startup working in the field of bioprinting. Its shop is located in São Paulo, Brazil. Since its opening, it has been developing projects for customizing bioprinting equipment and consulting services in the area of tissue engineering. 3DBS' services have been in demand both for the development of equipment as well as for its *Know How* within the field of bioprinting. Since its opening it has been developing diverse projects to meet specific demands of startups, research institutes and universities. Among these we can mention, In Situ Cellular Therapy, IPEN, Embrapa, UNICAMP, INCT Biofabris, UFRGS, UFRJ, USP/São Paulo.

In these months of operation, so far it has been observed that the main client is either the researcher who develops applications or the professors in the educational field. His main need is to supply missing knowledge to advance research since the field of bioprinting is extremely interdisciplinary and is in its early stages in Brazil. Thus, there is a need/demand for support to begin research in the field of bioprinting and personalized and close assistance to operationalize the lines of research. In addition, there are difficulties in importing equipment and resources, both from a price, as well as from a logistical and customs barrier. Among the elements that compose the value proposition of 3DBS we can highlight: reduction in the cost of bioprinting, customization for specific purposes, partnerships for the co–development of applications, possibility of printing of different materials and association with other technical methods such as electrospinning.

Among the next steps, 3DBS has been developing applications that aim to explore bioprinting products, and for this purpose it has been developing specific projects with the support of the São Paulo State Research Support Foundation (FAPESP) and partners such as the Federal School of Medicine of São Paulo (UNIFESP), the AC Camargo Cancer Center hospital, and the Faculty of Pharmaceutical Sciences of USP/São Paulo. Moving forward, we will detail the main aspects of these initiatives.

Figure 2 – 3DBS Bioprinters, models Genesis II and Octopus.

Ongoing 3DBS Projects and their impacts

Project I: Bioprinting of tubular structures and In Vitro models – Partnership with USP and FEM Unicamp – PIPE FAPESP phase II program support

Cardiovascular diseases are the leading cause of deaths in developed countries, particularly those that cause flow obstruction as is the case of atherosclerosis[14]. In addition to atherosclerosis, several vascular diseases and pathologies lead to aneurysmal degeneration, congenital malformation, vasculitis, and traumatic injuries requiring arterial bypass. Bypass or revascularization surgery is a surgical procedure that utilizes an autologous vascular graft, such as the patient's own saphenous vein or peripheral artery or an artificial graft[15]. Even today, the autologous graft is the gold standard; however, previous surgeries and medical comorbidities may limit the availability of these vessels.

Thus, synthetic vascular grafts play an important role in the treatment of these clinical conditions as 30% of patients that require bypass surgery do not possess adequate or sufficient autologous blood vessels[16].Polyethylene terephthalate(PET), Dacron and expanded polytetrafluoroethylene (ePTFE) are the biomaterials commonly used in vascular prostheses, awarding satisfactory results when used to replace or bypass large blood vessels. However, due to the blood flow velocity in small caliber vessels, the clinical performance of these grafts is inferior[17,18.] Although biologically inert, synthetic vascular prostheses are also susceptible to infections[19].

Due to the poor functional performance of commonly used biomaterials, strategies have been developed to reduce the factors that influence low permeability rates, namely acute thrombus formation and intimal hyperplasia[20,21]. Endothelialization of the luminal surface of the graft using autologous endothelial cells has become a successful procedure to improve long–term permeability rate (7 years) in artificial vascular grafts [22]. Studies show the use of autologous cells and genetically modified cells loaded in biological or synthetic matrices to construct tubular structures and subject them to mechanical and chemical stimuli in an attempt to develop a small caliber vascular graft[23,24]. As noted with the increasing demand for blood vessels and the problematic of existing therapies, tissue engineering as a multi and interdisciplinary discipline establishes three essential criteria for blood vessel development: i) to present biocompatible components with high tensile strength that provide mechanical support; ii) have a biocompatible elastic component that provides elastic reserve and prevents the formation of aneurysms (elastin fibers); iii) have a confluent endothelium that prevents intravascular thrombosis.

To achieve these goals, technologies that were previously used for other purposes have been adapted over the past decade to meet the demands of regenerative medicine and, specifically, tissue engineering. This is the case of 3D bioprinting, an adaptation of conventional 3D and electrospinning printing techniques, inherited by the textile industry, to produce nano and micro fibers.

