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From the Publisher's Desk

Welcome to Biotechnology Kiosk!

The March' 2022 issue of Biotechnology Kiosk (BK) is now live for our readers, featuring our regular sections as well as cutting-edge articles on surface modifications of biomaterials and 3D tissue constructs. Additionally, we have our editor picks and a popular article.

We hope our readers will enjoy delving into the latest research breakthroughs in various areas of medicine and biotechnology that are covered in this issue. We are eagerly awaiting your feedback, so please do not hesitate to share your thoughts with us.

We strive to provide high-quality content to our readers, and your suggestions are always appreciated. We hope you enjoy reading this issue of Biotechnology Kiosk, and we look forward to hearing from you soon.

Dr. Megha Agrawal & Dr. Shyamasri Biswas.

Editors-in-Chief, Biotechnology Kiosk

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Editor's Picks: Biotechnology Advances around the World

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Surface Modification of Advanced Biomaterials for Applications in the Pharmaceutical and Medical Fields

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Abstract

Lately, there has been a great deal of emphasis on developing novel biomaterials for next generation biomedical technologies. Especially, research efforts have focused on biomaterials that meet the demand for precisely engineered three-dimensional structures. These research efforts seek to design advanced biomaterials that mimic the natural environments of tissues more closely, and thus enhance the functional performance of these materials. To this end, surface modification/functionalization of biomaterials is considered pivotal to achieve the goals. Recent progress in biomaterials fabrication techniques has shown huge promise for surface engineering of biomaterials leading to realization of devices that have complex surface geometries for various biomedical applications in the pharmaceutical and medical fields. These include next generation drug delivery, diagnosis and biosensors, to name a few. In this review, we have highlighted important surface modification processes that have been employed for surface engineering of biomaterials. Further, an overview of the cellular response of surface modified biomaterial is presented. We have also discussed precise engineering of three-dimensional surface modification of biomaterials by initiated chemical vapor deposition (i-CVD) method. Notable biomedical applications have been described. Finally, we have presented a brief future perspective.

Keywords: Biomaterials, i-CVD, surface modification, drug delivery, pathogen.

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Introduction

The ability to control the interactions between biomaterials and living tissues is considered critical to optimize their therapeutic effects and disease diagnostics for clinical applications. However, it is quite difficult to gain such ability because most biomaterials including metals, polymers, hydrogels, carbons, and composites do not exhibit specific surface and bulk properties and desirable functions that are suitable for applications. It is essential that biomaterials have perfect properties for their effective interactions with surrounding tissues. To overcome the challenges, surface modification/engineering of biomaterials has been shown to play an important role in tailoring the surface of biomaterials. This surface engineering allows better adaptation to the physiological surroundings and deliver the required clinical performance [1,2,3].

An important aspect in the rational design of biomaterials is to ensure surface modification of the biomedical devices without compromising their bulk characteristics for better control of the chemical and physical properties of the bioactive surfaces. Bulk properties are initially considered for a biomaterial's suitability for an application. However, more important considerations are given to the physical aspects of the material surface as well as the chemistry that are critical to the function of many biomedical devices. Thus, physical and chemical surface modifications are of immense interest that seek to create a specific physical and chemical environment that offers a favorable cellular response in hard or soft tissue. For example, the physical environment including macro, micro, and even nanoscale features is considered in cases where tissue integration is desired. Creating a specific physical or chemical environment allows for cells to adhere, proliferate, and migrate [4].

Surface characteristics such as topographic and geometric features are especially targeted to gain the ability to regulate the cellular response. This allows to create specially designed bio scaffolds with specific surface functionalities via surface modification. This can subsequently offer several advantages compared to flat surface including cell adhesion and cell fate decision [5-14]. Pure chemical treatment of the material surface can result in oxideing/nitriding/carbiding a surface. It also includes surface functionalization as well as ion infusion. This can be achieved by single layer coatings, or multiple layers of coatings comprising different compositions [15-17]. Recent advances in surface modification techniques have allowed researchers to modify biomaterials to achieve required chemical and physical properties. These include biocompatibilities, surface functionalities, and mechanical strength that are sought in the field of tissue engineering, regenerative medicine, and biomedical devices. To this end, a range of surface

engineering strategies are devised in order to achieve desired biocompatibility and other functionality such as antimicrobial performance in-situ. Several techniques have been employed that include plasma and chemical vapor deposition, atomic layer deposition, and electro-chemical deposition, to name a few [4, 14, 15, 18-24].

In this review, we have described surface modified biomaterials and the associated cellular response and strategies for surface modification/engineering. While several surface engineering strategies have been discussed in the literature, our emphasis is on the solvent-free processes especially the emerging i-CVD method for atomic scale engineering and its applications.

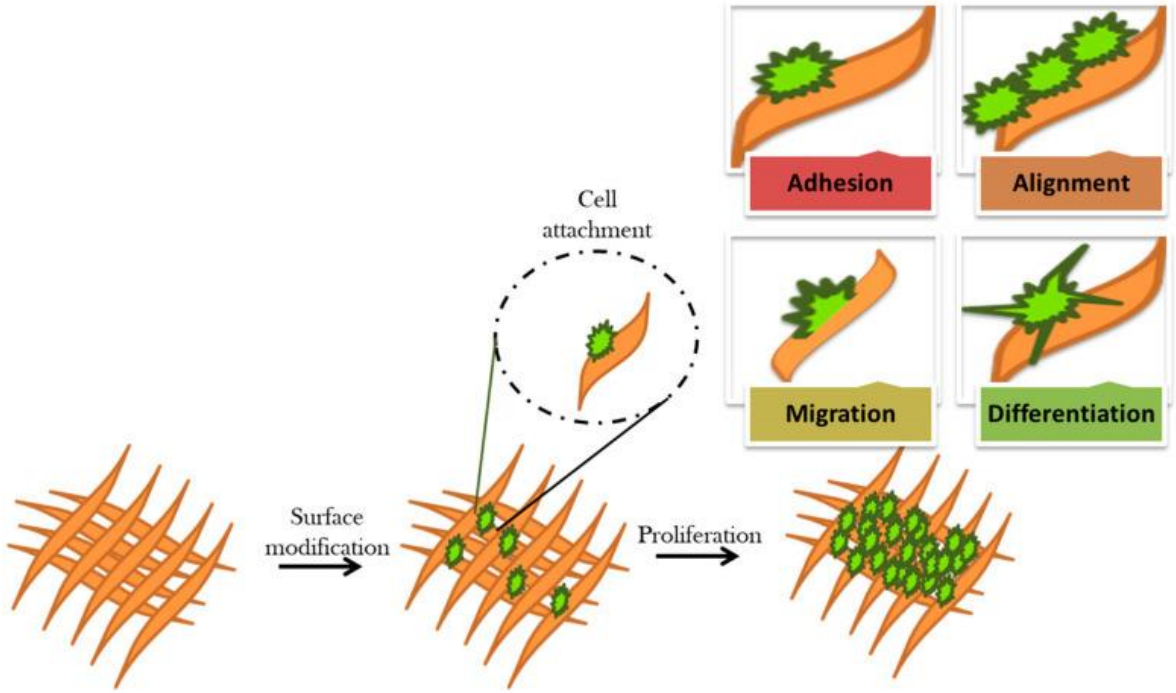

Figure 1: *Schematic depiction of surface modified biomaterial and the cellular responses that emerge due to the modification [Source: Int. J. Mol. Sci. (2021)].*

Surface Modified Biomaterial and the Associated Cellular Responses

Studies have shown that cellular responses such as cell adhesion, proliferation, differentiation and migration are dependent on surface microstructural topography along with the surface chemistry including surface interaction at the biomaterial–cell interface and surface energy/wettability [25-28]. Especially, changes in the biointerface have been shown to enable triggering specific cell signaling that can result in different cellular responses. Therefore, a major goal of the surface modification of biomaterials involves pathways that enable interaction with the surrounding tissues and biological fluids and elicit desired cellular responses (Figure 1) [20].

Researchers have shown that performance of biomaterials in living tissues can be altered depending on the types of biomolecule and bioactive agents along with properties of biomaterial surfaces that are applied for surface functionalization. Previous studies on surface modification effects have correlated the cellular behavior with the changes in surface chemistry, surface charge, hydrophilicity, surface topography, and softness and also stiffness of bio-materials. With respect to the connection of surface chemistry with wettability and surface charge, it has been shown that modified surface chemistry affects cell adhesion, cell shape, cell proliferation, and differentiation. In addition, surface chemistry has been shown to strongly affect materials' biocompatibility as well as immunogenicity [20].

