3D CELL CULTURE MARKET (3rd EDITION) 2020-2030

Dissertation submitted in partial fulfillment of the requirement for the degree of

BACHELOR OF TECHNOLOGY

IN

BIOTECHNOLOGY

By

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UNDER THE GUIDANCE OF

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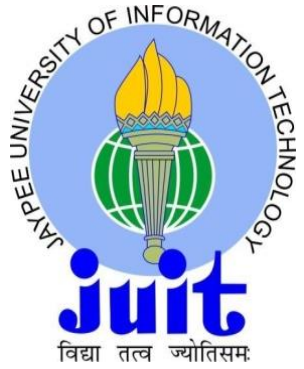

JAYPEE UNIVERSITY OF INFORMATION TECHNOLOGY, WAKNAGHAT
MAY 2020

DECLARATION

I hereby declare that the work reported in the B. Tech. academic report entitled **"3D Cell Culture Market (3rd Edition), 2020-2030"** submitted at **Jaypee University of Information Technology, Waknaghat** is an authentic record of any work carried out under the supervision of **Mr. Gaurav Chaudhary** and **Mr. Kanwar Gaurav**. I have not submitted this work elsewhere for any other degree or diploma.

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Certified that the above statement made by the student is correct to the best of our knowledge and belief. Roots Analysis owns the copyright of the findings presented in this report. Under no circumstances should this information be shared with other third party without the prior consent of the company.

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ACKNOWLEDGEMENT

This project is an outcome of continual work and intellectual support from numerous sources. Therefore, I would like to express my sincere thanks to the people who helped me the most throughout my project.

I owe my deepest gratitude to Mr. Gaurav Chaudhary, CEO, for providing me na opportunity to do internship in their prestigious organization. I am very grateful to Mr. Kanwar Gaurav for making it possible to carry out this project. Without his continuous optimism, enthusiasm, encouragement and support, this study may not have been accomplished as desired. Furthermore, I would also like to acknowledge with much appreciation the crucial role my team partner and senior Miss Prabhjot Kaur for her extremely valuable insights and directions at crucial learning points during the course of my project.

At last but not the least I am deeply grateful to all the members of Roots Analysis who rendered their help during the course of my training and my parents for their motivation, continual support and encouragement at all the stages of my life.

Abhishek Dogra

(161844)

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LIST OF ABBREVIATIONS

2D	Two Dimensional
3D	Three Dimensional
ECLA	European Classification System
ECM	Extracellular Matrix
EPO	European Patent Office
IPC	International Patent Classification
PPT	Power point
R&D	Research and Development
SEC	Securities and Exchange Commission
SEO	Search Engine Optimization
USPTO	United States Patent Trademark Ofiice
VC	Venture Capital

ABSTRACT

The project titled "*3D Cell Culture Market (3rd Edition), 2020-2030"* provides an extensive study of the rapidly growing market of 3D Cell Cultures and provides an outlook of the growing market of 3D Cell Cultures. With significant advances in medical sciences in the last two decades, there has been a paradigm shift in the field of 3D cell culture. The need to discover and develop new drugs has favored commendable progress in this area and promoted the use of cell-based approaches instead of biochemical assays. Lack of ideal cell cultures has provided the opportunity to 3D cell culture system to prove their potential and fill the void in the research and drug discovery. This report features an extensive study on the various scaffold based and scaffold free 3D culture systems. We identified over 50 3D bioreactors, 70 inserts / plates / other cultureware and 80 hydrogel / extracellular matrix (ECM) based products that are widely being used for a variety of research applications across the globe. In addition, several kits, assays and tools are also available to carry out cytotoxicity assessments, transfection and cell viability testing. Several players, including 3D Cell Culture developers, research institutes, contract manufacturing organizations, and government organizations are playing a critical role in the development and manufacturing of these products.

During my job, I worked on different modules of the project. These include drafting an introduction on 3D cell cultures, prepared database of 3D cell cultures, gathered data related to collaborations and partnerships, analyzed social media trend, collated data for patent analysis, VC and service providers in the 3D cell culture domain. Apart from this, I contributed in six additional projects namely, Ophthalmic Drugs Contract Manufacturing Market, Targeted Protein Degradation Market, STING, Oligonucleotides Synthesis, Modification and Purification Services Market, Novel Cell Sorting and Separation Market and Cell and Advanced Therapies Supply chain Management – Focus on Technological Solutions wherein I drafted several documents, such as press releases, SEO booklets, interview transcripts, company profiles, and appendix tables.

CHAPTER 1

COMPANY PROFILE

1.1 Company Overview

Roots Analysis Pvt. Ltd. is a business research and consulting firm, which specializes in providing in-depth business research and consulting services for bio/pharmaceutical industry. Focused on providing an informed and impartial view on key challenges facing the industry, the research is primarily driven by an in-depth analysis covering the following parameters:

- Research and development
- Technology evolution
- Existing market landscape
- Future Commercial potential
- Regulatory concerns
- Regional growth drivers
- Risks and opportunities

The firm has expertise in analyzing areas that have lacked quality research so far or require more focused understanding within the broader industry. Apart from writing reports on identified areas, the company also provide bespoke research / consulting services dedicated to serve our clients in the best possible way.

The business reports highlight trends ranging from commercial success / potential, technological developments and future outlook built around opportunities and threats.

The company majorly focus on areas spanning the following domains:

- Therapeutic segments
- Emerging technologies
- Medical devices
- Drug delivery
- Clinical trials

1.2 Research Methodology

The data presented in the reports has been gathered via secondary and primary research. For all our projects, we conduct interviews with experts in the area (academia, industry, medical practice and other associations) to solicit their opinions on emerging trends in the market. This is primarily useful for us to draw out our own opinion on how the market may evolve across different regions and technology segments. Wherever possible, the available data has been checked for accuracy from multiple sources of information.