The 3D printer used in this project was developed under the Phase I PIPE/FAPESP program by 3DBS startup. The equipment has two printer heads that allow you to work with two bioinks layer– by–layer in the same bioconstruct, as well as a photocuring system (ultraviolet light), HEPA filters, a camera for recording images during the bioprinting process and a fourth rotary axis with controlled speed and diameters for the generation of tubular structures (diameters between 2mm and 12mm) (Figure 3).

During Phase I of the PIPE program, tests were performed to validate the equipment, so we had the collaboration of the researcher Prof. Dr. Marcos Akira, from the Faculty of Mechanical Engineering at UNICAMP and Prof. Dr. Sang Won Han of the Center for Cellular and Molecular Therapy (CTCMOL) at UNIFESP. Bioinks with different compositions and rheological properties were tested analyzing printability, filament formation, injectability, the preservation of three–dimensional geometry after crosslinking and biocompatibility (cell viability) (***vide*** Figure 4).

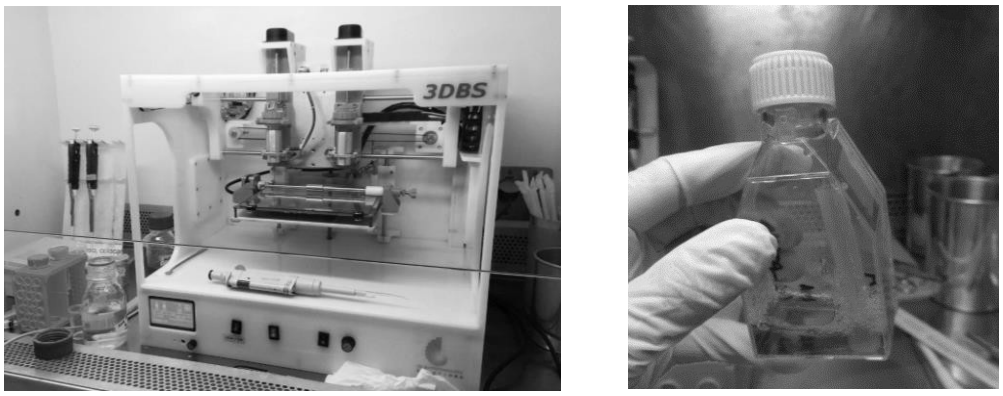


Figure 3 – 3D Bioprinter Model Genesis II from 3DBS startup. It possesses a fourth rotary axis for the generation of tubular structures (vascular grafts). Source: author.

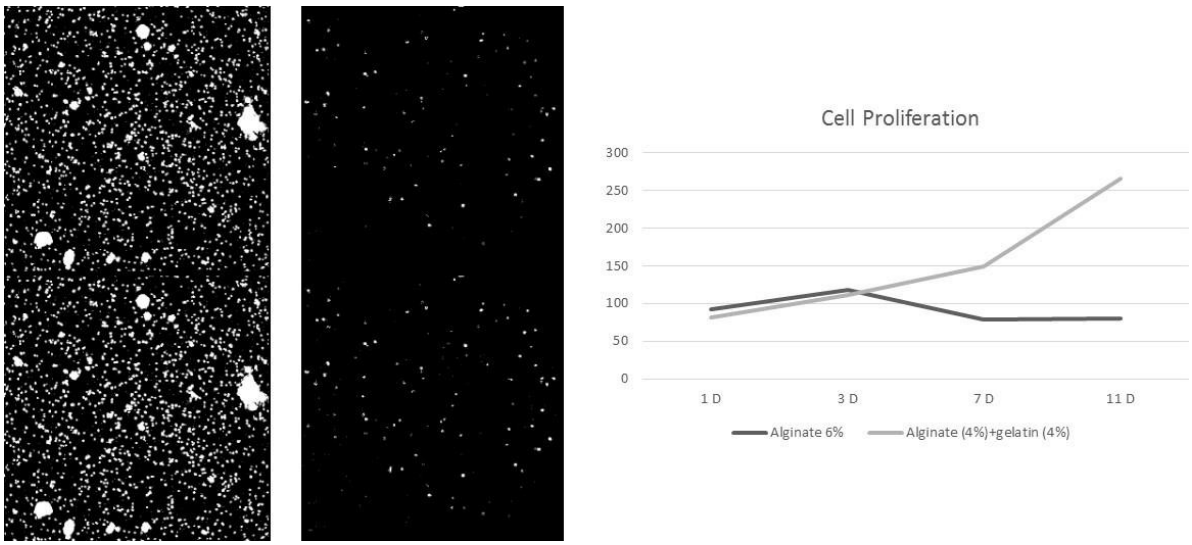


Figure 4 – On the left, tubular alginate (4%) +gelatin (2%) structures loaded with fibroblasts after 11 days of printing. On the right, tubular alginate (6%) structure loaded with fibroblasts. Cell viability is higher when gelatin is incorporated. We tested pure alginate bioink, alginate+gelatin compositions and alginate with laponite bioink. Source: author.

