Insilico or Organ on a chip in Pre-clinical and Clinical Trials

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Abstract: The organ-on-a-chip (OOAC) refers to a physiological organ biomimetic system built on a microfluidic chip. It involves biomaterial technology, cell biology and engineering combined together in a miniaturized platform. This reflects the structural and functional characteristics of human tissue and can predict response to an array of stimuli including drug responses and environmental effects. In this review, we introduce the concepts of OOAC and its application to the construction of physiological models, drug development, and toxicology from the perspective of different organs. We further discuss existing challenges and provide future perspectives for its application. These 'organs-on-chips' permit the study of human physiology in an organ-specific context, enable development of novel in vitro disease models, and could potentially serve as replacements for animals used in drug development and toxin testing.

Key words: Organ on a chip, Lab on chip, Biomimetic system, Microfluidic chip, Physiological models, Drug development, Toxicology

1.INTRODUCTION

In modern days highly used name is In-silico described under experimentation performed by the computers. In olden days In-silico represented the biological activities of In-vivo and In-vitro. In-silico pharmacology also known as computational therapeutics and also computational pharmacology. In-silico studies now a days most used term in global. Which is used to capture, analyses, integrated biological and medical data from various diverse sources with the help of software that contains developing techniques. These techniques are created computational models and stimulates that can be used to predict and hypotheses to explore and identified the advance medicine and therapeutics. These days pharmaceutical industries mostly dependent in the computational or silico studies. It helps to stimulate virtually and also make decision on drug discovery and development.

Microfluidics is a science and technology that precisely manipulates and processes microscale fluids. It is commonly used to precisely control microfluidic (10−9 to 10−18 L) fluids using channels that range in size from tens to hundreds of microns and is known as a "lab-on-a-chip"[1]. OOAC is a biomimetic that mimic the physiological functions of organ. This combines with chemical, biological and material science discipline. This is the reason it selected to "top ten emerging technology" in the World Economic Forum. OOAC have some abilities that control the parameters that includes; Contraction gradients, Shear force, Cell patterning, Tissue boundaries, Tissue-organ interaction. Organ-on-a-chip includes four components that are; (1) Microfluidics, (2) Living cell tissues, (3) Stimulation or drug delivery, (4) Sensing

Now a days single organ-on-a-chip fail to fully reflect on physiological complexity, functional changes, and integrity of organ function. That is the reason mostly used human organ-on-a chip it will balance the physiological activities of organs and also evaluates the functions of microfluids. In this physiological function of organs doesn't not require multiple organ chip because they cause unnecessary physiological activities.

Design concept:

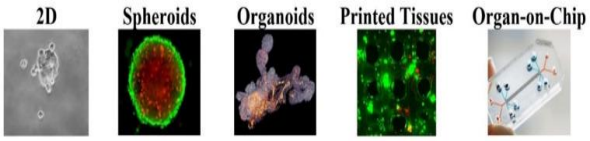

Figure: 1 Design concept of Organ on chip

Since the 1930s discovery of collagen as a component of connective tissue, a number of experiments have made scientific breakthroughs by creating environments for cell growth. This has been

accompanied by other interdisciplinary research, including biomechanics and mechatronics, to develop the technology[2]. The latest approaches are divided into 2D and 3D culture techniques (Figure 1). In 2D cultures, cells are grown as monolayers on flat surfaces, which are usually glass/polystyrene petri dishes[3]. As there is no mechanical support for the cells other than the flat plate, the shape is not controlled. To improve the shape factors that affect biofunction in vivo, microstructured substrates, such as cell adhesive islands and micro pillars, have been introduced[4]. This shape enhancement helps improve cell function in vitro, which has led researchers to incorporate more advanced environments into cell culture systems to create 3D models and develop techniques, such as sandwich culturing, microstructuring, and substrate stiffness modification[5]. Although 2D cultures allow low-cost assays, they cannot fully recapitulate the overall structure and physiological functions. Several reasons have been suggested for this failure, notably the uncontrolled access to oxygen and other ingredients in monolayer cultures and the lack of cell–cell and cell–matrix interactions[6]. There has been a significant incentive to move from semi-controlled flat environments to controlled 3D forms to fully ensure in vivo physiological properties.