The secondary sources of information include:

- Annual reports
- Investor presentations
- SEC filings
- Industry databases
- News releases from company websites
- Government policy documents
- Industry analysts' views

CHAPTER 2

INTRODUCTION

2.1 Chapter Overview

Cell culturing is a fundamental component of tissue culturing, wherein different plant, animal or microbial cells are grown in a medium, which provides essential requirements for their proliferation and maintenance. Cell culturing is used as a common tool to develop the model systems which are useful to study basic mechanism of human molecular and cell biology. The conventional culture models involve generation of adherent 2-dimensional (2D) cell monolayers, however, these models fail to mimic *in vivo* conditions. This led to the development and introduction of 3-dimensional (3D) cultures with an aim to improve the conditions and the microenvironment for cells to grow *in vitro*.

This chapter provides a brief introduction to the different types of 3D cell cultures. It features detailed information on the various categories of 3D cell cultures, their maintenance, selection of the appropriate cell culture, their various applications, and the advantages and challenges associated with different culture systems. In addition, it elaborates on the future prospects in this area.

Despite their superiority over other culture techniques, 3D cell cultures are still associated with several challenges. Some 3D matrices, such as hydrogels, are organic in nature and introduce organic impurities in the culture; this may result in batch-to-batch variations and inconsistent results. Further, application of these cultures at higher scales has still not very successful. Several consistency issues are observed when 3D cell cultures are used at varying scales of operation. Once these challenges are resolved, the 3D cell culture industry is likely to be more widely adopted by several researchers and research and development (R&D) experts, worldwide. Additionally, development of new technologies is likely to provide solutions to attain accurate, precise and a well-structured workflow. Eventually, the success of these advanced culture systems will be determined as their

application translates from research to mainstream therapeutics and several high-end applications.

2.2 2D to 3D Cell Culture Transition

Over the past few years, cell lines have emerged as a very important drug discovery research document. Cell lines essentially serve as model systems and are used to simulate *in vivo* conditions and study the effects of external factors or modulatory agents, in the laboratory. Over the years, there has been an evident transition from using biochemical assays (using purified drug targets) to cell-based assays (wherein the molecular target is overexpressed on certain model cell systems, such as Chinese Hamster Ovary (CHO), human embryonic kidney (HEK) 293 cells. Owing to their inherent tendency to better simulate the *in vivo* environment, 3D systems are increasingly being adopted for the development of such cell based assays.

According to a white paper titled, *3D Cell Culture: A Review of Culture Techniques*, released by BioTek in November 2015, an attrition rate of ~95% was reported for drug candidates that were developed / evaluated in 2D models as potential treatment options for cancer.

Table 2.1 provides information about the main distinctions between 2D and 3D cell cultures.

Table 2.1 **2D and 3D Cell Culture Differences**

S. No.	Cellular Characteristics	2D Cell Culture	3D Cell Culture
1	Morphology	Sheet-like flat and stretched cells in a monolayer of thickness 3 µm	Natural shape in spheroids, aggregate structures or ellipsoids formed in multilayer of dimensions 10-30 µm
2	Proliferation	Often proliferate at a faster rate than in *in vivo* conditions	May proliferate at a faster / slower rate compared to 2D-cultured cells depending on cell type and / or type of 3D model system
3	Exposure to medium / drugs	100% exposure of cells in monolayer to nutrients, growth factors or drugs that are distributed in the medium	High exposure of cells in the outer layers. The cells in the core receive less oxygen, growth factors, and nutrients from the medium, and tend to be in a quiescent or hypoxic state
4	Stage of cell cycle	Greater number of cells are likely to be in a similar stage of cell cycle as they are equally exposed to medium	Cells in the spheroids can be quiescent, proliferating, hypoxic or necrotic

S. No.	Cellular Characteristics	2D Cell Culture	3D Cell Culture
5	Gene / protein expression	As compared to *in vivo* models, the system displays differential gene and protein expression levels more frequently	The gene / protein expression profiles exhibited by cells in 3D culture are similar to those in *in vivo* tissue models
6	Drug sensitivity	Cells often perish due to treatment and drugs act effectively	Cells show greater resistance during treatment as compared to cells in 2D culture system; this enables better prediction of *in vivo* drug responses
7	Stem cell expansion	Poor stem cell expansion	Fast stem cell expansion
8	Interaction type	Unnatural interactions with the synthetic surface	Natural interactions with the surrounding cells
9	Cell viability	Similar to 3D cultures during the initial few (1-5) days, however, it shows better viability results when culturing is done for a prolonged time	Cell viability is slightly reduced when the culturing is carried out for a longer time period due to large size of the spheroids

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4026212/, https://www.biotek.com/resources/white-papers/3d-cell-culture-a-review-of-current-techniques/

3D spheroids consists cells which grow in various cell stages, such as proliferation, apoptosis, hypoxic, quiescent and necrotic. The outer layered cells of the spheroid that are exposed to the culture medium are hugely composed of proliferating and viable cells. Further, the cells present at the center are supposed to receive limited oxygen, nutrients and growth factors supply from the medium and thus, hypoxic or quiescent. This represents a state of cells which is generally seen *in vivo*. As morphological features and cellular interactions in 3D cell culture systems is similar to actual *in vivo* conditions, the cellular processes of such cells closely mimic what is seen *in vivo*.[1]

2.3 Application of 3D Cell Cultures

- **Drug Discovery and Preclinical Research:** With an aim to reduce the overall cost of drug development, 3D cell culture systems have emerged as a promising approach to reduce the gap between 2D models used traditionally and clinical studies in humans practiced *in vivo*. Improvements in emerging technologies and the development of 3D *in vitro* assays are expected to overcome most of the challenges associated with drug testing. On comparing with the 2D cell culture, 3D culture systems have demonstrated similar in vivo responses in terms of cellular responses to drug treatments. It is also shown in several studies that 3D models are more anti-cancer drugs resistant than 2D cultures.