Studies have highlighted responsiveness of cells to the topographical structure of the underlying biomaterial surface. Accordingly, cells have been shown to modulate their alignment and orientation along the surface. The main components of surface topography include surface roughness and surface patterns that determine. The emphasis has been on unique properties of surface topography patterns such as high stability, cost-effective manufacture, and easy controllability for controlling cell function and tissue regeneration. With respect to the effects of surface charges, researchers have shown different mechanisms for solid surfaces to make them neutrally, positively, and negatively charged for different functions. For examples, more cells can be attached to the positively charged surface compared to the negatively and neutrally charged surfaces. Furthermore, it has been shown that the effects of surface charge on cellular responses depend on the composition of biomaterials, cell type as well as tissue microenvironment. Regarding surface wettability and its effects, it is known that wettability features such as hydrophilicity and hydrophobicity correspond to the adhesive force between the liquid and solid material surface that results in the spreading of the liquid across a solid surface. Several studies have documented that while cells are typically attached and proliferated on a hydrophilic surface, proteins tend to bind onto hydrophobic surfaces. Last but not the least is the consideration on surface energy and cellular responses. Surface energy is recognized as one of the decisive factors for surface wettability of biomaterials. For example, Surfaces with low surface free energy have been shown to be less adhesive than those with high surface free energy. Especially for tissue engineering applications, it has been sown that biomaterials with total surface energies of about 100–129 erg cm−2 are more suitable for tissue regeneration. Further, the non-optimal range of total surface energies is thought to be within about 16–20 erg cm−2 to support cell adhesion, proliferation, and differentiation. The

stiffnesses of underlying substrate and local extracellular matrix have also been considered to be guiding factors for cell morphology and fate decision [20, 29, 30].

Conventional and Emerging Surface Engineering Strategies for Biomaterials

From a purely materials perspective, surface engineering is often considered to overcome the challenges of loss of quality of a material due to fatigue/fracture, wear and destruction as a result of mechanical sliding interaction and corrosion or decorative defects. Previous studies showed surface engineering strategies helpful in inducing surface tolerant properties to combat detrimental environmental conditions or external forces [31-33]. With respect to biomaterials, surface engineering has been shown to impart cell adhesion, passage, growth, differentiation and also functionality. Surface engineering can also influence roughness that can be leveraged to control the effectiveness of coating [20, 34, 35].

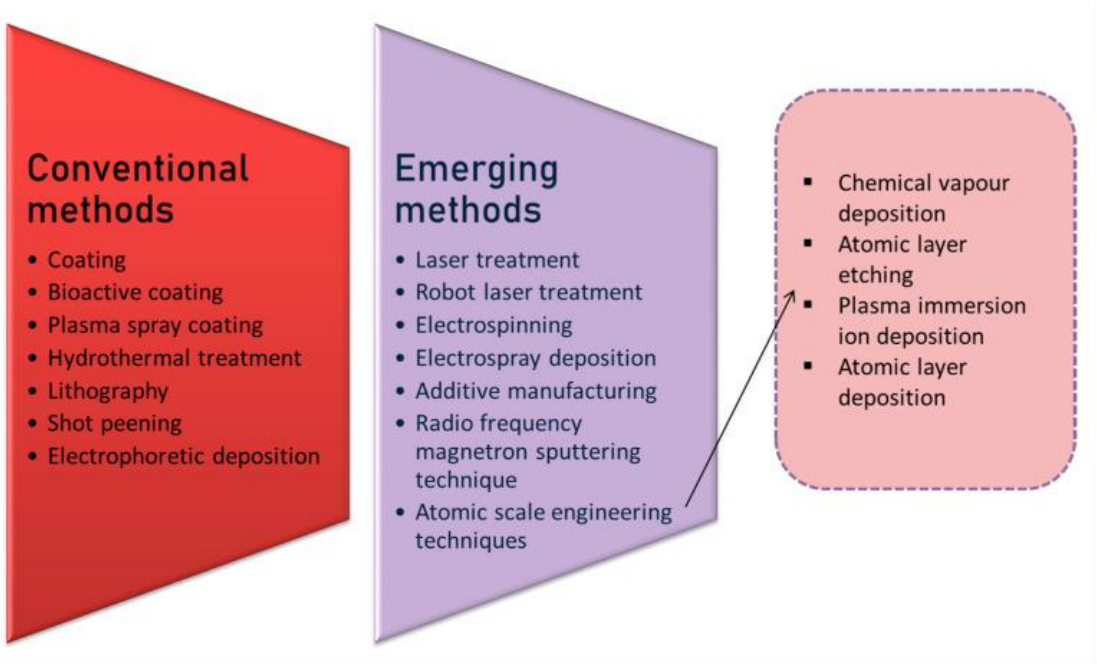

Figure 2: *Commonly used conventional and emerging surface engineering techniques are listed that include coating, lithography, laser treatment, hydrothermal treatment, plasma spraying, plasma immersion ion deposition, radio frequency magnetron sputtering technique, chemical vapor deposition, atomic layer deposition, electrospray deposition, and electro-spinning deposition etc. Atomic scale engineering techniques are also described [Source: Int. J. Mol. Sci. (2021)].*

Several nanofabrication and microfabrication techniques for applying surface topography have been considered that include electron beam lithography or photolithography; replica casting or molding; self-assembling systems; particle synthesis; microcontact printing; sandblasting;

electrospinning; and chemical etching etc. For simplicity, surface engineering methods have been divided in two categories. These are conventional surface engineering methods that deal with coating, bioactive coating, plasma spray coating, hydrothermal, lithography, shot peening, and electrophoretic deposition and emerging surface engineering methods such as laser treatment, robot laser treatment, electrospinning, electrospray, additive manufacturing, and radio frequency magnetron sputtering technique) (Figure 2) [20].

Lately, researchers have paid much more attention to emerging surface modification methods that are considered more advanced and innovative techniques. Emerging methods are considered advantageous because they can be employed for obtaining improved biocompatibility that is otherwise very difficult to achieve by conventional modifying techniques. Most recent advances point towards machine learning and atomic scale engineering techniques [36]. Machine learning methods are rather in a very nascent stage, where a computer learns the information. This subsequently provides data and the system functions according to the data. On the other hand, atomic scale surface engineering is a series of methods that are considered most promising emerging techniques to alter the surface topography at the atomic and molecular scale (<100 nm) (Figure 2) [20]. These techniques are currently driving the biomaterial research that deals with fabricating a material with improved understanding of surface interactions by modifying internal components. Further, from pure applications point of view, atomic scale engineering can be leveraged for designing a commercial product with excellent antimicrobial and other biomedical functional properties for applications in advanced pharmaceutics and medicine [37-42].

In the following sections, we will describe the main process of initiated chemical vapor deposition 'i-CVD' for the surface modification of biomaterials along with notable applications of i-CVD.

Initiated Chemical Vapor Deposition: Atomic Scale Engineering of Three-Dimensional Surface Modification of Biomaterials

Atomic-scale engineering has recently emerged very promising for three-dimensional (3D) surface modification of biomaterials. Techniques such as chemical vapor deposition, atomic layer etching, plasma immersion ion deposition, and atomic layer deposition correspond to the subsection of emerging technology that has been shown superior over conventional methods for improved control and flexibility at finer length scales. Recent advances in technologies have shown promise to meet the demand for better control of biomaterial surfaces. These advances are aimed at the atomic scale and molecular scale engineering while incorporating functional bio-active agents for

enhanced in-situ performance of new biomedical devices such as implants. Several studies have used functional agents that include synthetic materials such as monolithic ZnO, quaternary ammonium salts, silver nanoclusters, titanium dioxide, and graphene and also natural materials, for example, chitosan, totarol, botanical extracts, and nisin for atomic scale engineering [43-47].

Recently, iCVD has emerged as a top-of-the-line have technique for atomic scale engineering and as a damage-free method for sensitive biomaterials to modify the surface of biomaterials and various biomedical devices in a controlled fashion. The technique i-CVD is considered highly beneficial for the conformal deposition of various functional biopolymer films. This deposition can be done onto many kinds of bio-surfaces without restrictions on the substrate material or geometry, which is otherwise not possible to achieve by conventional solution-based surface functionalization methods. It has been shown that with proper structural design, it is possible to achieve required functionality to the biomaterial surfaces by the functional polymer thin film via i-CVD. Such functionality can be achieved while maintaining the fine structure thereon [48].

The technique iCVD offers a number of advantages that include the mild deposition condition and also the deposition process that can be proceeded in solvent-free and near-room temperature condition. In a typical iCVD process, the initiator and monomers are first vaporized and introduced simultaneously into the vapor phase reactor that is maintained under vacuum. Subsequently, the injected monomers are adsorbed onto the surface of substrates, while the initiators decomposed thermally via hot filament to form radicals. This results in triggering free-radical polymerization reaction at the substrate surface that is maintained near at room temperature (less than 50oC). This finally leads to the biopolymer or biomaterial film growth from the surface (Figure 3) [48].

The surface modification techniques based on iCVD process have been shown to be capable of engineering the surface of the non-conventional substrates as well, which allows for the rational design of biomaterial platforms. This subsequently enables to control the adsorption/immobilization of bioactive molecules to broaden the utility of biomaterials for a wide range of advanced technical approaches for biomedical applications. Therefore, the developments in atomic scale surface engineering using iCVD have proven to be very useful in the field of biomedical applications by realizing conformal coating of biological and medical devices have are comprised of a range of miniature structures [48].