The "spheroid culture" system is one of the first 3D methods used for studying tumor models, biology, tissue engineering, and transplantation therapies[7]. There are several techniques for this culturing system, such as hanging drops, pellet culture, and magnetic levitation[8].

Alternative 3D culturing methods that better represent in vivo physiology led to "organoids". To allow easy comparison with spheroids, organoids produce more complex tissues and facilitate the study of tissue-specific functions. They are widely used for various applications, such as disease pathology, drug toxicity, and personalized treatment[9]. In addition, organoids are not suitable for the study of stromal, vascular, neural, and immune cells because it is not possible to apply mechanobiological stimuli, such as the flow and the "shear stress" as well as the cyclic strain. It is impossible to model and study the vasculature and apply various shear stresses[10].

Another approach became interesting, namely the use of "printed tissues". The layer-by-layer deposition of 3D scaffolds with high accuracy at the microscale improves cell response and provides a multifunctional environment for highly efficient cell culturing. There are some limitations, such as the lack of precise cell placement and inability to grow cells at high cell density. Although the production of a vascular network using 3D printing techniques is challenging, emerging technologies and improvements in research have been used to overcome these limitations[11].

Microfluidics is considered to be the complementary discipline that can make up for any shortcomings and improve upon existing standards. Microfluidics can be defined as the study of fluid-flow phenomena in microscale. Today, more applications can be found in the field of biology, chemistry, the environment, energy, and biomedicine. Therefore, microfluidic devices can be considered as one of the rapidly developing fields of science and technology and are increasingly used in many research areas[12]. Recently, pharmaceutical technologies have become proponents of microfluidic applications as microphysiological systems enable faster drug development and better cost management, provide effective drug selection with low risk, and enable effective drug production in human models[13].

Organ on Chip technology, which generates fully functional in vivo-like organ units in physiologically relevant mechanobiological environments, overcomes the limited resources available for preclinical testing for drug screening and delivery and thus reflects a great inclination towards the use of microfluidic devices. Three-dimensional microfluidic chip models are cultured with cells accompanied by controlled external mechanical parameters to simulate an accurate physiological environment for studying the interactions between cells, tissues, and drugs. This interdisciplinary technology not only recapitulates the basic cellular structure of organs, but also mimics the function of a given organ in vitro[14]. OOCs are widely used to study various organs and tissues, including lung, liver, intestine, brain, and blood-brain barrier (BBB), as well as multiple organs together, enabling many major breakthroughs for the understanding of human cell biology, disease physiology, and drug development, while providing superior alternatives to animal models that often fail to predict clinical trial outcomes.

2. MATERIALS USED IN CHIP PRODUCTION

2.1 Polydimethylsiloxane (PDMS)

PDMS is the most common material used for the fabrication of microfluidic devices, and OOCs in particular. It is a silicon-based elastomer and has extremely advantageous properties, namely economic feasibility, transparency, oxygen permeability, and biocompatibility, also shows good compliance with various microfabrication techniques, such as soft lithography or molding. The absorption of hydrophobic molecules is a drawback that negatively affects the results of toxicity, efficacy, and also PK/PD (pharmacokinetics/pharmacodynamics) predictions[15]. There are increasing attempts to improve the properties of PDMS-made chips by surface modifications using plasma treatment, UV treatment, and coating.

2.2 Glass

Glass is one of the oldest materials in the development of microfluidic devices is glass. There are three types of glass used in this field: (i) soda lime, (ii) quartz, and (iii) borosilicate. They are a mixture of silicon dioxide (SiO_2), the base material of glass, with other oxides, such as CaO and MgO. Many advantages have been reported on the use of glass in microfabrication, and OOCs in particular, such as transparency, resistance to mechanical stress, hydrophilicity, and biocompatibility. It shows lower drug absorptivity compared to PDMS[16]. Major problem is that it can lead to channel plugging as the low gas permeability of glass.

2.3 Thermoplastics

Recently, thermoplastics have been increasingly proposed for the fabrication of microfluidic devices due to the limitations of PDMS and glass-based chips in terms of surface treatment instability, processing techniques, and the absorption of molecules (PDMS). Interesting properties that make thermoplastic polymers attractive for OOCs, including low cost, low density, biocompatibility, and easy fabrication[17].

