FIRST 3D PRINTING AND MEDICAL APPLICATIONS SYMPOSIUM (3DPMA - 2019)

NEAR EAST UNIVERSITY, HOSPITAL HALL No: 101

5 JULY 2019

ABSTRACT BOOK

SYMPOSIUM CHAIRPERSON & EDITOR:

Terin Adalı

ORGANIZED BY:

1- NEU - TISSUE ENGINEERING AND BIOMATERIALS RESEARCH CENTER (NEU-CTEB)
2- NEU-3D LABORATORIES
3- RESEARCH CENTER OF EXPERIMENTAL HEALTH SCIENCES (DESAM)
4- NERITA

PREFACE

The era of biotechnology is evolving rapidly. Emerging trends including CRISPR/Cas9 system for genome editing, smart implantable biosensors, biomaterials, nano-drug delivery systems, 3D printing and microfluidic chips are revolutionizing the field.

The need for personalized medicine - therapies tailored to the needs of each patient is having a major impact on healthcare as we start seeing more and more research and biotech firms going in that direction.

Undoubtedly, biofabrication is a highly integrated arm of biotechnology and biomimicry applications such as 3D in vitro models and 3D bioprinting currently hold a great potential in the field of regenerative medicine.

As Near East University, we are excited to encourage research and innovation and will remain supportive of novel and inspiring technologies which eventually may translate into biomedical applications.

Prof. Dr. Tamer Şanlıdağ

Vice President

Near East University

PREFACE

The health related fields of science are going through a number of paradigm shifts. The personalized medicine trends force bio manufacturers to address smaller number of groups of parents' even individuals. This cannot be achieved without progresses like 3D printing technologies. The reason is that, this New Era would enable not only additive manufacturing capability but also long demanded targeted approach in biotechnology research labs as standard setting. We welcome as NERITA the scope of the "1st 3D PRINTING AND MEDICAL APPLICATONS SYMPOSIUM" as a critical to further collaboration of scientists and creation of a new work in – progress namely Bio 3D Task Force.

The outcomes will also hopefully be translated into startups, research and doctoral education.

Prof. Dr. Murat Özgören

Technology Consultant of Chairman of Broad of Trustees

1st 3D PRINTING AND MEDICAL APPLICATIONS SYMPOSIUM

(3DPMA-2019)

PROGRAM

5 JULY 2019

09:00 – 09:15 REGISTRATION

09:15 – 09:30 OPENING SPEECH

09:30 – 10:00

1- Prof. Dr. Nesrin Hasırcı

"3D PRINTING IN TISSUE ENGINEERING"

10:00-10:30

2- Prof. Dr. Seda Vatansever

"3D CULTURE, PRINTING and STEM CELL APPLICATION"

10:30 – 11:00

3- Assoc. Prof. Dr. Terin Adalı

"3D PRINTING and BIOINKS"

11:00 - 11:30 COFFEE BREAK

11:30 – 12:00

4- Assoc. Prof. Dr. Kerem Teralı

"3D PRINTING IN DRUG DEVELOPMENT"

12:00 – 12:30

5- Assoc. Prof. Dr. Emil Mammadov

"FROM IMAGE TO OBJECT: PATIENT SPECIFIC 3D PRINTING"

12:30 – 13:30

6- Assist. Prof. Dr. Buket Baddal

"MICROFLUIDIC ORGAN-CHIPS: APPLICATIONS IN DRUG DISCOVERY AND INFECTIOUS DISEASE."

13:30-14:00

ROUND TABLE DISCUSSION: "THE CHALLENGES AND FUTURE OUTLOOK OF 3D BIOPRINTING MEDICAL APPLICATIONS"