[1] Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4026212/

- **Cancer Research:** There are several cell lines and 3D models that are available for cancer research and drug development. It is worth mentioning that complex 3D model systems are also being developed to mimic the tumor microenvironment with high accuracy. The cancerous cells cultivated in a 3D system differ in structure, depending upon the cell line used. Kenny *et al* categorized the 3D spheroid's structures which were generated by a panel of 25 breast cancer cell lines into four groups including, round, unorganized mass, grape-like and stellate structures.
- **Virology Research:** The development of 3D cell culture systems mimicking the *in vivo* viral life cycle is encouraging the development of novel discoveries and strategies in the field of viral infection. Moreover, tissue engineering techniques involving 3D culture systems have the potential to allow virologists to design infection models combining the direct manipulation and readouts of tissue culture with the virus-based intricacy of animal models. As compared to standard culture and animal models, it offers the possibility to recapitulate specific higher-order interactions while preserving the ability to rapidly modify distinct components of the system. Hence, persistent research in the field of tissue engineering will more readily ensure the precise positioning of matrix, cells and soluble factors, and interactions between these components to capture the properties important in viral infection.
- **Genetic Engineering and Gene Therapy Research:** A study utilizing hanging drop plates demonstrated that 3D spheroids led to the improvement of gene expression profiles of HepaRG cells. It highlighted that 3D cultured HepaRG spheroids exhibited enhanced expression of genes related to both drug and cellular metabolic pathways, such as glucose and lipid metabolism. Further, exposure of cytochrome P450 (CYP) enzymes to corresponding inducers led to increased mRNA levels under 3D conditions. This data demonstrated that such 3D culture systems (hanging drop method) have the potential to improve liver-specific characteristics, including lipid metabolism, without the use of any special biomaterials. Additionally, the system enabled high-throughput assay and hence, may become a useful tool for screening of potential drugs.

2.4 3D Cell Cultures: Advantages and Disadvantages

3D cell culture has demonstrated the capability to overcome the disadvantages associated with the 2D cell culture system. The varying cell proliferation zones and non-uniform

exposure of cells (to media and the drug candidate under evaluation) within a 3D structure makes it a better culture system than 2D cell culture. Other advantages associated with 3D culture system are outlined below:

- ***Mimics in vivo 3D environment:*** 3D cell culture is a reliable tool to study complex cellular mechanisms with a close duplication of the natural *in vivo* environment. The behavioral outcome of the cells is almost a replication of their responses inside the living system. Additionally, similar gene and protein expression levels are observed in 3D culture systems and *in vivo* models.
- ***Evaluation of drug toxicity and cellular responses:*** These systems can be used to study the toxic effects of the drugs on the cells and the molecular response of the cells, when they are subjected / exposed to different chemicals or biological components.
- ***Applications in diverse areas:*** These are well represented model systems that can be manipulated for the interest of research. In addition to the applications in pharmaceutical research, such as in oncology, drug and toxicity screening and stem cells, 3D cultures are used to develop epidermal or skin models of various body systems for cosmetic applications, such as in plastic surgeries.
- ***Favorable oxygen and nutrient gradient:*** After a prolonged incubation time, spheroids / cell aggregates (generated via 3D culture system) grow in size and become deficient in oxygen and nutrients. This is similar to the *in vivo* condition in tumor cells and hence, can be used to carry out drug toxicity studies to generate accurate results.
- ***Increase in cell-to-cell and cell-to-ECM interactions:*** Cells are embedded in the ECM of 3D cell culture system where they grow, proliferate and polarize as per organ of origin to form perfect spheres (for normal cells) or distorted structure (for malignant cells). The ECM supports the movement of cells within their spheroids that is similar to that in the living tissue. Hence, the matrix supports increased signaling pathway activation, cell differentiation, migration, survival and growth.
- ***Multicellular culture systems:*** 3D cell culture system supports co-culturing of multiple cell types to more closely mimic the *in vivo* conditions. The multicellular system offers a model for studying the role of stromal cells in growth, metastasis and treatment outcomes of tumors.
- ***Modification of culture environment:*** The culture environment in a 3D system can be modified to incorporate factors or proteins found in a particular tumor microenvironment.

- ***Less use of animal models:*** The 3D system is known to reduce the gap between *in vitro* and *in vivo* drug screening, thereby reducing the usage of animal models.

On the other hand, there are a few drawbacks associated with 3D cell culture; these are outlined below:

- ***Incomplete replication of in vivo environment:*** 3D cell culture is still just a model that represents the native state of the cells and cannot fully replicate the exact *in vivo* conditions.
- ***Absence of validated assay methods:*** Lack of validated assay methods disrupts the process of monitoring the biological mechanisms accurately.
- ***Risk of heterogeneity:*** There is a risk of heterogeneity of the cell population within a spheroid. The matrices may be composed of membrane extracts that contain undesired components, such as viruses or growth factors or some unknown substances. Some matrices are made up of components of animal origin that allow attachment of the cells, but are not proficient in cell removal or recovery. Hence, variability in biologically derived matrices may lead to non-reproducible experimental results. Additionally, the spheroids generated in different 3D models specifically for drug discovery may vary greatly in size, thereby, leading to high variability within the same flask / well.
- ***Expensive culture system:*** The process becomes expensive in case of large-scale studies and high throughput assays for drug discovery applications as compared to traditional 2D culture system.
- ***Lack of vasculature:*** Vasculature, which is known to play a major role in tumor growth and survival, and treatment outcomes, is not found in 3D models.

CHAPTER 3

MARKET OVERVIEW

3.1 Chapter Overview

In the last few years, 3D cell culture market has undergone tremendous transformation in terms of availability of different types of products, including 3D cultureware, hydrogels / ECMs and 3D bioreactors. The primary classification of these products depends on the scaffold format, based on which they are categorized as scaffold based or scaffold free systems. These are further segregated into various sub-types; few examples include solid scaffolds, microcarriers, microfluidic systems and suspension cultures.