There are some limitations in the use of thermoplastic polymers: (i) not all manufactured polymers are transparent (e.g., polyether ether ketone (PEEK) and polypropylene (PP)), which makes microscopic observation or imaging impossible; (ii) some have strong auto fluorescence properties and are not suitable for detection purposes; (iii) they have poor gas permeability, which has a negative impact on long-term cell culture (such as OOCs).

3. OOC TECHNOLOGIES

OOC contains two types of chips that are; Single organ-on-a-chip Model: Each organ contains on chip, Multiple organ-on -a-chip Model: Also known as human organ-on-a-chip.

3.1 Lab- on- chip:

A lab- on-a-chip is a device that integrates one or several laboratory functions on a single chip that deals with handling particles in concave microfluidic channels. It has been developed for over a decade. Advantages in handling particles at such a small scale include lowering fluid volume consumption(lower reagents costs, lower waste), adding portability of the bias, adding process control(due to quicker thermo-chemical responses) and dwindling fabrication costs. Also, microfluidic inflow is entirely laminar(i.e., no turbulence). Accordingly, there's nearly no mixing between neighboring aqueducts in one concave channel. In cellular biology confluence, this rare property in fluids has been abused to more study complex cell actions, similar as cell motility in response to chemotactic stimulants, stem cell isolation, axon guidance, subcellular propagation of biochemical signaling and embryonic development[18]. Transitioning from 3D cell- culture models to OOCs 3D cell- culture models exceed 2D culture systems by promoting advanced situations of cell isolation and tissue organization. 3D culture systems are more successful because the inflexibility of the ECM gels accommodates shape changes and cell- cell connections – formerly banned by rigid 2D culture substrates. nonetheless, indeed the stylish 3D culture models fail to mimic an organ's cellular properties in numerous aspects,(5) including tissue- to- tissue interfaces(e.g., epithelium and vascular endothelium), spatiotemporal slants of chemicals, and the mechanically active microenvironments(e.g., highways' vasoconstriction and vasodilator responses to temperature differentials). The operation of microfluidics in organs- on- chips enables the effective transport and distribution of nutrients and other answerable cues throughout the feasible 3D tissue constructs. Organs- on- chips are appertained to as the coming surge of 3D cell- culture models that mimic

whole living organs' natural conditioning, dynamic mechanical properties, and biochemical functionalities[19].

3.2 Brain- on-a-chip:

Brain- on-a-chip bias produce an interface between neuroscience and microfluidics by

1) improving culture viability.
2) supporting high- outturn webbing.
3) modeling organ- position physiology and complaint in vitro/ ex vivo, and
4) adding high perfection and tunability of microfluidic devices.

Brain- on-a-chip devices gauge multiple levels of complexity in terms of cell culture methodology. Devices have been made using platforms that range from traditional 2D cell culture to 3D tissues in the form of organotypic brain slices.

Overview of organotypic brain slices

Organotypic brain slices are an in vitro model that replicates in vivo physiology with fresh outturn and optic benefits, therefore pairing well with microfluidic devices. Brain slices have advantages over primary cell culture in that tissue architecture is saved and multicellular relations can still occur. There's flexibility in their use, as slices can be used acutely(lower than 6 hours after slice harvesting) or dressed for latterly experimental use. Because organotypic brain slices can maintain viability for weeks, they allow for long- term goods to be studied. Slice-grounded systems also give experimental access with precise control of extracellular surroundings, making it a suitable platform for relating complaint with neuropathological issues. Because roughly 10 to 20 slices can be uprooted from a single brain, beast operation is significantly reduced relative to in vivo studies. Organotypic brain slices can be uprooted and dressed from multiple beast species(e.g., rats), but also from humans[20].