Moderator: Prof. Dr. Murat Özgören

3D PRINTING IN TISSUE ENGINEERING

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Three-dimensional (3D) printing technology, which is also known as additive manufacturing or rapid prototyping, plays an important role in tissue engineering (TE) applications especially in the production of scaffolds having predetermined shape and property, so that they can be used in medicine for the personalized treatments. In general, biocompatible ceramics, metals, polymers, composites are used and if desired biodegradability is added to these scaffolds. In some cases, hydrogels (named as bioink) are printed with cells in order to enhance healing and regeneration process of the host tissue. The most commonly used bioinks are agarose, alginate, collagen, methacrylated gelatin (GelMA), methacrylated hyaluronic acid (HAMA), and polyethylene glycol dimethacrylate (PEGDMA). 3D printed scaffold should match the properties of the tissue or organ which is going to be inserted. Although there are different applications of 3D printed scaffolds in TE, frequently examined ones are for regeneration of bone, cartilage, skin, nerve and blood vessels. For bone and cartilage TE, due to its low Tg and mechanically strong nature, poly(ε-caprolactone) (PCL) is the preferable polymer. In many cases, inorganic materials as nano hydroxyapatite (HAp) and tricalcium phosphate (TCP) are included to mimic the mineralized bone structure [1]. Mesenchymal stem cells (MSCs), chondrocytes or growth factors can be added on the 3D printed matrices. In case of skin TE, two-layer or three-layer skin constructs are produced to treat the severe burns or chronic wounds. Mostly collagen, chitosan, alginate or fibrin are printed together with fibroblasts and keratinocytes. For nerve TE, neural stem cells, glial cells, primary cortical neurons, astrocytes, and Schwann cells are used with bioinks. Addition of vascular endothelial growth factor enhances elongation, axonal and directional growth, and regeneration of the nerve cells [2]. For all tissues, one main challenging point is vascularization which can be enhanced by incorporation of human umbilical vein endothelial cells (HUVECs). Use of smart materials which are responsive to external stimuli such as temperature, light, magnetic field, etc., and change their properties under the influence of external signals are the basis of 4D printing [3]. This talk will give a general information about the applications of 3D and 4D printed systems in tissue engineering area.

[1]. Buyuksungur, S., et. al., 2017, Biomater. Sci. 5:10, 2144-2158. doi:10.1039/C7BM00514H.
[2]. Pati, F., et. al., 2014, Biomaterials 37, 230-241. doi: 10.1016/J.BIOMATERIALS.2014.10.012.
[3]. Mitchell A., et al., 2018, Additive Manufacturing 24, 606–62. doi.org/10.1016/j.addma.2018.10.038

3D CULTURE, PRINTING and STEM CELL APPLICATION

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Regenerative medicine which is use stem cells may provide alternative strategies for effective treatment. Stem cells have great potential to differentiate other somatic cells. There are two main types of stem cells: embryonic and adult stem cells. Each type of stem cells has its own advantages as well as limitations, therefore, for using of them during in vivo regeneration therapies, their properties have to be well analyzed. Tissue engineering are the use of cells and materials to mimic in vivo biological tissues. Once bioprinting is established, the use of stem cells as the cellular material was first used. To use in vivo material for treatment, the transferred tissue-material or cells have to be functional in vivo and their properties have to be similar after in vivo transfer. Therefore 3D culture condition which provides similar microenvironment condition with in vivo is important to differentiate or proliferate of cells. Different stem cells can be culture into 3D condition which uses biomaterials such as matrigel, collagen, kitosan etc. If you are interest in adult stem cells you have to provide their vivo conditions. During the talk, different types of stem cells (dental pulp, germ, adipogenic, mesenchymal etc) will give their 3D culture condition, using them for clinical approach studies.

[1]. Ozdal-Kurt F, Vatansever HS. Potential Clinical Use of Differentaited Cell From Embryonic or Mesenchymal Stem Cells in Orthopedic Problems. Current Stem Cell Research & Therapy, Vol 11 (6), 522-529, 2016.
[2]. Irvine SA, Venkatraman SS. Bioprinting and Differentaition of Stem Cells. Molecules. 21 (9): 1188, 1-23, 2016.
[3]. Lindsay CD, Roth JG, LeSavage BL, Heilshom SC. Bioprinting of Stem Cell Expansion Lattices. Acta Biomater. May, 2019. Doi: 10.1016/j.actbio.2019.05.014.