3.2 Overall Market Landscape

Close to XX players are driving the activity in the domain of 3D cell cultures. The current market is segmented or characterized by the presence of several small-sized and mid-sized firms. Some of the established players and non-industry players are engaged in the field of 3D cell culture. It is important to highlight that the landscape for 3D cell culture systems is presently well distributed across various regions of the globe, including North America (primarily the US), EU (, The Netherlands, France, Germany, Italy, Portugal, Spain, and The UK), Asia (China, India, Japan, Singapore, Switzerland and Taiwan) and Middle East.

3.3 Database Building

Database is a list of products, drugs or molecules that have been gathered from multiple sources such as public records and company websites (including investor presentations). It governs the structure of the overall report and acts as the most important aspect in drafting the report insights. Hence, it must be robust, exclusive and finely structured, in order to produce accurate analysis.

In our study, we found that different companies are developing different types of 3D cell culture products. Based on this, our database has been segmented into Hydrogels / ECMs, 3D cultureware (inserts / plates / other 3D dishes) and 3D bioreactors.

Table 3.1 **3D Cell Culture Products: List of ECMs / Hydrogels**

S. No.	Company	Technology / Products	Headquarters	Scaffold Format	3D Culture Sub-type	Method / Material
1	101Bio	Col-Tgel	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen
9	Advanced BioMatrix	PureCol	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen (Bovine Hide Pepsin Extracted)
14	Advanced BioMatrix	VitroCol	US	Scaffold Based	Hydrogel / Scaffold	Human Based: Collagen I or Collagen III
19	Advanced BioMatrix	Nutragen	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen (Bovine Hide Pepsin Extracted)
24	Advanced BioMatrix	RatCol Rat Tail Collagen I	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen (Rat Tail Tendon)
34	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen I or Collagen III (Porcine Hides)
42	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen I, Collagen III (Bovine)
49	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen I (Bovine)
59	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Human or Animal Based: Collagen
67	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Human or Animal Based: Collagen I
75	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Human Based: Collagen I
84	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Polymer Based: Polycaprolactone (Porous)
103	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Chemical Based: Protein Based
110	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Animal Based: Collagen I (Bovine or Rat Tendon)
122	Company aa	Product aa	UK	Scaffold Based	Hydrogel / Scaffold	Plant Based: Alginate
126	Company aa	Product aa	Taiwan	Scaffold Based	Hydrogel / Scaffold	Human or Animal Based: Collagen, Cellulose or Galactose (Porous)
129	Company aa	Product aa	Taiwan	Scaffold Based	Hydrogel / Scaffold	Chemical Based: Gelatin (Porous)
133	Company aa	Product aa	Scotland	Scaffold Based	Hydrogel / Scaffold	Chemical Based: Peptide
137	Company aa	Product aa	US	Scaffold Based	NA	Chemical Based: Polycarbonate polyurethane-urea (Porous)
140	Company aa	Product aa	US	Scaffold Based	Hydrogel / Scaffold	Chemical Based: Hyaluronic Acid with Chitosan

Source: Roots Analysis

The various kinds of commercially available 3D cultureware include attachment resistant cell culture plates, ECM coated plates, microfluidic systems, micropatterned surfaces, solid scaffolds and suspension culture systems. During the course of our research, we could identify xx cultureware products. Table 3.2 provides a list of 3D inserts, plates and dishes along with information on their scaffold format, sub-type and the developer.

Table 3.2 **3D Cell Culture Products: List of 3D Cultureware**

S. No.	Company	Technology / Products	Headquarters	Scaffold Format	3D Culture Sub-type	Method / Material
1	3D Biomatrix	Perfecta 3D Hanging Drop Plates	US	Scaffold Free	Suspension Culture	Hanging Drop Plate
2	3D Biotek	3D Insert-PCL	US	Scaffold Based	Solid Scaffold	Polymer Based: Polycaprolactone (Porous)
3	3D Biotek	3D Insert-PS	US	Scaffold Based	Solid Scaffold	Polymer Based: Polystyrene (Porous)
4	3D Biotek	3D Insert-PLGA	US	Scaffold Based	Solid Scaffold	Polymer Based: Poly(lactic-co-glycolic acid) (Porous)
5	3D Biotek	3D Insert with Nanomesh	US	Scaffold Based	Solid Scaffold	Polymer Based: Polycaprolactone, Polystyrene (Porous)
6	Company X	Product X	US	Scaffold Based	Solid Scaffold	Polymer Based: Polystyrene or Polycaprolactone (Porous)
7	Company X	Product X	UK	Scaffold Based	Solid Scaffold	Polymer Based: Poly-L-lactide (Fibrous)
8	Company X	Product X	US	Scaffold Based	Solid Scaffold	Human or Animal Based: Collagen I
9	Company X	Product X	US	Scaffold Based	Solid Scaffold	Human or Animal Based: Collagen I
10	Company X	Product X	US	Scaffold Based	Solid Scaffold	Human or Animal Based: Collagen I
11	Company X	Product X	Singapore	Scaffold Based	Microfluidic System	Microfluidic Plate
12	Company X	Product X	US	Scaffold Based	Solid Scaffold	Human or Animal Based (Bovine): Collagen
13	Company X	Product X	US	Scaffold Based	Solid Scaffold	Human or Animal Based: Collagen
14	Company X	Product X	US	Scaffold Based	Solid Scaffold	Chemical Based: Collagen and other ECM products
15	Company X	Product X	US	Scaffold Based	Solid Scaffold	Polymer Based: Poly-L-Lysine
16	Company X	Product X	US	Scaffold Based	Hydrogel Coated Plates	NA
17	Company X	Product X	US	Scaffold Free	Microfluidic System	Organ-on-chip
18	Company X	Product X	US	Scaffold Free	Microfluidic System	Microfluidic Plate
19	Company X	Product X	US	Scaffold Free	Suspension Culture	NA
20	Company X	Product X	EU	Scaffold Based	Solid Scaffold	Polymer Based: Polycaprolcatone

Source: Roots Analysis

The third type of 3D cell culture systems are 3D bioreactors, which offer the advantage of large-scale production of cells. They are available either as single use / disposable systems or are autoclavable. During our research, we captured xx such bioreactors. Table 3.3 provides details on these 3D bioreactors along with their developer and its headquarters.