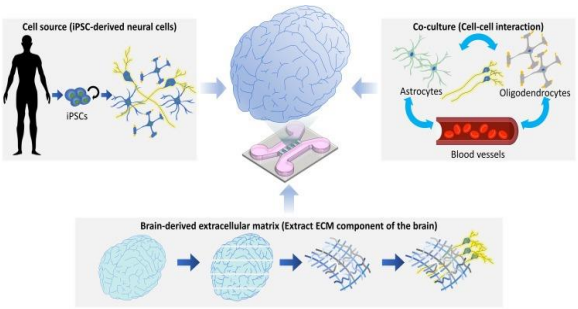

Figure: 2 Brain on chip

APPLICATIONS:

Microfluidic devices have been paired with organotypic slices to ameliorate culture viability. The standard procedure for cultivating organotypic brain slices(around 300 microns in consistence) uses semi-porous membranes to produce an air- medium interface, but this technique results in prolixity limitations of nutrients and dissolved gases. Because microfluidic systems introduce laminar inflow of these necessary nutrients and gases, transport is bettered and advanced tissue viability can be achieved[21]. In addition to keeping standard slices feasible, brain- on-a-chip platforms have allowed the successful culturing of thicker brain slices(roughly 700 microns), despite a significant transport hedge due to consistence. As thicker slices retain further native tissue architecture, this allows brain- on-a-chip devices to achieve further" in vivo- like" characteristics without immolating cell viability. Microfluidic devices support high- outturn webbing and toxicological assessments in both 2D and slice cultures, leading to the development of new therapeutics targeted for the brain. One device was suitable to screen the medicines pitavastatin and irinotecan combinatorically in glioblastoma multiform. These webbing approaches have been combined with the modeling of the blood- brain barrier(BBB), a significant chain for medicines to overcome when treating the brain, allowing for medicine efficacity across this hedge to be studied in vitro[22]. Microfluidic BBB in vitro models replicate a 3D terrain for bedded cells(which provides precise control of cellular and extracellular terrain), replicate shear stress, have further physiologically applicable morphology in comparison to 2D models, and give easy objectification of different cell types into the device. Because microfluidic devices can be designed with optic availability, this also allows for the visualization of morphology and processes in specific

regions or individual cells. Brain- on-a-chip systems can model organ- position physiology in neurological conditions, similar as Alzheimer's disease, Parkinson's disease, and multiple sclerosis more directly than with traditional 2D and 3D cell culture ways. The capability to model these conditions in a way that's reflective of in vivo conditions is essential for the restatement of curatives and treatments. also, brain- on-a-chip devices have been used for medical diagnostics, similar as in biomarker discovery for cancer in brain tissue slices.

Limitations:

Brain- on-a-chip devices can get shear stress on cells or tissue due to overflow through small channels, which can affect in cellular damage. These small channels also introduce vulnerability on trapping of air bubbles that can disrupt flow and potentially get damage to the cells. The wide use of PDMS in brain-on-a-chip devices has some downsides. Although PDMS is cheap, malleable, and transparent, proteins and small molecules can be absorbed by it and latterly bloodsucker at unbridled rates. Permeability in these models are limited due to the limited perfusion and complex, inadequately defined figure of the recently formed microvascular network[23].

3.3 Gut- on-a-chip:

It contains two microchannels that are separated by the flexible porous Extracellular Matrix(ECM)- carpeted membrane lined by the gut epithelial cells Caco- 2, which has been used considerably as the intestinal hedge. Caco- 2 cells are cultured under robotic isolation of its maternal cell, a mortal colon adenocarcinoma, that represent the model of defensive and absorptive properties of the gut. The microchannels are fabricated from PDMS polymer. In order to mimic the gut microenvironment, peristalsis-such like fluid inflow is designed[24]. By converting suction in the vacuum chambers along both sides of the main cell channel bilayer, cyclic mechanical strain of stretching and relaxing are developed to mimic the gut actions. likewise, cells suffer robotic villus morphogenesis and isolation, which generalizes characteristics of intestinal cells. Under the three-dimensional villi scaffold, cells not only gain, but metabolic conditioning are also enhanced. Another important player in the gut is the microbes, videlicet gut microbiota. Numerous microbial species in the gut microbiota are strict anaerobes. In order toco-culture these oxygen intolerant anaerobes with the oxygen favorable intestinal cells, a polysulfone fabricated gut-on-a-chip is designed. Oral administration is one of the most common methodologies for medicine administration. It allows patients, especially out-patients, to self- serve the medicines with minimum possibility of passing acute medicine responses and in utmost cases pain-free. The medicine's action in the body can be largely told by the first pass effect. The gut, which plays an important role in the mortal digestive system, determines the effectiveness of a medicine by absorbing its chemical and natural properties widely. While it's expensive and time consuming to develop new medicines, the fact that the gut- on-a-chip technology attains a high position of outturn has significantly dropped exploration and development costs and time for new medicines.