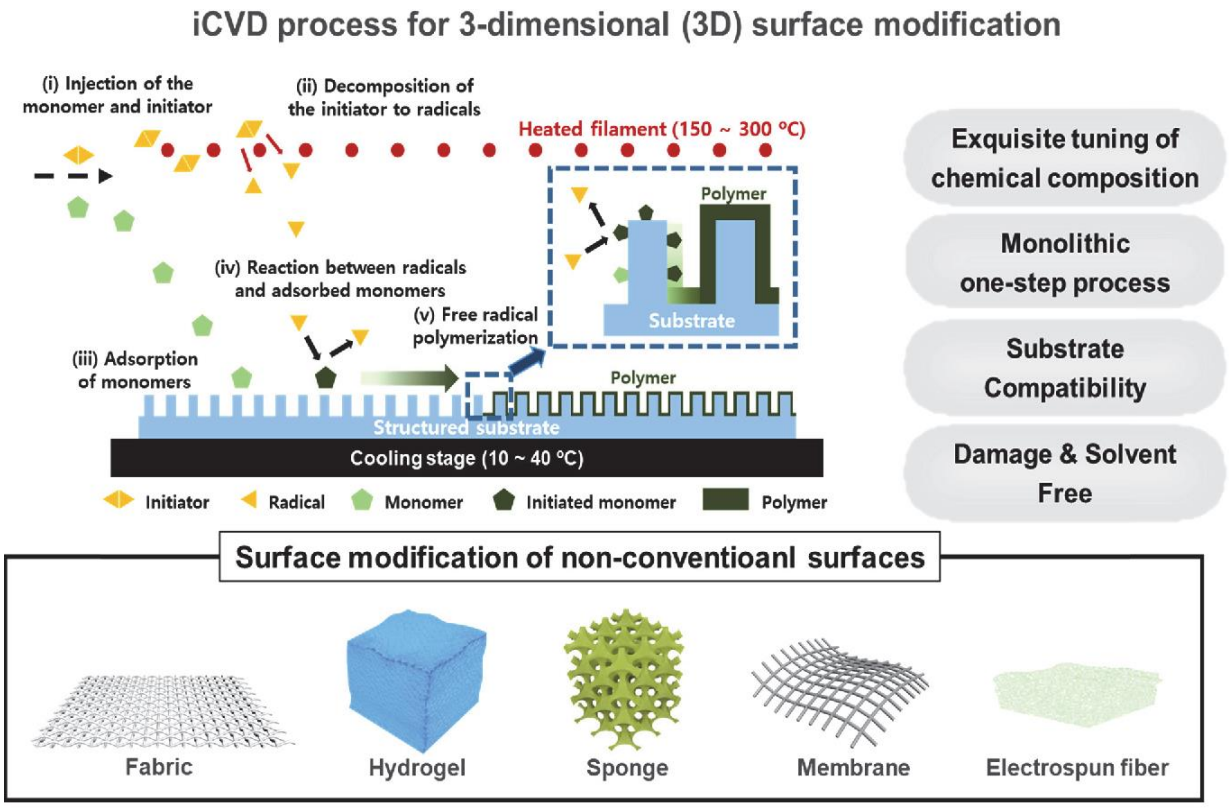

Figure 3: *(i-v) Schematic depiction of iCVD technique for surface modification of three-dimensional structures including fabric, hydrogel, sponge, membrane, and electrospun fiber. It shows vaporized monomers and initiators that are injected into the iCVD reaction chamber along with the injected initiators that are subsequently thermally decomposed into the radicals. Further, the injected monomers are then adsorbed onto the surface of the structured substrate and the process then allows the radicals to be transferred to the adsorbed monomers, which triggers free-radical polymerization reaction and the subsequent growth of biopolymer film from the surface [Source: Biotechnol Bioproc E (2021)].*

i-CVD Technique for Controlled Drug Delivery

There have been significant research efforts for safe drug delivery through mucosae. Such drug delivery offers advantageous characteristics including accurate dose control and the avoidance of premature metabolism of vulnerable drugs by oral administration. However, there is a challenge involving body fluid in mucosae that may dissolve the drug and releasing it to unwanted directions [49-51].

To address the challenge of unwanted dissolving of drug, researchers showed the promise of iCVD technique to control the drug delivery rate and direction to the target region by area selective incorporation of surface functionality. They used area-selective functionalization of membrane to provide Janus property that exhibited a great potential for drug delivery applications. To this end, a Janus patch was developed for mono-directional drug

delivery. In this process, a polyester fabric was coated with poly (3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluorodecyl methacrylate) (pHFDMA) film by iCVD process (Figure 4) [48, 52]. Subsequently, base-catalyzed hydrolysis was applied to one side of the substrate that rendered hydrophilic surface containing carboxylic acid residues. Further, while the hydrophilic surface allowed the coating of hydrogel incorporated with resveratrol that enhanced the adhesion of patch to mucosa, the hydrophobic surface prevented wetting by body fluids. It was shown in this study that the developed Janus patch enabled controlling the exact dose with intended directional drug release without allowing the water penetration. Further, researchers showed the applicability of this approach to various kinds of porous materials such as Nylon mesh or paper and not restricted to polyester fabric only [48, 52].

Surface-Modified Porous Sponge for Isolating Foodborne Pathogen

It is widely recognized that rapid and efficient detection of pathogenic bacteria from food is critically important to prevent epidemic food poisoning. However, the challenges lie in the isolation of pathogenic bacteria from spoiled food, which is further hampered by the lack of proper cell cultivation and/or isolation methods [53, 54]. Conventional methods suffer from complex, time-consuming culturing steps that result in low scalability, and high operation cost. To overcome these challenges, researchers demonstrated an alternative approach for the isolation of pathogenic bacteria directly from food using a surface-modified, highly porous sponge via iCVD process (Figure 5) [55]. In this study, a hydrophobic polymer, poly(2,4,6,8-tetravinyl-2,4,6,8-tetramethyl cyclotetra-siloxane) (pV4D4) was deposited conformally by iCVD on amphiphilic three-dimensional (3D) melamine sponge. This was done to incorporate hydrophobicity as well as oleophilicity to the porous sponge surface for absorbing oil component selectively from food extracts. Researchers demonstrated that the surface-modified sponge was capable of the isolation of Escherichia coli O157:H7 (E. coli O157:H7) from heterogeneous mixture with oil/water/food particles with high efficiency compared to artificial model system. The surface-modified sponge developed could pave the way for the development of a novel biotechnology platform for oil/water separation and isolation of foodborne pathogens directly from heterogeneous mixture that could enhance the efficiency of molecular diagnostics [55].

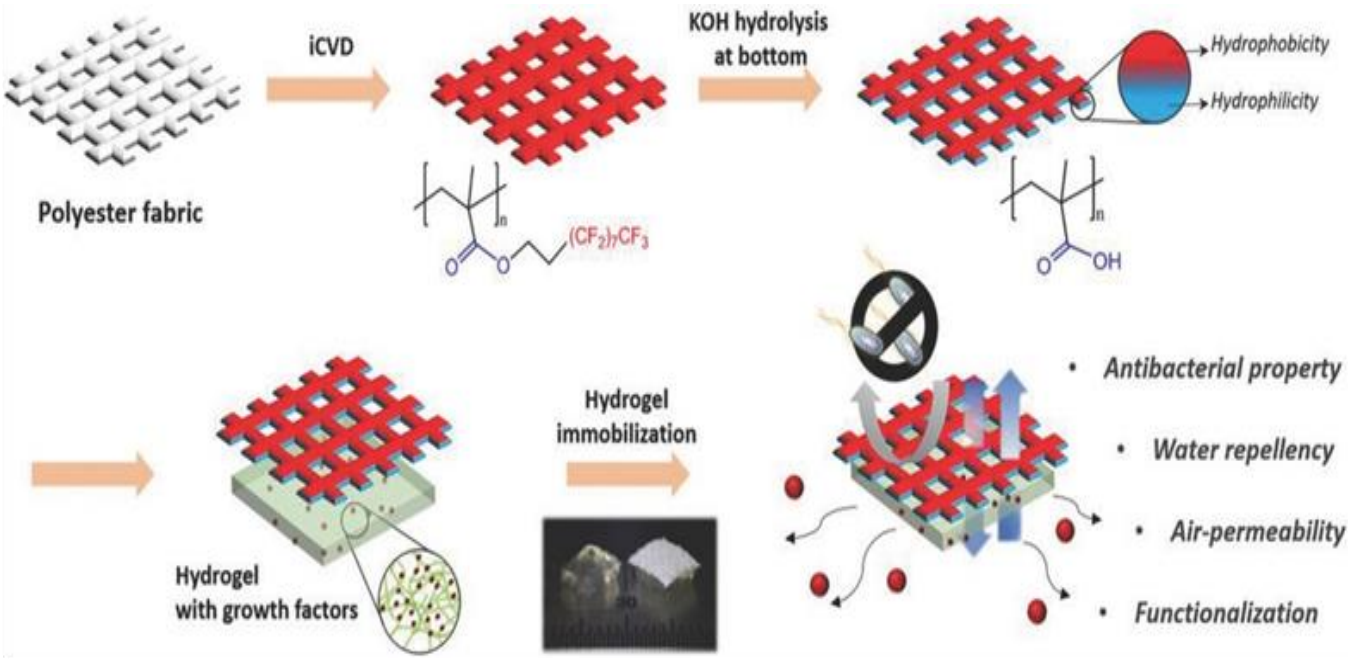

Figure 4: *A schematic illustration that shows the fabrication steps of gelatin methacrylate (GelMA) hydrogel-immobilized Janus membrane and in-vivo skin regeneration [Source: Adv. Healthcare Mater (2017)].*