Table 3.3 **3D Cell Culture Products: List of 3D Bioreactors**

S. No.	Company Name	Product	Headquarters
1	3D Biotek	3D Perfusion Bioreactor	US
2	Accellta	Maxells	Israel
3	Antleron	Undisclosed	Belgium

S. No.	Company Name	Product	Headquarters
4	Applikon Biotechnology	Applikon micro-Matrix micro-bioreactor system	Netherlands
5	BiSS TGT (Bangalore Integrated System Solutions Tissue Growth Technologies)	DermiGen Bioreactors	India
6	Company xx	Product xx	India
7	Company xx	Product xx	US
8	Company xx	Product xx	US
9	Company xx	Product xx	US
10	Company xx	Product xx	US
11	Company xx	Product xx	US
12	Company xx	Product xx	US
13	Company xx	Product xx	US
14	Company xx	Product xx	US
15	Company xx	Product xx	US
16	Company xx	Product xx	US
17	Company xx	Product xx	US
18	Company xx	Product xx	US
19	Company xx	Product xx	Switzerland
20	Company xx	Product xx	US

Source: Roots Analysis

CHAPTER 4

PATENT ANALYSIS

4.1 Chapter Overview

Patent act as an exclusive right granted for an invention, which might be a process or product that provides a new of something, or offers a new technical solution to a problem. It gives its owner the legal rights to exclude others from making, using or selling an invention for a limited period of years in exchange for publishing a promoting public disclosure of the invention.

Patent analysis helps in getting an overview of the technologies the competitors are working on. The chapter highlights an elaborative patent analysis considering the patents filed in the field of 3D cell cultures. For this analysis, we have taken into account only those patents that have been filed / granted since 2014.

4.2 Data Collection

For the purpose of this analysis, information on the relevant patents was extracted from a reliable database, *lens.org*. This website is a service of Cambia, an independent non-profit institute. The Lens is a joint venture of Cambia and Queensland University of Technology. Therefore, all the available patents were extracted in order to perform exhaustive analysis.

Table 4.1 provides the information about the patents filed / granted in 3D cell culture domain during the period of 2015- Q1 2020.

Table 4.1 Patent Analysis: List of Patents

S. No	Jurisdiction	Kind	Publication Number	Lens ID	Publication Date	Publication Year
56	US	B2	US 9213025 B2	086-335-301-459-259	42353	2015
83	CN	A	CN 106929417 A	162-376-427-317-446	42923	2017
85	US	A1	US 2019/0249134 A1	181-585-651-224-420	43692	2019
105	US	B2	US 9631173 B2	004-719-629-313-34X	42850	2017
106	US	B2	US 9932551 B2	055-736-709-436-344	43193	2018

110	US	B2	US 9828576 B2	044-631-677-416-006	43067	2017
111	US	A1	US 2015/0203809 A1	012-817-696-197-712	42208	2015
124	WO	A1	WO 2018/044990 A1	184-188-677-073-034	43167	2018
138	EP	A1	EP 2879794 A1	114-072-821-954-87X	42165	2015
139	EP	A4	EP 2879794 A4	085-619-695-970-065	42466	2016
140	SG	A	SG 10201700670W A	003-161-893-861-752	42824	2017
141	SG	A	SG 11201500417P A	137-404-862-731-894	42093	2015
144	CN	A	CN 104703698 A	141-513-793-636-494	42165	2015
173	EP	A4	EP 3383997 A4	173-311-418-801-406	43796	2019
191	US	B2	US 10532355 B2	029-710-979-237-275	43844	2020
212	WO	A1	WO 2016/195480 A1	102-201-691-641-391	42712	2016
213	US	B2	US 9029150 B2	022-653-647-849-600	42136	2015
224	JP	A	JP 2018102291 A	103-944-915-949-904	43286	2018
251	KR	A	KR 20170074503 A	180-909-389-164-240	42916	2017
263	EP	A1	EP 3298125 A1	071-060-271-252-657	43187	2018
285	WO	A1	WO 2019/033171 A1	040-205-983-516-526	43517	2019
310	EP	B1	EP 3019589 B1	048-456-326-102-080	42872	2017
353	WO	A1	WO 2019/195795 A1	184-795-329-268-34X	43748	2019
376	EP	A4	EP 3411470 A4	090-884-149-987-327	43747	2019
379	EP	A1	EP 3456811 A1	182-726-323-360-266	43544	2019
382	US	A1	US 2018/0312792 A1	185-351-894-515-779	43405	2018
402	US	B2	US 9764505 B2	106-009-107-566-309	42997	2017
447	WO	A1	WO 2018/156023 A1	074-947-760-520-241	43342	2018
465	EP	B1	EP 2975115 B1	150-801-476-110-985	43719	2019
479	EP	B1	EP 2633033 B1	086-303-731-799-45X	42466	2016
491	WO	A1	WO 2019/071297 A1	099-678-473-327-03X	43573	2019
492	EP	B1	EP 2633032 B1	035-630-168-549-037	42060	2015
530	AU	B2	AU 2011/322363 B2	163-228-927-611-109	42194	2015
531	WO	A1	WO 2019/121984 A1	198-551-759-212-298	43643	2019
537	US	B2	US 9097702 B2	152-669-526-925-822	42220	2015
564	WO	A1	WO 2019/043130 A1	157-246-773-839-339	43531	2019
583	WO	A1	WO 2019/084622 A1	087-125-225-074-234	43594	2019
599	WO	A1	WO 2017/213529 A1	167-456-849-448-616	43083	2017
606	WO	A2	WO 2016/154082 A2	006-579-384-569-339	42642	2016
607	US	A1	US 2016/0369241 A1	022-824-078-593-652	42726	2016
611	US	A1	US 2016/0116453 A1	192-777-574-870-001	42488	2016
612	US	A1	US 2018/0113114 A1	013-421-996-816-728	43216	2018
618	US	A1	US 2019/0376015 A1	138-398-204-171-248	43811	2019
630	WO	A1	WO 2018/036910 A1	169-534-722-205-741	43160	2018
631	US	A1	US 2019/0119647 A1	165-123-006-142-311	43580	2019
666	AU	A1	AU 2014/264548 A1	074-619-942-362-210	42327	2015
671	US	B2	US 10227556 B2	155-669-046-636-684	43536	2019
672	US	A1	US 2017/0067009 A1	193-234-189-320-13X	42803	2017
673	US	A1	US 2019/0203169 A1	070-961-241-548-408	43650	2019