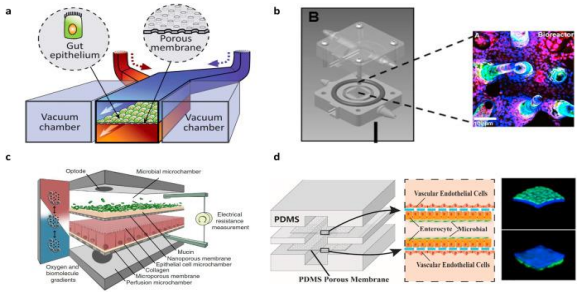

Figure 3 Gut on Chip

Modeling Inflammatory bowel disease(IBD):

Indeed, though the cause for inflammatory bowel disease(IBD) is fugitive, its pathophysiology involves the gut microbiota. Current methods of converting IBD are using seditious cues to spark Caco- 2. It was set up that the intestinal epithelium endured a reduction in hedge function and increased cytokine attention. The gut- on-a-chip allowed for the assessment on medicine transport, immersion, and toxin as well as implicit developments in studying pathogenesis and interactions in the microenvironment overall. also, the gut- on-a-chip allows the testing of anti-inflammatory goods of bacterial species[25].

Modeling radiation- convinced cell injury

The chip was used to model mortal radiation-convinced injury to the intestine in vitro as it abstracted the injuries at both cellular and tissue levels. Injuries include but not limited to inhabitation of mucus product, creation of villus benumbing, and deformation of microvilli[26].

3.4 Lung-on-a-chip:

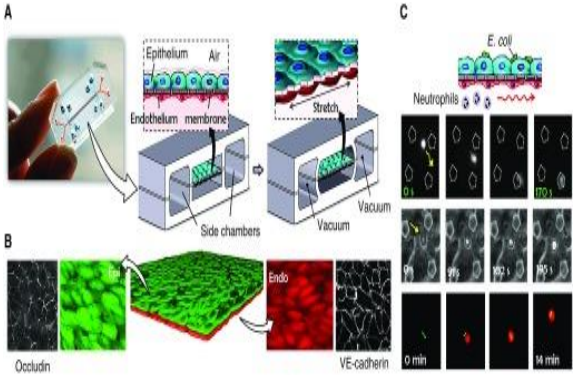

Figure: 4 Lung on Chip

Lung- on-a-chips are being designed in a trouble to ameliorate the physiological applicability of being in vitro alveolar- capillary interface models. Such a multifunctional microdevice can reproduce crucial structural, functional and mechanical properties of the mortal alveolar- capillary interface(i.e., the abecedarian functional unit of the living lung). Dongeun Huh from Wyss Institute for Biologically Inspired Engineering at Harvard describes their fabrication of a system containing two nearly apposed microchannels separated by a thin(10 µm) pervious flexible membrane made of PDMS[27]. The device largely comprises three microfluidic channels, and only the middle one holds the pervious membrane. Culture cells were grown on either side of the membrane mortal alveolar epithelial cells on one side, and mortal pulmonary microvascular endothelial cells on the other. The compartmentalization of the channels facilitates not only the inflow of air as a fluid which delivers cells and nutrients to the apical surface of the epithelium, but also allows for pressure differences to live between the middle and side channels. During normal inspiration in a human's respiratory cycle, intrapleural pressure diminishments, driving an expansion of the alveoli. As air is pulled into the lungs, alveolar epithelium and the coupled endothelium in the capillaries are stretched. Since a vacuum is connected to the side channels, a decrease in pressure will cause the middle channel to expand, therefore stretching the pervious membrane and latterly, the entire alveolar- capillary interface. The pressure- driven dynamic motion behind the stretching of the membrane, also described as a cyclic mechanical strain(valued at roughly 10), significantly increases the rate of nanoparticle translocation across the pervious membrane, when compared to a static interpretation of this device, and to a Trans well culture system. In order to completely validate the natural accuracy of a device, its whole- organ responses must be estimated. In this case, experimenters foisted injuries to the cells