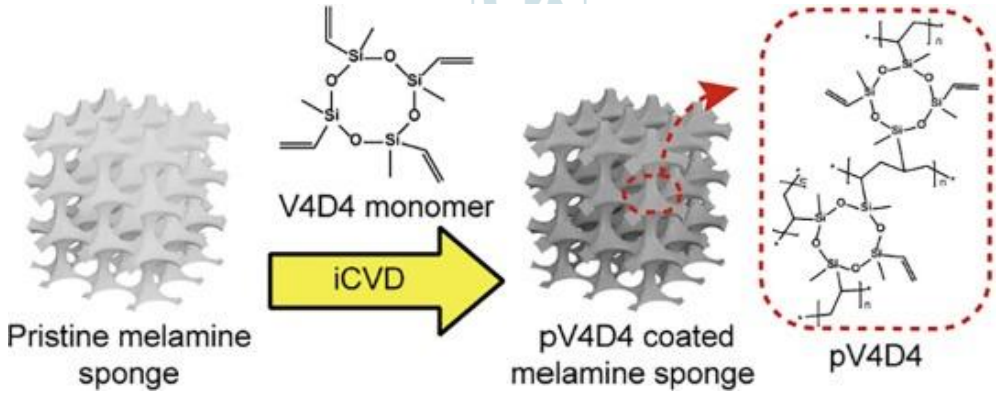

Figure 5: *The application of iCVD is shown for conformal coating of pV4D4 on 3D melamine sponge for isolating food borne pathogen [Source: Food Chemistry (2019)].*

Modification of Microchip for DNA Extraction: Enhanced Capturing Efficiency for Point-of-Care Molecular Diagnostics

It has been shown that nucleic acid (NA) extraction and purification corresponds to one of the most important steps for NA-based molecular diagnosis. However, the conventional methods have severe limitations due to many issues that include long processing time, complicated steps, requirement of trained personnel and potential

inhibition caused by chaotropic agents and/ or residual reagents [56-59]. To address these challenges, researchers demonstrated a surface-modified NA extraction microchip (SNC) by introducing poly(2-dimethylaminomethyl styrene) (pDMAMS) film engaged directly on the microchip surface via iCVD process (Figure 6) [60].

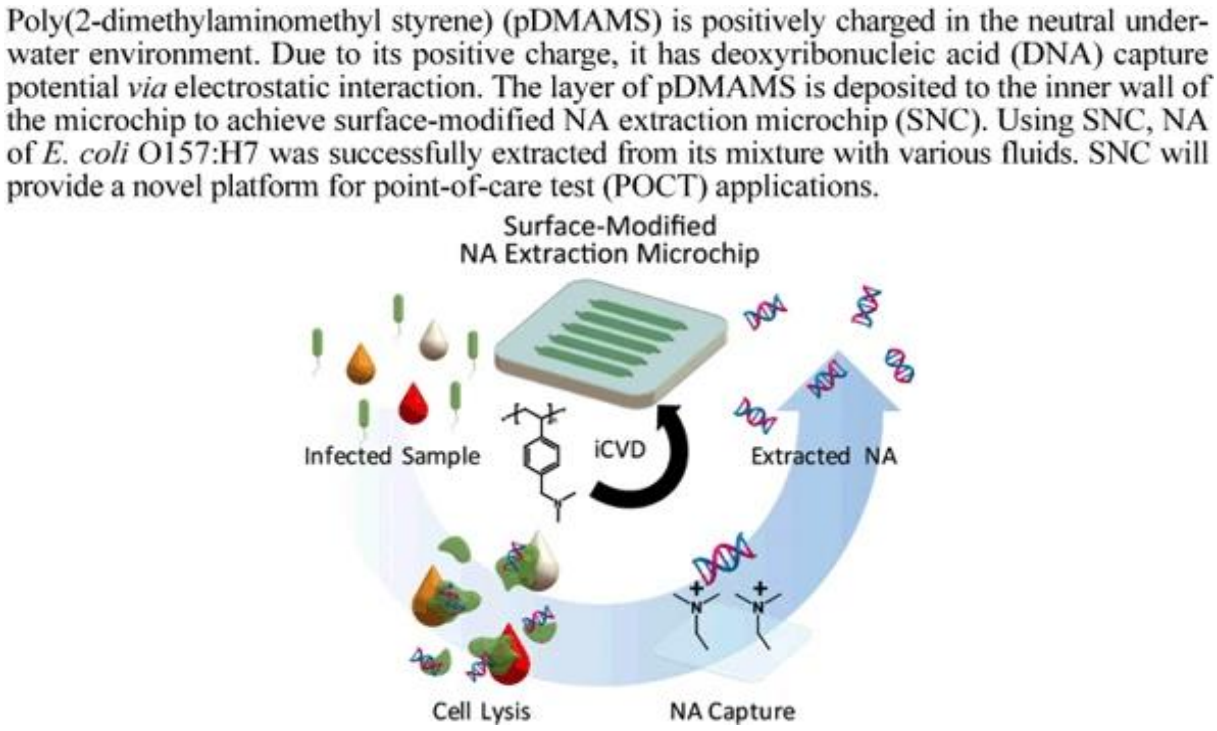

Figure 6: *Development of iCVD enabled surface-modified nucleic acid (NA) extraction microchip for point-of-care molecular diagnostics [Source: Macromol. Res. (2020)].*

Conclusion & Future Perspective

We have described surface modification/engineering methods that are increasingly being employed in three-dimensional surface modification of clinically grade biomaterials. Surface engineering of biomaterials is considered pivotal in preserving the functional attributes of biomaterial. Studies have shown that it can be leveraged to enhance its effectiveness and sustainability by adding a functional layer to the surface. In addition, changing the surface texture is another viable route for effective surface modification of biomaterials. It has been shown that such surface engineering could help prevent corrosion and erosion and also promotes osseointegration while enhancing biocompatibility especially in tissue engineering applications. In addition, surface modification has been shown to induce self-healing property, resists friction and wear, and improve cell adhesion while

reducing thrombogenicity that results in desired transport characteristics, and minimizes the risk of microbial infections.

Recent research advances in initiated chemical vapor deposition (i-CVD) for biofunctionalization of biopolymer thin films have shown tremendous promise in pharmaceutical and medical fields. Several studies have shown notable advances in the field of i-CVD biopolymer films on different substrate materials that include immobilization of bioactive molecules, site-specific conjugation, and facile control of physio-chemical property of implants and biomedical devices. Studies have also demonstrated the deposition of biopolymeric thin films in vapor phase monomers that can substantially facilitate adjusting the polymer compositions. This is believed to be a hallmark of i-CVD technique that allows precise topological and chemical control of medical implants with complex three-dimensional shapes. However, the development of i-CVD functional polymer coatings for various medical devices is still considered in its early stage. In future studies, i-CVD technique is expected to make significant contributions in the design and production of superior biological and medical devices. This could be achieved by providing substrate-independent polymer coatings with nondestructive way. We anticipate that future studies will also include further development and optimization of i-CVD technique that will allow mass production and quality control of polymer-coated medical device for seamless transition of laboratory investigation to clinical practice. To this end, in term of substrate-independent polymer coatings with nondestructive way, iCVD technique is expected to make more significant contributions in the design and production of advanced biological and medical devices.

Another area of future interest is in-depth biological assessment of polymer-coated surface that is required for direct surface contact of cell/tissue. This is to gain new insights into the biomolecular mechanism underlying the series of cellular response on the functional polymer surface. This will lead to a deeper investigation on the interactions of i-CVD polymer-functionalized surface and cell/tissue surface that will provide great advantages for the rational design of the surface chemistry and develop elaborate medical devices responding to unmet medical needs. It is believed that compared to conventional solution-based processes, the advantageous i-CVD process will help overcome the technical challenges that are often faced in nonclinical and clinical pre-market assessments in both device manufacture and functional performance.

With respect to next-generation bio-scaffold designs, the application of biomaterials may focus on addressing concerns with respect to their biodegradability and cell toxicity. This could be a major goal especially in view of the still

unknown prolonged in-vivo cytotoxicity, effectiveness, and fate of surface engineered scaffolds. Thus, it may shed light on understanding the surface properties of scaffolds along with their effects on cellular behavior. This could help overcome the technical barriers toward their design of better scaffolds. In addition, future studies could involve surface modification of scaffolds by bioactive molecules. This could be achieved by creating substrates with desired properties that could pave the way to future breakthroughs involving instructing cellular behavior in terms of attachment, proliferation, and differentiation. In summary, it would be prudent to focus on research that enables greater insights of long-term in-vivo fate of surface engineered biomaterials that could be leveraged to further expand this exciting field for transition from laboratory to safe clinical applications.

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3D Tissue Constructs from the Ground Up for Game Changing New Applications in Tissue Engineering and Regenerative Medicine

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Abstract

In view of the very expensive modern healthcare system, sudden loss or failure of organs and tissues could pose a very difficult and costly medical problem to patients. Further, the limited supply of organs globally that a patient can afford for replacement in the event of an organ failure makes the problem even more challenging and complicated. These medical and healthcare challenges have triggered research and developments into tissue engineering to advance the field of regenerative medicine. Especially, the research focus has been on the design, development and optimization of a cell-scaffold-microenvironment to promote the regeneration of various types of tissue including skin, cartilage, bone, tendon and cardiac tissue, to name a few. Studies have been undertaken to produce functional three-dimensional (3D) tissue substitutes or constructs that are based on bio scaffolds from the ground up. To this end, bioprinting strategies have been considered for fabrication of complex 3D functional living tissues or artificial organs. Here, we describe some notable advances in laser bioprinting enabled tissue engineering, which is a rapidly emerging field in 3D bio fabrication technology for applications in regenerative medicine.