3D PRINTING AND BIOINKS

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The worldwide demand for the organ replacement or tissue regeneration is increasing steadily. Building human tissues via 3D printing and additive manufacturing based technology has received particular attention due to its process flexibility and versatility of manufacturing from materials containing living cells [1]. The main component of the 3D bioprinting is the bioink, which is crucial for the development of functional organs or tissue structures. The development of bioink materials allows scientists to manipulate biological and biochemical environments as well as living cells to create complex biological constructs. This study reviews bioink materials used in 3D bioprinting processes including scaffold-based and scaffold-free bioink materials, such as hydrogels, microcarriers, dECM and cell aggregates [2]. Limitations and strengths of each bioink material are elucidated and their characteristics are evaluated based on several criteria including their compatible bioprinting modalities, bioprintability, cell viability and proliferation, biomimicry, resolution, affordability, scalability, practicality, mechanical and structural integrity, bioprinting and post-bioprinting maturation times, tissue fusion and formation post-implantation, degradability, commercial availability, immunogenicity, and applications. Extensive research on 3D bioprinting over the past decade is a sign of its wide applications and promises in tissue engineering [3]. However, to overcome challenges such as vascularization, biomanufacturing issues, and unfit properties, more research on boink development and 3D bioprinting techniques is required. Further expansion of multimaterial hydrogels, development of more accurate bioprinting methods, and combining different printing techniques are some of the most important areas that can help advance the applications of bioprinting in tissue engineering. This work gives an overview of recent developments in 3D cell printing and bioinks and provides technical requirements for engineering human tissues. Finally, we propose suggestions on the development of next generation therapeutics and diagnostics.

[1]. Jang, J., et. al., 2018, Biomaterials 156, 88 – 106. doi: 101016/j.biomaterials.2017.11.030.
[2]. Web, B., et. al., 2017, Bioprinting 8, 8 - 12. doi: 10.1016/bprint.2017.09.001.
[3]. Derkhshanfar, S., et al., 2018, Bioactive Materials 3, 144 – 156. doi.org/10.1016/bioactmat.2017.11.008

3D PRINTING IN DRUG DEVELOPMENT

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Drug development is an ambitious and challenging endeavour. It starts with the identification of a pharmaceutically promising compound, the potential of which is further explored in near-exhausting physiological and molecular analyses. In their recent estimate, Wong and colleagues report a high drug failure rate during the whole early-phase development of new medicines [1]. This, no doubt, imposes an overwhelmingly large financial burden on the pharmaceutical industry. Consequently, there is a growing need for innovative technologies to support drug development, especially through enabling rapid identification of suitable drug candidates with desirable pharmacodynamic and pharmacokinetic properties at a minimal cost. Three-dimensional (3D) printing technology, which is also known as additive manufacturing technology, involves building parts layer-by-layer, adding material until certain shapes are achieved. In fact, 3D printing is an umbrella term for existing and emerging modern technologies in a variety of domains, ranging from engineering to biology, which allow for the construction of complex objects (such as drug products, human organs) from building materials (such as drugs and inactive ingredients, living cells) [2]. Thanks to the advancements in 3D printing, research bioscientists have been able to create structurally and functionally accurate human tissues well suited to acute or chronic toxicity testing as well as metabolic studies [3]. Such biorelevant human tissue models are likely to minimize the number of animals required for preclinical studies, leading to lowered costs and reduced time-to-market. The present talk aims at offering both a glimpse into the drug development process and an overview of novel 3D printing strategies that can be applied to the whole early-phase development of new medicines.

[1] Chi Heem Wong, Kien Wei Siah, Andrew W. Lo, Estimation of clinical trial success rates and related parameters, *Biostatistics*, Volume 20, Issue 2, April 2019, Pages 273–286, DOI: 10.1093/biostatistics/kxx069

[2] Neil Savage, Technology: the promise of printing, Nature, Volume 540, Issue 7632, December 2016, Pages S56–S57, DOI: 10.1038/540S56a

[3] Atheer Awad, Sarah J. Trenfield, Alvaro Goyanes, Simon Gaisford, Abdul W. Basit, Reshaping drug development using 3D printing, *Drug Discovery Today*, Volume 23, Issue 8, August 2018, Pages 1547–1555, DOI: 10.1016/j.drudis.2018.05.025