For data collation, several keywords were used that covered the overall scope of the report. These were the uniquely formed keywords in order to extract most accurate data from the *lens.org*. Below is the list of keywords used to collate the data:

- "3D Cell Culture" OR "3 dimensional cell cultures" OR "three dimensional cell cultures" OR "3 D cell culture"
- "organ-on-chip" OR “organ-on-a-chip” OR "3D organ chip" OR "three dimensional organ chip" OR "3 D organ chip
- "organoid" OR "3D organoid" OR "3 D organoid" OR "three dimensional organoid"
- "3D spheroid" OR "three dimensional spheroid" OR "3 D spheroid"
- "three dimensional scaffold" OR "3D scaffold" OR "3 D scaffold"
- "3D hydrogel" OR "three dimensional hydrogel" OR "3 D hydrogel"
- "3D bioreactor" OR "3 D bioreactor" OR "three dimensional bioreactor"

Patents obtained from each keyword were downloaded and all the data was collected into a single sheet where further analysis were done.

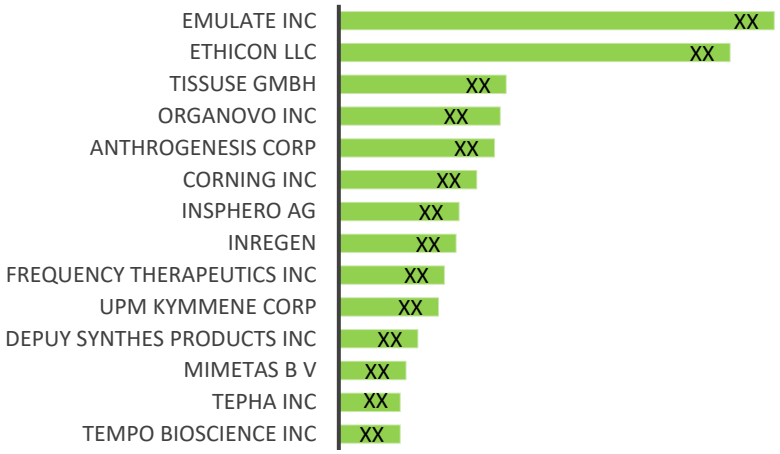
4.3 Data Analysis

The collected data was further utilized for performing the analysis. The idea behind performing the analysis is to procure the detailed examination of the various parameters. For this particular analysis, we took different parameters under considerations and on that basis, analysis performed.

4.3.1 Analysis by Most Active Industry Players

Figure 4.1 highlights the distribution of most active industry players on the basis of patents filed / granted.

Figure 4.1 **Most Active Players: Distribution by Number of Patents**

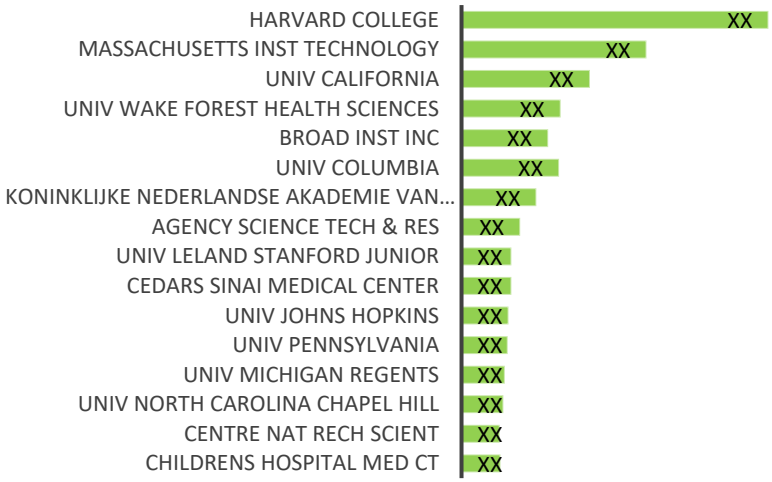


Source: Roots Analysis

4.3.2 Analysis by Most Active Non-Industry Players

Figure 4.2 highlights the distribution of most active non-industry players on the basis of patents filed / granted.

Figure 4.2 **Most Active Players: Distribution by Number of Patents**

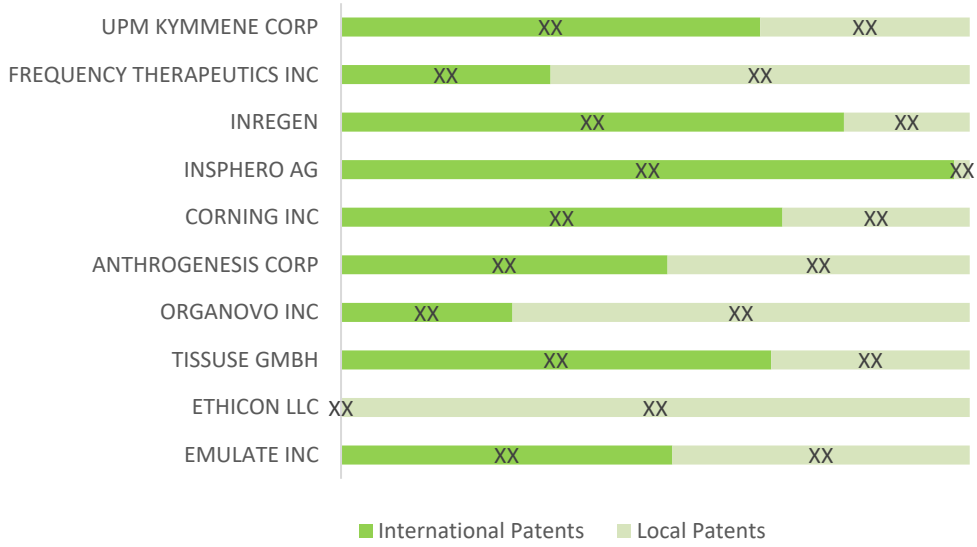


Source: Roots Analysis

4.3.3 Analysis by Geography

Figure 4.3 provides information on the distribution of companies on the basis of their location of headquarter.