Keywords: 3D bioprinting, laser assisted bioprinting, tissue engineering, artificial organs.

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Introduction

The sudden loss or failure of organs and tissues is a serious medical condition. Failure of organs is widely recognized as a difficult and costly problem in modern healthcare. Further, the patient's problem becomes even more challenging in view of the limited supply of organs globally. To address these issues, there has been a steady growth of research on tissue engineering that especially involves the fabrication and design of 3-dimensional (3D) artificial scaffolds and a cell-scaffold-microenvironment that mimics human tissue for the development of artificial organs. The goal is to promote the regeneration of various types of tissue including skin, liver, cartilage, bone, tendon and cardiac tissue, to name a few [1-5].

3D tissue constructs are usually built by a combination of biocompatible and bioactive biomaterials with/or without cells and bioactive factors. Such constructs are developed from the ground up with the aim to replace or sustain the regeneration of tissues. Studies have shown scaffolds as the key element for tissue regeneration, which can be leveraged to provide the necessary mechanical support and a physical structure for the transplanted cells to attach and grow. This can be achieved together with maintaining their physiological functions. To obtain best performance, the key parameters to control are cell density along with cell spatial 3D organization that govern cell behavior and fate [6-9]. With respect to scaffolds, a bone scaffold for tissue engineering is of enormous interest due to the ever-growing demand of new biomedical implants. To be able to generate fully functional properties, bone scaffolds need to have favorable biocompatibility or cytocompatibility. This is essential to provide a surface for cells that can adhere, proliferate, differentiate and secrete extracellular matrix (ECM). Further, it has been shown that cell adhesion and migration, vascularization and new tissue ingrowth are influenced by pore size and interconnectivity.

All these factors imply that a high-performance scaffold must simultaneously support the growth of different cell types and tissues, each with specific mechanical properties, chemical gradients, cell populations, and geometric structures. Several conventional fabrication methods including electrospinning, fiber deposition, freeze-drying, gas foaming, and salt leaching have been considered for manufacturing 3D scaffolds.

However, these methods have limitations that do not allow precise control of internal structural features and topology. Especially, current traditional methods have complex design constraints that restrict the applicability of these methods particularly in serious medical conditions that include repairing clinically relevant injuries, organs, and other complex tissues. This has

motivated researchers to develop new techniques for the accurate fabrication of multifunctional scaffolds [1, 10-14].

Bioprinting is an emerging technique for 3D tissue constructs from the ground up. The technique employs biomaterials, cells, and/or bioink to fabricate prospective scaffolds to mirror the structural, compositional, and functional aspects of various human tissues. Several bioprinting methods including inkjet-based bioprinting, pressure-assisted bioprinting, and laser-assisted bioprinting have been employed for applications in regenerative medicine. The fabricated scaffolds have been characterized based on biocompatibility, cellular microenvironment, cell proliferation, vitality, and morphology [15].

Among other bioprinting methods, laser bioprinting is considered most promising for 3D tissue engineering and for fabrication of multifunctional bioscaffolds. Here, we will present some notable advances in laser bioprinting for 3D tissue constructs for applications in regenerative medicine.

Bioprinting Strategies

Recent advances in biofabrication have led to the development of Bioprinting, which is a rapidly emerging 3D biofabrication technology. Bioprinting is employed to precisely dispense cell-laden biomaterials for the construction of complex 3D functional living tissues or artificial organs. Figure 1 shows a typical 3D printing technical route, which is aided by 3D imaging software [1]. 3D bioprinting is considered a transformative technology because it allows more accurate personalized manufacturing of biomedical devices that need to be created to the patient's own specifications. In addition, bioprinting technology has a vast potential in a range of other applications that include creating more accurate non-biologic and biologic research models for research purposes, for example, spatial and temporal trauma in cancer research [1].

Recent studies have suggested that the design and manufacturing of living tissues and organs by 3D bioprinting could be leveraged in future to be implanted into patients safely with no side effects. In view of the enormous promise of bioprinting, researchers across the globe are currently exploring this technique to pattern cells or fabricate several different tissues and a whole host of functional organs, for example, blood vessels or cardiac patches, just to name a few. Bioprinting strategies are still in its early stages of developments. It is believed that with further advances, the versatile bioprinting may address the issues of growing organ shortage in the world by providing a high-throughput method for cell patterning at the micrometer scale for broad biomedical engineering applications. However, current approaches have to overcome technical challenges that include high-resolution cell

deposition, controlled cell distributions, vascularization, and innervation within complex 3D construct tissues to achieve the desired potential of 3D bioprinting [16-21].

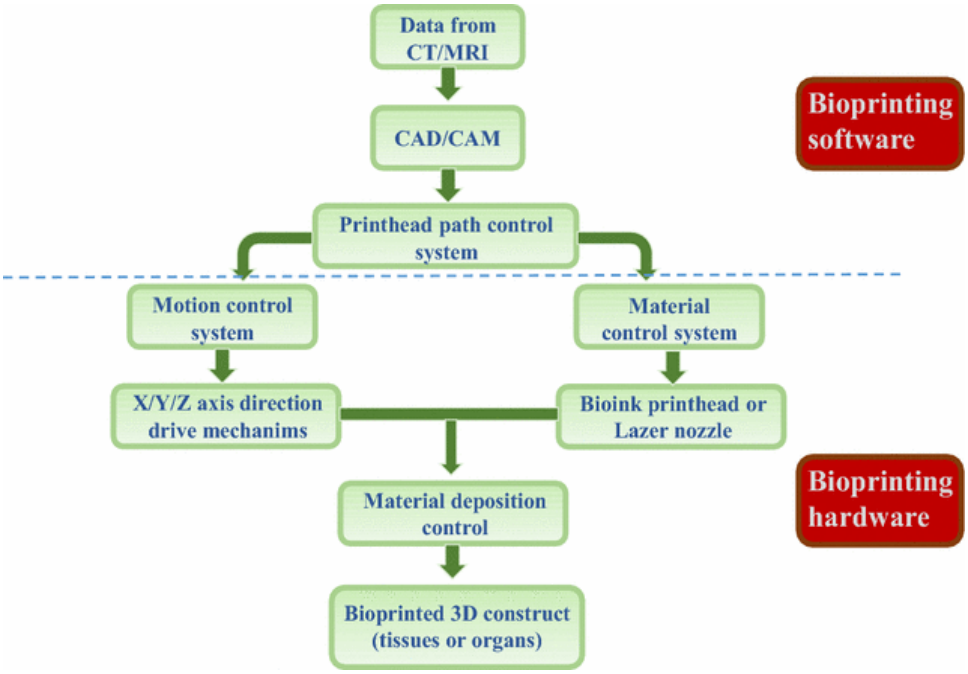

Figure 1: *A typical workflow is shown for the general process of 3D bioprinting [**Source:** Journal of Translational Medicine (2016)].*

Laser Assisted Bioprinting: A Potential Game Changing Biofabrication Technology for 3D Tissue Constructs

To address the technical challenges in 3D bioprinting, recent developments in laser based bioprinting has been shown very promising in 3D tissue constructs from the ground up. Laser based 3D printing allows fabrication of tissue-like structures that have the exact physiological functionality of their native counterparts. In addition, it allows printing cells and liquid materials with a cell- or picoliter-level resolution that is believed to be a game changer in 3D tissue engineering and fabrication of artificial organs. Further, this technology can enable study on cellular interactions and to fabricate cell-based biosensors due to its capacity to spatially control cell position and cell density. It has additional advantages such as automation, reproducibility, and high throughput. Thus, it makes the process compatible with the industrial scale fabrication of 3D constructs of physiologically relevant sizes [22, 23].

The laser based bioprinting process is essentially a direct-write method that allows droplet deposition of cells or biomaterials within a fluidic phase. With respect to the pace of the process, a MHz range speed can be obtained,

where a near infrared pulsed laser beam is employed that is coupled to a scanning mirror and a focusing system. Further, this process involves a transparent substrate, which is usually coated with a thin layer of laser-absorbing material along with a second thicker layer of biomaterial that is made of hydrogel with embedded cells to be printed [24, 25]. Laser pulses are then focused into the laser-absorbing layer (Figure 2) [26]. This step is often referred to Dynamic-Release-Layer (DRL), which corresponds to the underlying process of vaporization in the focal region that generate a vapor bubble. This bubble then expands by vapor pressure that subsequently propels the adjacent biomaterial forward. This eventually helps it to get deposited as a droplet at a predefined position on a collector slide. Researchers have shown that the high energy created by the incidence of the laser beam can create a cavitation that can eventually propel a microdroplet, containing cells, towards the receiving substrate. Such a configuration can be a 2D support or an exposed 3D in-vivo tissue [24-26].