3.5 Pulmonary inflammation:

Pulmonary seditious responses number a multistep strategy, but alongside an increased product of epithelial cells and an early response release of cytokines, the interface should suffer an increased number of leukocyte adhesion molecules. In Huh's trial, the pulmonary inflammation was dissembled by introducing medium containing a potent pro-inflammatory mediator. Only hours after the injury were caused, the cells in the microfluidic device subordinated to a cyclic strain replied in agreement with the preliminarily mentioned natural response.

Pulmonary infection:

Living E-coli bacteria was used to demonstrate how the system can indeed mimic the ingrain cellular response to a bacterial pulmonary infection. The bacteria were introduced onto the apical surface of the alveolar epithelium. Within hours, neutrophils were detected in the alveolar compartment, meaning they had transmigrated from the vascular microchannel where the pervious membrane had phagocytized the bacteria. also, researchers believe the implicit value of this lung- on-a-chip system will prop in toxicology operations. By probing the pulmonary response to nanoparticles, researchers hope to learn further about health risks in certain surroundings and correct preliminarily complexified in vitro models. Because a microfluidic lung- on-a-chip can more exactly reproduce the mechanical properties of a living mortal lung, its physiological responses will be hastily and more accurate than a Trans well culture system. Nonetheless, published studies admit that responses of a lung- on-a-chip do not yet completely reproduce the responses of native alveolar epithelial cells.

3.6 Heart on Chip:

Cardiovascular deaths are leading cause of human mortality. The myocardium is a major component of the heart. The beating of cardiomyocytes (CMs) can be used to directly assess drug effects and is directly related to heart pumping. Human induced pluripotent stem cells (iPSCs) have recently attempted to be used

for drug discovery and drug safety tests in various target organs as a resource of human somatic cells. Recent studies of drug safety tests using human iPSC-derived cardiomyocytes (CMs) opened a gate to use human cells that show greater fidelity than those used in hERG tests[28]. Nevertheless, the substantial limitation of the methods based on single cells is that they can only detect phenomena occurring in single cells per se[29] and still fail to show the actual kinetics of native myocardial tissues resulting from the interaction of multiple cells in heart tissue, which is composed of not only CMs but also other cell lineages such as vascular cells and stromal cells.

Biomimetic human heart tissue-like structures composed of various cardiac cell lineages would be desirable for more precise evaluations of physiological heart function in response to candidate drugs. We have been investigating biomimetic cardiac tissue sheets as cardiac microtissues derived from human iPSCs that are composed of various cardiovascular cells using temperature-responsive culture dishes as a heart tissue surrogate to recapitulate human heart tissue function, which would serve as an optimal resource for preclinical drug discovery and safety tests[30].

To apply biomimetic human heart tissue-like structures, such as, mentioned human iPSC-derived cardiac microtissues, to drug discovery and cardiac toxicity tests, it is indispensable to develop a bioassay system to convert the small pulsations of cardiac microtissues into indicators of tissue function with higher sensitivity and versatility compared to those of previously reported systems based on cantilever or force measurement devices[31]. Organ-on-a-chip is an emerging concept to recapitulate organ function using polymeric organo silicon compounds such as polydimethylsiloxane (PDMS) by utilizing Micro Electromechanical Systems (MEMS) technology, which would be applied for the establishment of the bioassay system[32]. MEMS-based organ-on-a-chip technology potentially facilitates the establishment of micro devices recapitulating heart pump function as a highly sensitive bioassay system for drug discovery and cardiac toxicity tests.

The device records the contraction of CMs to reveal drug effects. The chip represented a preclinical assessment of drug cardiac efficacy. Direct visualization and quantitative analysis was performed, which was not permitted in traditional cell culture or animal models. This platform represents an advance in the field and provides standard functional 3D heart models. This makes the device an innovative and low-cost screening platform to improve the predictive power of in vitro models. This platform can be used for a variety of biomedical applications. The advances in drug development have important implications for cardiovascular tissue because cardiotoxicity is often seen in drug trials and is one of the main reasons clinical trials are suspended or drugs are withdrawn from the market.