Figure 4.3 **Leading Players: Distribution by Geography**



Source: Roots Analysis

4.3.4 Analysis by CPC Symbols

CPC is a bilateral patent classification system that has been developed jointly by the European Patent Office (EPO) and the United States Patents and Trademark Office (USPTO). It is based on the pervious European Classification (ECLA) system, which was a more specific and detailed version of the International Patent Classification (IPC) system. Figure 4.4 presents the information on CPC symbols.

Figure 4.4 **Patent Analysis: Distribution by CPC Symbols**

Row Label	A	B	C	D	E	F	G	H	j	K	L	M	N	P	Q	R	S	T	W	Y	Total
A61		519	22	1		1253			19	4483	7099	176	86	134	77						13868
C12												2095	10028	39	494	1				94	12751
G01			4			1	3	2	14	3	7	4	1962			33	30	26			2,089
B01				133		60			332		1384										1,909
C08		75				47	175	7	405	64	583										1,356
C07		3	85	135		34		13		1025											1,295
H01		8				34	45		88		528	177		1	9						890
B29		1	232	18						156	48										455
A01										221			110								331
D01		2	5	131		87															225
G06						111				30			10		4			52			207
B33																				197	197
Y10																	52	133			185
B32		146																			146
C04		121																			121
Y02				12	16									5				2	2		37
D10		95																			95
C09		4		44					6	28											82
C01		52					2							24							78
B82																				72	72
Total		1026	348	474	16	1627	225	22	864	6010	9649	2452	12196	203	584	34	82	213	2	363	

Source: Roots Analysis

CHAPTER 5

PARTNERSHIPS AND COLLABORATIONS

5.1 Chapter Overview

3D cell culture is top-notch area that has found a renewed focus in the past few years. Several collaborations have been witnessed by the companies involved in this domain aiming at discovering and developing drugs, delivery systems and technology platforms in order to utilise 3D cells as a culture option.

In this chapter, we have provided information on the various partnerships / collaborations that have taken place in the last decade.

5.2 Types of Partnerships and Collaborations

Over the years, due to the increase in emergence of the 3D cell culture domain, stakeholders in the industry are adopting a variety of partnership models to collaborate with other industry / non-industry companies / organizations. Some standard models have been briefly mentioned below:

- **Acquisition:** An agreement in which one company acquires all or majority of the shares and assets of another company.
- **Merger:** Type of agreement wherein one company combines their business operations and merge into single entity.
- **Clinical Trial Agreement:** A type of agreement which occurs to perform clinical trials related to the product candidate with / to a partner company.
- **Joint Venture:** A type of agreement in which two or more companies come together to form a new company.
- **Manufacturing and Supply Agreement:** A type of agreement where one company opts the services of other company for manufacturing purposes only.
- **Product Development Agreement:** A type of agreement in which two companies come together for the development of a product or drug.

- **Product Commercialization Agreement:** A type of agreement in which one company signs an agreement with other companies to commercialize their product candidate.
- **Product Development and Commercialization Agreement:** Agreements wherein one company signs an agreement with other companies to Co-develop and Co-commercialize their product candidate.
- **Licensing Agreement:** These agreements takes place when one company licences its proprietary patented technology or product to other company.
- **R&D Agreement:** In such type of partnerships, two companies signs an agreement to conduct research & development studies.

5.2 Data Collation

Various instances of industrial and non-industrial collaborations was gathered. The data was collected from multiple sources including press releases, public records, surveys, and company sources. This secondary research governs the structure of the overall report and acts as the most important step in drafting the insights. Hence, it must be robust, exhaustive and finely structured, in order to produce accurate analysis.

Such collected data helps us to determine the growth of 3D cell culture market and arousing interest of different pharmaceutical players in this niche field.

Table 5.1 highlights some of partnerships gathered for the analysis.

Table 5.1 Partnerships and Collaborations: List of Partnerships

S.No.	Company	HQ	Partner(s)	Partner's HQ
1	abc bioapply	Switzerland	BioConcept	US
2	abc bioapply	Switzerland	AnaPath	Switzerland
3	Company xx	Woodinville, US	Company xx	US
4	Company xx	Rotherham, UK	Company xx	Basal, Switzerland
5	Company xx	Boston, US	Company xx	
6	Company xx	Florida, US	Company xx	Basal, Switzerland
7	Company xx	Florida, US	Company xx	Florida, US
8	Company xx	Enschede, Netherlands	Company xx	France
9	Company xx	Enschede, Netherlands	Company xx	Netherlands
10	Company xx	Zurich, Switzerland	Company xx	Zurich, Switzerland
11	Company xx	Zurich, Switzerland	Company xx	Switzerland
12	Company xx	Zurich, Switzerland	Company xx	Switzerland