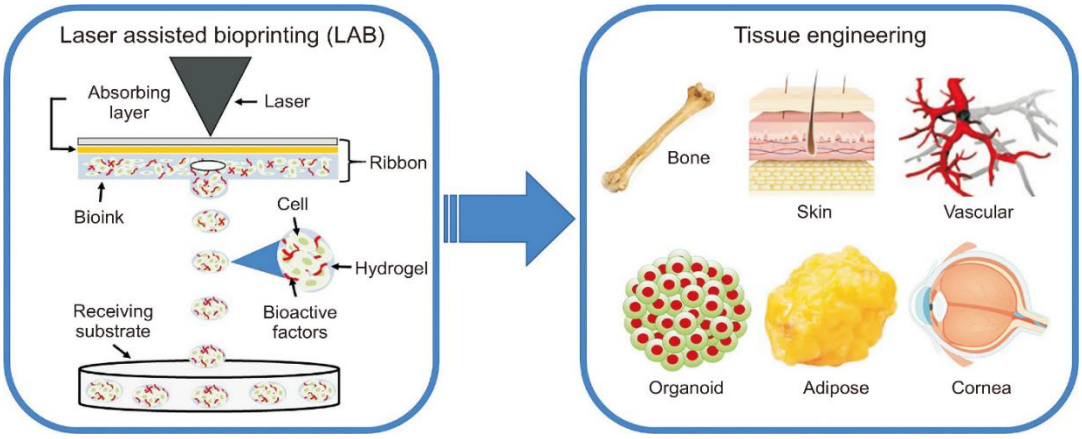

Figure 2: *Schematic depiction of different parts of laser assisted bioprinting along with various tissue engineering applications of fabricated different 3D tissue constructs [Source: Med Lasers (2021)].*

Another advantage of laser based bioprinting is its nozzle-free hardware. This allows avoiding the problem of cell clogging and thus helps overcoming the issues encountered in other bioprinting approaches. This can be achieved while providing the desired control on the density and microscale distribution of cells along with their viability and to attain higher speeds of deposition. Additionally, the technology enables an unprecedented printing precision at the micrometer scale. This provides the opportunity to achieve an ultimate control over cell organization for 3D tissue constructs from the ground up for a number of personalized medicine and healthcare applications [25]. In the following sections, we will take a look at some of the important applications of laser assisted 3D bioprinting.

Guided Regeneration of *In-Vivo* Bone Tissue by Laser Bioprinting of Mesenchymal Stromal Cells

Mesenchymal Stromal Cells 'MSCs' are known as multipotent progenitor cells that have the capacity to differentiate into a variety of cell types including osteoblasts, adipocytes, chondrocytes, tenocytes and skeletal myocytes. Additionally, these cells also have immunomodulatory properties that can be purified from different tissues (*e.g*. bone marrow, adipose tissue, umbilical cord). Studies have shown that MSCs have the capacity to secrete protective biological factors. This attribute makes them as one of the most suitable cell sources for tissue regeneration approaches [27, 28].

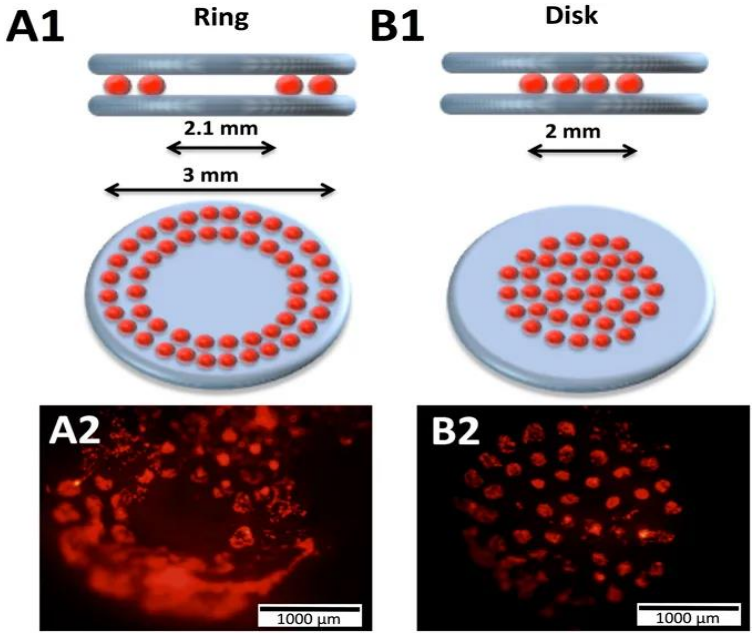

Figure 3: *Laser assisted bioprinting for in-situ printing of mesenchymal stromal cells for in-vivo bone regeneration applications (it shows a ring (A1) with and a disk (B1) along with representative fluorescence images of ring (A2) and disk (B2) printed cells inside the calvaria defect in mice) [Source: Scientific Reports, (2017)].*

In a notable study, researchers combined the printing of hydroxyapatite (HA) with MSCs, D1 cell line and investigated the impact of two different cell-printing geometries that have distinctive cellular repartitions (disc or ring) on bone repair capabilities [25]. Subsequently, two HA-collagen disks were printed before and after the cellularized ink printing in order to confine the printed cell spots to the calvaria defect. This was also done to provide an osteoconductive matrix to the printed cells. Figure 3 shows a schematic representation of the in-vivo laser based bioprinting geometries that were tested with a ring (A1) with external and internal diameter of 3 and 2.1 mm, respectively, and a disk (B1) with 2 mm diameter [25]. Two layers of HA-collagen ink

were printed underneath and over the cellularized ink layer in this study that employed two geometries. Figure 3 shows representative fluorescence images of ring (A2) and disk (B2) printed tomato-positive (D1) cells inside the calvaria defect in mice that were obtained immediately after printing. Further, researchers observed a significant increase in terms of bone formation in the case of HA collagen material and with D1 cells in a disk geometry post printing. Thus, a key finding was reported that involved testing different cell printing geometries and different cellular arrangements that impacted bone tissue regeneration differently. This work paves the way to new avenues on the development of *in-situ* laser bioprinting strategies for the building of 3D tissue constructs from the ground up [25].

Laser Bioprinting for Cardiovascular Repair/Regeneration and Pharmacological Applications

Cardiovascular disease (CVD) is thought to be a major cause of morbidity and mortality worldwide. CVD is associated with serious medical conditions such as congenital heart disease, acute coronary syndrome, hypertension, and arrhythmias that emanate from the faulty cardiovascular system. This fatal disease account for >17.5 million deaths per year, and that is estimated to increase to 23.6 million by 2030 [29-33]. To gain insights into CVD, it is critical to understand the cardiovascular system, which is a very important part of human body that includes the heart, blood vessels (arteries, veins, arteriovenous shunts, and capillaries), and lymphatic vessels. It is known that the cardiovascular system corresponds to a closed loop transport system that carries blood and lymph for circulation throughout the body. Laser based bioprinting for cardiovascular repair and regeneration is currently of huge interest that offers hope in providing new solutions to these very challenging and complicated problems in future healthcare sector dealing with CVD [33].

While the bioprinting technique for cardiac tissue constructs is still in its early stages, It is generally believed that the laser based 3D bioprinting would be a feasible approach in the future to produce a robust, and physiologically relevant, cardiac model. This could be realized by replicating in-vivo tissue composition, geometry, and complexity of the cardiovascular system, in general. 3D bioprinting can be leveraged to create complicated cardiovascular implants with biomimetic features that are capable of recapitulating both the native physiochemical and biomechanical characteristics of the cardiovascular system. Ongoing studies on micro-physiological models of the 3D bioprinted heart have focused mostly on generating the myocardium, valve, and vessels. Additionally, researchers are also focusing on the design and development of a bioartifical heart valve that

mimics the structural and the functional aspect of a native valve for use as an implantable device. To achieve the goals, one viable clinically attractive approach being considered is in-situ heart valve tissue engineering that employs cell-free synthetic, biodegradable scaffolds to create living valves right inside the heart of a patient. Figure 4 schematically shows notable advances in 3D bioprinting cardiovascular tissues/models for regeneration and pharmacological modeling applications [33].