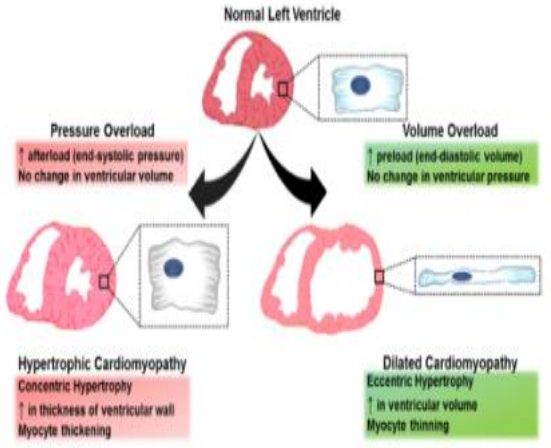

Figure: 5 Heart on Chip

3.7 Kidney on Chip:

Modeling Tubulo interstitial Disease:

Kidney-on-a-chip shows promise for disease modeling, owing to its closer resemblance to in vivo conditions. Investigators, including us, have shown that kidney-on-a-chip shows a better response to injury markers in response to nephrotoxic compounds.

Cisplatin nephrotoxicity was evaluated in the kidney-on-a-chip using human proximal tubular cells[33]. Cisplatin was introduced into the bottom space, and cisplatin-induced cellular damage was monitored to the cells for 24 hours. During the following 72 hours, shear stress was helpful for facilitating recovery of the injured cells and associated biomarkers. Shear stress in the devices can facilitate translocation of aquaporin-2 and relocation of actin cytoskeleton in the kidney-on-a-chip using primary cultured inner medullary collecting duct cells of rat kidneys, which is a good example of a physiological experiment using kidney-on-a-chip. Moreover, renal tubular epithelial cells are continuously exposed to the changes of extracellular microenvironment, e.g., transepithelial osmotic

gradient, and changes of luminal or interstitial pH. The effects of these physiological factors on the functions of renal tubular cells could also be investigated by exploiting microfluidics[34]. If the offending antigens or mechanisms of the diseases are well identified, disease modeling can be easily fabricated in the kidney-on-a-chip. Kidney injury models using nephrotoxic drugs may be simple candidates for the application. Kidney-on-a-chip is only one compartment of an eventual multiorgans-on-a-chip system[35]. To research drug metabolism, renal excretion or metabolism should not be omitted. However, some multiorgans-on-a-chip systems have been using kidney tubular cells not for evaluating renal excretion, but for measuring kidney injury. Animal renal clearance is usually higher than human renal clearance. Using pharmacokinetic data from animal models runs the risk of underestimating human nephrotoxicity. Applications of human kidney-on-a-chip may fill such gaps through control of drug concentrations and flow rates that mimic human drug clearance or metabolism.

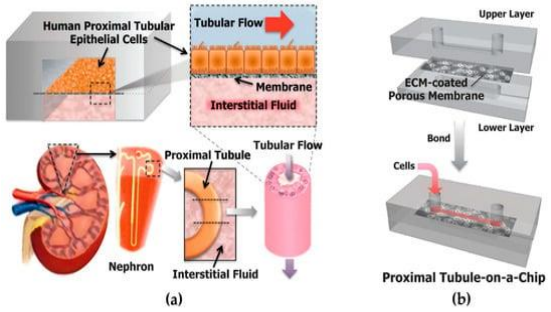

Figure: 6 Kidney on Chip

3.8 Multi Organ On Chip:

Single organ chips fail to fully reflect the complexity, functional changes, and integrity of organ function. The “multi-organ-on-a-chip”, is referred to as the “human-on-a-chip” which simultaneously constructs multiple organs attracting obvious research attention. Multi-organs-on-a-chip culture cells of different organs and tissues simultaneously which are connected by channels (bionic blood vessel), to achieve multi-organ integration, permitting the examination of interactions to establish a system[36]. These can be separated into static, semi-static and flexible approaches. Static multiple organs are integrated into single connected devices. In semi-static systems, the organs are joined via fluidic networks with Transwell®-based tissue inserts. In the flexible system, individual organ-specific platforms are interconnected using flexible microchannels. In such systems, the flexible nature is advantageous and recreates multiple organs. Although the multi-organs-on-a-chip concept remains in its infancy, major breakthroughs have been made, including the design of two-organs, three-organs, four-organs and ten organs on the chip.