13	Company xx	UK	Company xx	UK
14	Company xx	Scotland UK	Company xx	NY
15	Company xx	Scotland, UK	Company xx	Indonesia
16	Company xx	Scotland, UK	Company xx	Indonesia
17	Company xx	Scotland, UK	Company xx	US
18	Company xx	Scotland, UK	Company xx	UK
19	Company xx	Scotland, UK	Company xx	UK
20	Company xx	UK	Company xx	UK
21	Company xx	USA	Company xx	NY
22	Company xx	Germany	Company xx	US
23	Company xx	Germany	Company xx	Netherlands
24	Company xx	Spain	Company xx	France
25	Company xx	Lithuania	Company xx	Japan
26	Company xx	Finland	Company xx	Finland
27	Company xx	Finland	Company xx	Finland
28	Company xx	Radnor, US	Company xx	Pennsylvania, US
29	Company xx	Germany	Company xx	UK
30	Company xx	Germany	Company xx	UK
31	Company xx	Germany	Company xx	Milan, Italy
32	Company xx	Schlieren, Switzerland	Company xx	Waltham, US
33	Company xx	Schlieren, Switzerland	Company xx	NY
34	Company xx	Schlieren, Switzerland	Company xx	Bethesda, US

Different parameters were taken into consideration while building the database for this analysis which includes the basic company information of both partnering companies. Several parameters included are:

- Product Name
- Year of Collaboration
- Focus Area
- Type of 3D cell culture
- Type of Indication
- Type of Therapeutic Area
- Financial Information

CHAPTER 6

SOCIAL MEDIA ANALYSIS

7.1 Chapter Overview

Due to the vast potential of social media, public relations as well as a marketing tool has motivated a number of stakeholders in the biopharmaceutical sector to become active on such online platforms. Several eminent players and key players in this industry share insights on their work and keep their followers up to date on all their initiatives. Very large number of individuals follow various pharmaceutical and biotech companies on Twitter and Facebook to track important events and announcements. In addition, distributors and consumers are also free to express their views regarding a particular model / product / technology on such platforms. Therefore, tracking all such activities on social media often provides valuable insights that cannot be ignored.

This chapter includes a short discussion on 3D cell culture's growing popularity on social media platform, Twitter. For this analysis, we found the tweets featuring specific keywords related to this domain and presented a snapshot of how the public opinion about such products / systems have evolved in the period between 2017 and 2020.

7.2 Data Collection

The tweets were extracted for the 3D cell culture products presented in the database. The data was collected in the form of tweets that industry or non-industry players have posted on Twitter during the period 2017-February 2020. Hence, all the available tweets were collated in order to perform exhaustive analysis. For this analysis, we found the tweets featuring specific keywords related to this domain. Uniquely formed keywords were formed to extract most accurate data from the Twitter. The list of keywords used is mentioned below:

- "3D Cell Cultures" OR "3 dimensional cell culture" OR "three dimensional cell culture" OR "3 D Cell culture"

- "organ-on-chip" OR “organ-on-a-chip” OR "3D organ chip" OR "three dimensional organ chip" OR "3 D organ chip
- "organoid" OR "3D organoid" OR "3 D organoid" OR "three dimensional organoid"
- "3D spheroid" OR "three dimensional spheroid" OR "3 D spheroid"
- "three dimensional scaffold" OR "3D scaffold" OR "3 D scaffold"
- "3D hydrogel" OR "three dimensional hydrogel" OR "3 D hydrogel"
- "3D bioreactor" OR "3 D bioreactor" OR "three dimensional bioreactor"

All the relevant tweets were downloaded and collated into a single sheet for carrying out further analysis.

7.3 Data Analysis

The data was utilized for conducting the social media analysis. Different parameters were taken into consideration for performing the analysis and on that basis, analysis is performed. The List of different parameters is mentioned below:

- Year-wise distribution of Tweets
- Type of Product
- Type of Application

CHAPTER 7

ADDITIONAL PROJECTS

8.1 Targeted Protein Degradation

In addition to the project assigned to me, I also contributed in other project namely, Targeted Protein Degradation. Below is the list of things I covered in this project:

- Press Release
- SEO Booklets
- Additon Report Figures in PPT
- Additon Tabulated Data in Excel
- Appendices in PPT
- Company Profiles in PPT

8.2 Stimulator of Interferon Genes

In this project, I drafted various chapter. Following is the list of chapters:

- Grant Analysis
- Publication Analysis
- VC Funding Analysis
- Partnership and Collaboration Analysis
- Start-up Health Indexing

8.3 Oligonucleotides Synthesis, Modification and Purification Services

In this project I worked on drafted some end stage documents that are listed below:

- Press Release
- SEO Booklet

8.4 Ophthalmic Drugs Contract Manufacturing

Below is the list of end stage documents that were drafted by me for this project:

- Press Release
- SEO Booklet

CHAPTER 9

CONCLUSION

Cells grown in 3D cultures exhibit properties that closely mimic *in vivo* behavior. Studies have suggested that, in contrast to 2D systems, cells grown in 3D systems demonstrate a marked improvement cell to cell and cell to ECM interactions, which influence both their morphology and spatial organization. Such features make 3D cell cultures suitable for several applications that may not have been possible with cells grown in 2D cultures.

The 3D culture market today is populated with a wide variety of products to facilitate research in different application areas. XX% of 3D cell culture products collated during our study are scaffold based systems, of which XX% are hydrogels / ECMs and XX% are cultureware (inserts, plates, other dishes). Additionally, XX scaffold free systems are available / being developed to serve different purposes in R&D.

Overall, 3D cultures have emerged as essential tools to facilitate research in the biomedical space by addressing the need of improving the accuracy and productivity of the studies. Even though these systems have still not gained a major foothold in the cell culture industry, introduction of novel 3D approaches has prompted several researchers to shift their attention from 2D to 3D systems. With several therapeutics in the pipeline, 3D cultures are expected to make a significant contributions to research with its potential to deliver high quality outputs, and helps to reduce the gap between experiments carried out *in vitro* and animal studies.

Within this project, we will conduct in-depth market study and analysis of the 3D cell culture market. The analysis have been done by considering various aspects including partnerships, patent analysis, and social media analysis of 3D cell culture market that boosts its research aspect to the market domain and many more analysis are to be included.

Through this internship, I am able to develop business acumen in the biopharmaceutical industries. This training has helped me to create better understanding of an analytical sense of biopharmaceutical market. Also, I was able to enhance my intellectual skills.

CHAPTER 14

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