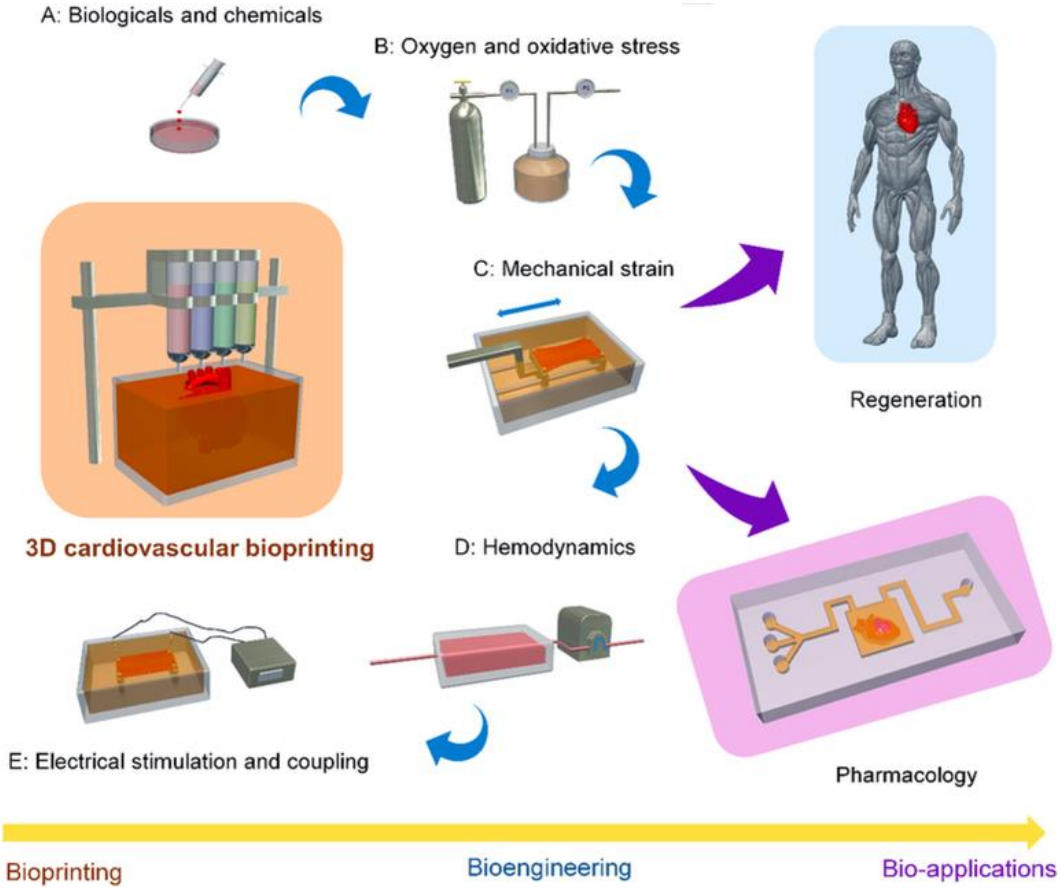

Figure 4: *Schematic diagram showing techniques of 3D cardiovascular bioprinting along with bioengineering methods, and bio-applications in regenerative medicine and pharmacology [Source: Adv. Drug Deliv. Rev. (2018)].*

In an earlier study, researchers showed that mesenchymal stem cells (MSC) could inhibit apoptosis of endothelial cells in hypoxic condition, increase their survival, and stimulate the angiogenesis process. To investigate in detail, researchers employed Laser-Induced-Forward-Transfer (LIFT) cell printing technique and prepared a cardiac patch seeded with human umbilical vein endothelial cells (HUVEC) and human MSC (hMSC) in a defined pattern for cardiac regeneration (Figure 5) [8].

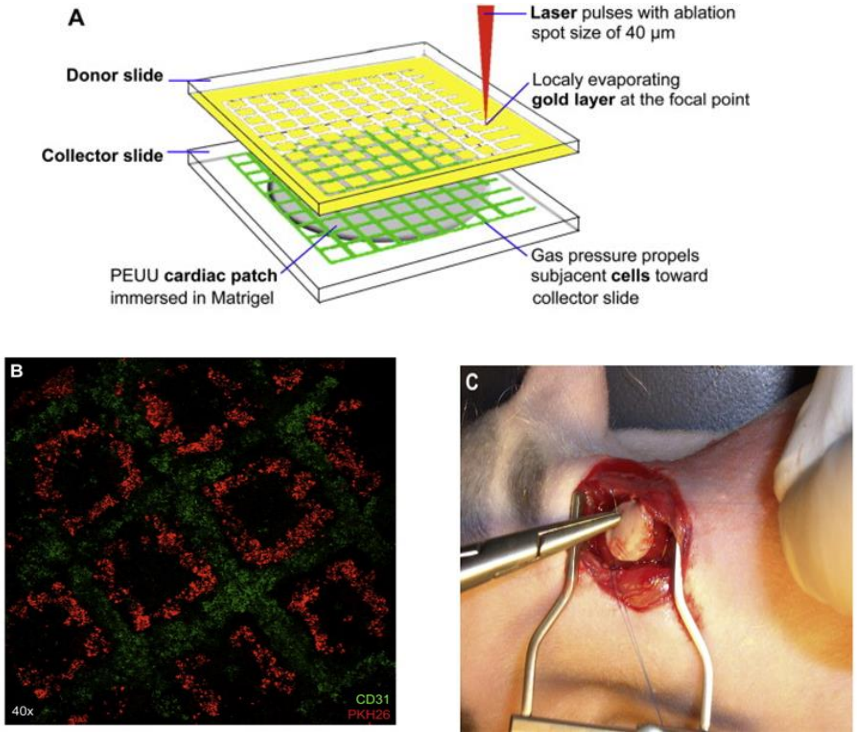

Figure 5: *(A) Schematic representation of laser-based cell printing showing cardiac patch manufacturing. (B) Fluorescent image of micropatterned hMSCs (red) and hUVECs (green). (C) Cardiac patch implanted into rat myocardium [Source: Biomaterials (2011)].*

In their study, researchers seeded HUVEC and hMSC in a defined pattern on a Polyester urethane urea (PEUU) cardiac patch. Subsequently, they cultivated cardiac patches in-vitro and transplanted in-vivo to the infarcted zone of rat hearts. It was demonstrated that LIFT-derived cell seeding pattern modified growth characteristics of co-cultured HUVEC and hMSC. This resulted in an increased vessel formation. In this study, major functional improvement of infarcted hearts was found following transplantation of a LIFT-tissue engineered cardiac patch. Researchers concluded that LIFT-based Tissue Engineering of cardiac patches for the treatment of myocardial infarction might improve wound healing and functional preservation [34].

Laser Bioprinting of Skin Constructs: Cure for Difficult-To-Repair Extensive Burns and Full-Thickness Skin Wounds

It is widely recognized that repairing extensive burns and full-thickness skin wounds is a significant medical challenge. This is especially true considering deep damage to the skin that happens in these serious medical conditions. The existing skin graft technology based on Autologous Split-thickness Skin Graft (ASSG) is limited for applications due to the shortage of

donor skin tissues, which is a serious problem. Skin bioprinting is considered very promising that may provide a novel alternative to ASSG therapy. It is believed that laser assisted bioprinting can address this problem that can provide a potential solution. The main advantage of employing laser-based skin bioprinting is the availability of skin constructs fabricated by using *in-vitro* expanded cells from skin biopsy that would mitigate the problem of shortage of donor sites encountered in ASSG.

Studies have suggested the possibility of bioprinting of skin tissue constructs that can lead to the development of skin equivalents for wound healing therapy. To this end, researchers have fabricated skin constructs using biomaterial scaffolds with or without cells to create skin tissues that are suitable for transplantation. In this process, skin tissues are usually collected from patients in skin bioprinting by skin biopsy. This can be then cultured *in-vitro* to obtain enough number of cells. Subsequently, cultured skin cells are mixed with biomaterials and then delivered to a 3D bioprinter for fabrication of customized skin as prescribed by the patient's specific requirements [34-37].

Ongoing studies have focused on to address technological challenges for the development of bio-mimetic functional skin for clinical applications. For example, a related study conducted on laser based bioprinting of skin tissue demonstrated direct printing of amniotic fluid-derived stem cells (AFSCs) onto full-thickness skin wounds (2 cm × 2 cm) of nu/nu mice using a pressure-driven, computer controlled bioprinting device (Figure 6) [38].

In this study, AFSCs and bone marrow-derived mesenchymal stem cells were suspended in fibrin-collagen gel and mixed with the thrombin solution (a crosslinking agent) that were then printed onto the wound site. Researchers then employed the bioprinter that was used to deposit two layers of a fibrin-collagen gel by depositing a layer of thrombin, a layer of fibrinogen/collagen, a second layer of thrombin, a second layer of fibrinogen/collagen, and a final layer of thrombin (Figure 6) [38].

Human stem cell based corneal tissue mimicking structures using laser-assisted 3D bioprinting and functional bioinks

The cornea is the transparent anterior part of the eye, which is a critical part for vision. Corneal blindness due to trauma or diseases is a serious ophthalmic condition that affects millions of people worldwide. Therefore, a significant volume of research has been devoted to meet the high demand for developing methods to produce more native-like 3D corneal structures [39-41]. In a recent study, researchers produced 3D cornea-mimicking tissues using human stem cells and laser-assisted bioprinting (LaBP).