FROM IMAGE TO THE OBJECT: PATIENT-SPECIFIC 3D PRINTING

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3D printing for preoperative planning in orthopedic, maxillofacial, spinal, cardiac, and oncologic surgery is currently the most prominent topic in published literature. Modern medical imaging workstations offer the possibility of converting patient images into 3D models. This process is also possible by uploading the DICOM images into freely available open source imaging software options. The software allows segmentation of the image, which means selecting the region of interest in slices and converting it to a solid 3D object. This object is further transferred to the mesh software for digital cleanup and preparation for printing. This method allows surgeons to prepare for surgery and reduce intraoperative decision time, particularly in complicated cases. 3D printed stereolithographic replicas were shown to be extremely useful in planning reoperations for previous coronary bypass surgery. At the same time, this method also allows the surgeon to manufacture patient and lesion-specific guides for orthopedic, spinal, and maxillofacial surgeries. Printed models may also aid the patient to understand the planned surgical procedure better, and, at the same time, the models may be reserved for both student and resident training. However, current literature lacks randomized controlled studies to prove the proposed positive effects of 3D printing on surgical planning. We may see studies on these aspects after the current hype slows down leaving space for unbiased research. Patient-specific implant printing perhaps is the most promising aspect of 3D printing in the field of surgery. The images obtained from patients allow the surgeon to plan the surgery with a 3D printed model. At the same time, this image may be reconstructed, and an implant tailored for the specific needs of the particular patient may be modeled with the dedicated software. This approach is already being practiced by several centers and commercial companies, and patient-specific implants are being manufactured using 3D printing [1].

[1] Mammadov E. Three-Dimensional Printing in Medicine: Current Status and Future Perspectives. Cyprus Journal of Medical Sciences 2018;3(3):186-8.

MICROFLUIDIC ORGAN-CHIPS: APPLICATIONS IN DRUG DISCOVERY AND INFECTIOUS DISEASE

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Before a lead compound goes through a clinical trial, preclinical studies utilize two-dimensional (2-D) *in vitro* models and animal models to study the pharmacodynamics and pharmacokinetics of that lead compound. Current preclinical studies most often do not accurately represent the efficacy and safety of a lead compound in humans, resulting in a high failure rate of drugs that enter clinical trials and an increase in associated costs. Although animal experiments are indispensable for preclinical screening in the drug discovery process, various issues such as ethical considerations and species differences remain. 2-D models comprised of host cells grown on flat surfaces as monolayers do not retain their original organ functions and morphologies, and therefore are unable to accurately predict drug efficacy and toxicity. These failures drive the need for more representative models of human organ systems for screening in the preclinical phase of drug development [1]. Organ-on-chips are biomimetic micro-physiological systems which serve as on-chip cell culture device created with microfabrication techniques and contains continuously perfused chambers inhabited by living human-derived cells that simulate tissue- and organ-level physiology in an organ-specific context. Microfluidic organ-on-chip technology, also called the human emulation system, creates microenvironments that go beyond conventional 3-D *in vitro* models by recapitulating the critical tissue–tissue interfaces, spatiotemporal chemical gradients, and dynamic biomechanical forces such as fluid shear, stretch, compression of living organs [2]. This technology has been used to develop specialized *in vitro* disease models with the possibility of using patient-specific cells for personalized medicine as well as predictive surrogate platforms to model host-pathogen interactions in infectious diseases [3]. Targeted by the pharmaceutical industry, organ chips provide a powerful platform for accelerating new drug development and toxicity screening. The present talk aims to give an overview of the organ-on-chip technology and discuss its applications to drug discovery and development.

[4] Mittal R, Woo FW, Castro CS, Cohen MA, Karanxha J, Mittal J, Chhibber T, Jhaveri VM. Organ-on-chip models: Implications in drug discovery and clinical applications. *J Cell Physiol.* 2019 Jun;234(6):8352-8380. doi: 10.1002/jcp.27729

[5] Chan CY, Huang P, Guo F, Ding X, Kapur V, Mai JD, Yuen PK, Huang TJ. Accelerating drug discovery via organs-on-chips. *Lab Chip*. 2013 Dec 21; 13(24): 4697–4710. doi: 10.1039/c3lc90115g

[6] Kimura H, Sakai Y, Fujii T. Organ/body-on-a-chip based on microfluidic technology for drug discovery. *Drug Metab Pharmacokinet.* 2018 Feb: 33(1):43-48. doi: 10.1016/j.dmpk.2017.11.003