Project II: Bioprinting of In vitro tumor models – partnership with AC Camargo Cancer Hospital

Despite substantial progress in cancer research over the past century, the World Health Organization (WHO) has reported that the incidence of cancer worldwide has increased from 12.7 million in 2008 to 14.1 million in 2012, and the estimate for the next two decades is that this incidence will increase to 25 million, with the greatest impact on low and middle income countries[26]. Applied to oncological investigations, bioprinting allows the creation of in vitro three–dimensional structures with cellular complexity and heterogeneity similar to that found in an in vivo tumor microenvironment, characteristics that are not observed in conventional two–dimensional models[27]. One of the mechanisms of cancer biology that can best be best understood through the use of three–dimensional bioprinting models is metastasis, the leading cause of cancer death worldwide.

Accurate models of human tumors are needed to understand how complex stromal tumor interactions contribute to tumor growth, progression and therapeutic response. Models of genetically modified mice and cancer cell xenografts in immunocompromised mice have allowed the study of tumors in the presence of a tumor microenvironment, but these models are expensive, time consuming, do not include human stroma, and can be difficult to manipulate. Several advances have been made for *in vitro* culture methods in attempts to better recapitulate the complex in vivo tumor microenvironment[28, 29, 30, 31].

Matrix–based models, such as collagen or Matrigel, or scaffold–free heterotypic co–culture models, including multicellular tumor spheroids, allow the integration of additional cell types into 3D culture.

Highlighting the importance of three–dimensional in vitro models for the study of cancer and cell interactions for oncogenesis, three–dimensional systems, when compared to 2D systems, demonstrated significant changes in the genic expression, proliferation, and tumorigenic phenotype profiles[32, 33, 34]. 3D bioprinting has been used in a variety of approaches in an attempt to generate cancer models that simulate spatially defined microenvironments[34, 35]. The spatial orientation of cells within bioprinted tissues allows the investigation of tumorigenic phenotypes, such as cell migration, as well as the analysis of spatial heterogeneity. Together, these results suggest that bioprinted tissues may be useful for drug response studies and analysis of cytostatic versus toxic effects of therapies.

In practice the use of 3D models for cancer drug testing will promote a faster transfer of basic knowledge to the clinic, increase the effectiveness of treatments and lower the costs of drug development as effectiveness tests become more accessible. In addition, it will allow the development of new experimental protocols for the study of tumor biology, especially the mechanisms of metastasis.

Conclusions

The sectoral innovation system of TE and bioprinting has a solid foundation within the academic circle, represented by consolidated groups and lines of research in different universities. The system is starting to present signs of commercial exploration of different application and correlate areas, among these, the supply of equipment and resources for bioprinting, consulting and specific training. The regulatory framework has also been established and implemented by ANVISA based on the regulatory experiences of other countries.

In general, it is worth mentioning that the field of bioprinting is incipient in the world, with the main commercial players beginning to consolidate in the last decade. What has been seen is a consistent expansion of mainly the number of startups emerging in the market within the last couple of years. From a perspective of actions to leverage the expansion of this system, the fact that it is an emerging market provides a wide range of opportunities to formulate strategies for the promotion of Leapfrogging, that is, the notion that areas with less developed technology or economic foundations can advance rapidly through the adoption of specific mechanisms of support without having to go through intermediate steps.

In this sense, to promote the interaction of actors with each other and with investors is an important induction mechanism, both to promote the contact between different related areas of knowledge, as well as to provide long–term financing. Having access to long–term financing is vital especially for developing applications that require clinical testing. Thus, reducing the entrepreneur's risk by providing access to public or private resources can stimulate the development of new startups by fostering bench–to–market movement. On the other hand, to stimulate the demand for applications through specific public bidding can be an interesting resource because it allows entrance in the market of innovative applications in the health field in a controlled manner. In addition, it legitimizes new technologies by supporting the initial formation of this market.

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