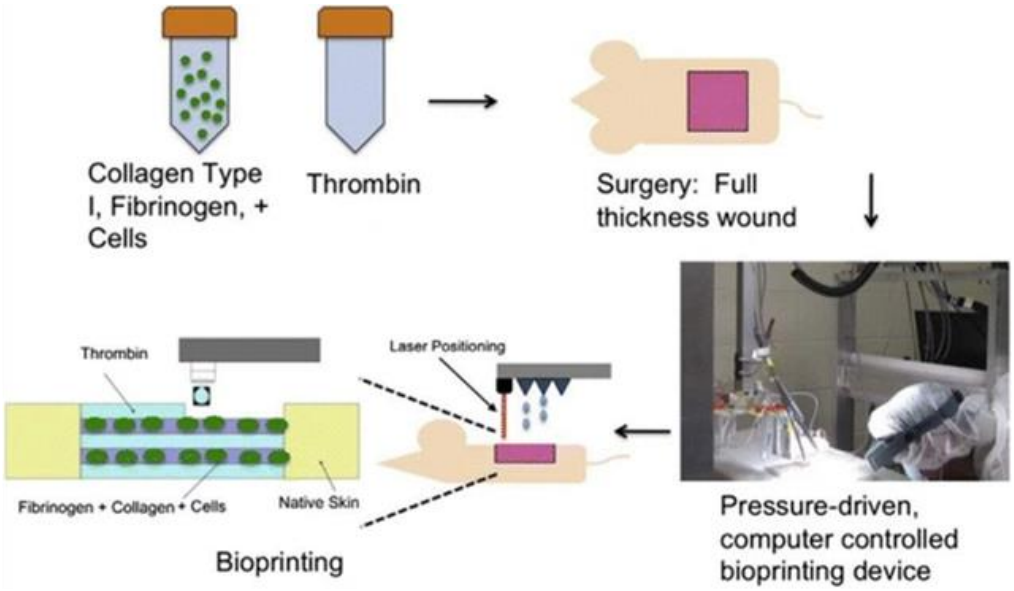

Figure 6: *A schematic depiction of the approach of in-situ laser based bioprinting of artificial skin [Source: Burns & Trauma (2018)].*

Researchers used human embryonic stem cell derived limbal epithelial stem cells (hESC-LESC) as a cell source for printing epithelium-mimicking structures. Whereas human adipose tissue derived stem cells (hASCs) were used for constructing layered stroma-mimicking structures. It was shown that the development and optimization of functional bioinks was a crucial step towards successful bioprinting of 3D corneal structures (Figure 7) [42]. Further, in this study, recombinant human laminin and human sourced collagen I served as the bases for the functional bioinks. Researchers employed two previously established LaBP setups based on laser induced forward transfer, with different laser wavelengths and appropriate absorption layers [42]. In this study, researchers bioprinted three types of corneal structures that included stratified corneal epithelium using hESC-LESCs, lamellar corneal stroma using alternating acellular layers of bioink and layers with hASCs, and finally structures with both a stromal and epithelial part. The printed constructs were then evaluated for their microstructure, cell viability and proliferation, and key protein expression (Ki67, p63α, p40, CK3, CK15, collagen type I, VWF).

Further, the 3D printed stromal constructs were also implanted into porcine corneal organ cultures that showed both cell types maintained good viability after printing. This was the first study to demonstrate the feasibility of 3D LaBP for corneal applications using human stem cells and successful fabrication of layered 3D bioprinted tissues that mimicked the structure of the native corneal tissue [42].

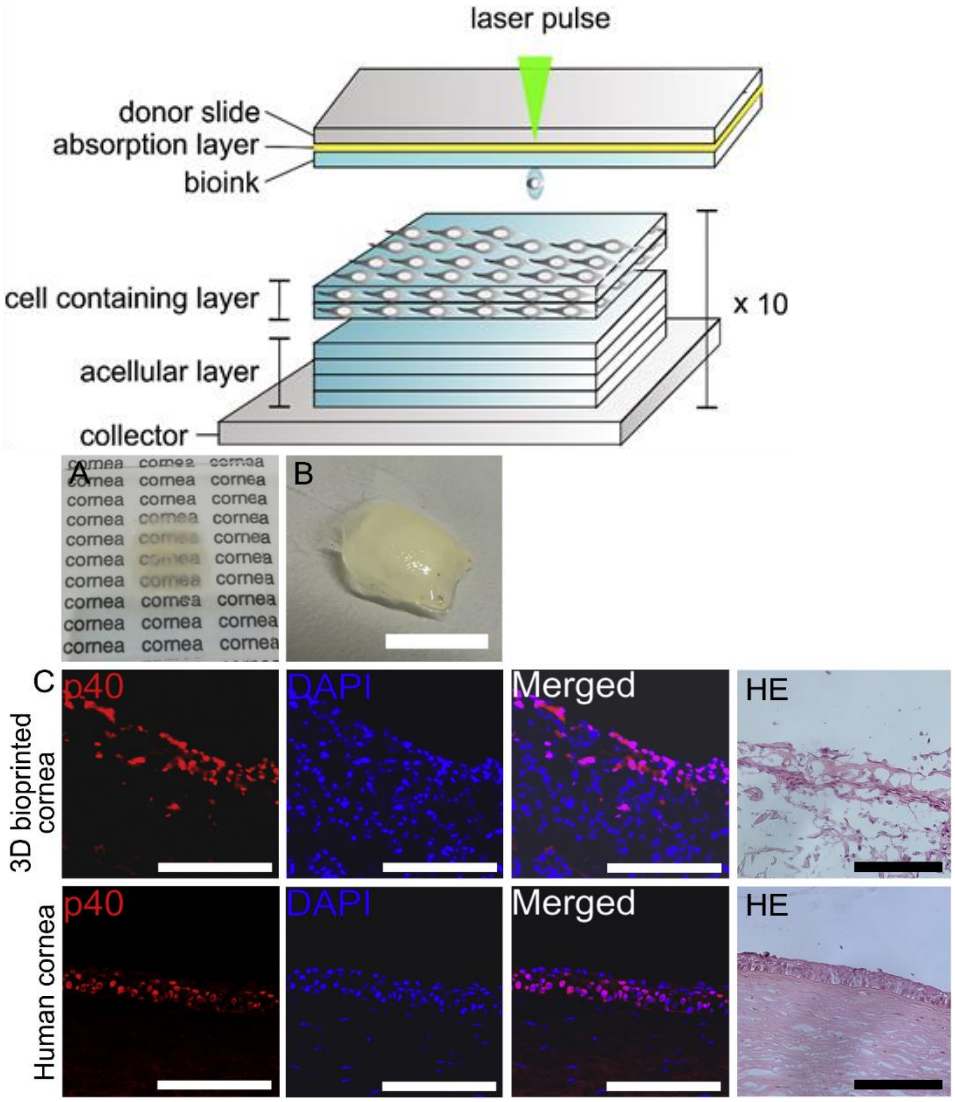

Figure 7: *(Top) Schematic diagram of the laser-assisted bioprinting system and printing of the 3D stromal mimicking structures. (Bottom) (A-C) a proof-of-concept to fabricate tissue-engineered cornea using both investigated human stem cell types (the bioprinted 3D cornea fabricated on PET substrate showing moderate transparency, while printing on non-transparent Matriderm® substrate was required to avoid shrinkage of the structure during culture). It also shows comparison between the 3D bioprinted corneal tissue and the native human cornea (Hematoxylin and eosin (HE)-staining shows the structure of the bioprinted tissue) [Source: Biomaterials (2018)].*

Conclusion

We have presented an overview of laser based bioprinting of 3D tissue constructs, which is considered a very promising area of current research and developments into tissue engineering and regenerative medicine. Laser based 3D bioprinting is a multidisciplinary field that is bringing together experts in cell biology, mechanical engineering, biotechnology, biomaterials science and laser science and engineering, to name a few. Studies conducted so far have shown tremendous potential of stem-cell

bioprinting as a source for renewable human tissue that offers a technological breakthrough in creating organs that are biocompatible. In this regard, early research on various types of artificial tissues have shown promise using bioprinted stem cells from liver to brain.

More studies will probably be needed in the field of personalized 3D printing technology. One specific area is fabricating artificial pancreas for diabetic patients. It is believed that future studies will focus on printing micro-organs that include pancreas islet tissues that function in the absence of the complete pancreas structure. This will benefit hundreds of millions of diabetic patients around the globe. However, the challenge will be to address a series of regulatory hurdles in the specified printed product. We anticipate a transition of printing adult stem cells to clinical trials and eventually to medical industry in the near future. The future of laser assisted 3D bioprinting in tissue engineering looks very promising.

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Infectious Disease

Deficiency in vitamin D and COVID-19 severity

Vitamin D is widely recognized for its health benefits and especially for its role in bone health. Studies have suggested that low levels of vitamin D have been associated with a range of complex medical conditions that include autoimmune, cardiovascular, and infectious diseases, to name a few. During and post COVID-19 pandemic, health officials encouraged people to take vitamin D, due to its well perceived role in promoting immune response that could protect against COVID-19.

In a new study, researchers from Israel showed a correlation between vitamin D deficiency and COVID-19 severity and mortality. The study was among the first to analyze vitamin D levels prior to infection. The findings facilitated a more accurate assessment than during hospitalization, when levels may be lower secondary to the viral illness.

This study was published in the journal PLOS ONE (Pre-infection 25-hydroxyvitamin D3 levels and association with severity of COVID-19 illness. PLOS ONE, 2022; 17 (2): e0263069 DOI: https://doi.org/10.1371/journal.pone.0263069) by researchers from the Azrieli Faculty of Medicine of Bar-Ilan University in Safed, Israel and the Galilee Medical Center in Nahariya, Israel.

Researchers studied the records of 1,176 patients admitted between April 2020 and February 2021 to the Galilee Medical Center (GMC) with positive PCR tests that were searched for vitamin D levels measured two weeks to two years prior to infection. It was found that patients with vitamin D deficiency (less than 20 ng/mL) were 14 times more likely to have severe or critical case of COVID than those with more than 40 ng/mL.

The interesting finding was about mortality among patients that showed 2.3% with sufficient vitamin D levels was in contrast to 25.6% in the vitamin D deficient group.

This study makes significant contribution to a continually evolving body of evidence suggesting that a patient's history of vitamin D deficiency could be a predictive risk factor associated with poorer COVID-19 clinical disease course and mortality.

Compiled and Edited by Dr. Megha Agrawal and Dr. Shyamasri Biswas.


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