In 2010, Van et al. were the first to combine liver and intestines in a microfluidic device. The intestine and liver slices functioned on the chip and demonstrated its applicability to organ interactions including the regulation of bile acid synthesis. This system enabled in vitro studies and provided insight into organ–organ interactions. A larger number of organs have since been concentrated onto individual chips. Organ chips are required to maintain stable fluid connection, avoid bacterial contamination, and monitor cell viability throughout the culture process. Fabricated pumpless, user-friendly multi-organs-on-a-chip which were easily assembled and operated. Satoh et al. reported a multi-throughput multi-organon-a-chip system formed on a pneumatic pressure-driven medium circulation platform that was microplate-sized (Fig. 7)[37]. This system possesses the following advantages for application to drug discovery: simultaneous operation of multiple multi-organ culture units, design flexibility of the microfluidic network, a pipette-friendly liquid handling interface, and applicability to experimental protocols and analytical methods widely used in microplates. This multi-organ culture platform will be an advantageous
research tool for drug discovery.

OOAC technology has developed rapidly in recent years and has enhanced our knowledge of all the major organs. Others not discussed in this review include blood vessels[38], skin[39], skeletal muscle[40], and CNS[41].

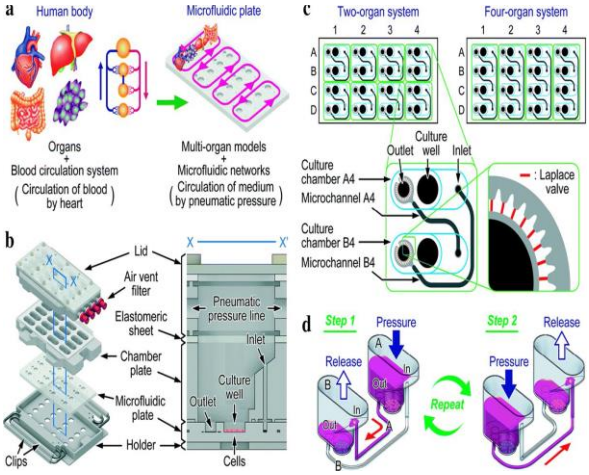

Figure: 7 Multi Organ on chip

DISCUSSION

Organ-on-chips provide a novel and unique platform for research on various diseases by contributing to both diagnosis and treatment approaches, which are important research areas for improving global health. In drug development it is the time and cost savings, a strong motivation for this technology, as in the elimination of in vivo animal testing. There are specific features that make it a potential alternative and breakthrough tool in the field. These include 3D culture and cell–cell interactions, the ability to apply mechano biological stimuli, online monitoring of testing, and low testing cost.

The design of a chip is a combination of physiological and mechanical concepts governed by material and fabrication concepts. An organ-on-chip cannot fully recapitulate all the features of an organ, but only the most important functions that are crucial in terms of the physiological concepts and based on the scientific question being asked. Thus, the design is closely related to the goal of the research and simplifications are required to develop a viable design. The physiochemical properties of the flow, such as pH and dissolved oxygen, can change during testing and have a large effect on the biological performance, so that deviations exhibit erratic behavior. The use of online monitoring techniques is a prerequisite for improving the accuracy. Conventional or innovative micro electromechanical on-chip systems can be selected or designed. The materials are another crucial factor affecting the whole process of design and fabrication. The materials should not interfere with the experiments; so, they must be compatible with the culture environment and test compositions. The selection of materials according to the desired criteria make microfabrication more complex and also more expensive. Therefore, a number of common materials which have some basic properties, such as gas permeability, optical clarity, and rapid prototyping, are usually of interest[43]. One possible solution in this regard is surface modification approaches that alter the material to have little impact on the test compositions, even if some of them are temporary and do not cover the entire time of the experiments.

ORGAN ON A CHIP SYSTEM: REGULATORY AUTHORITIES AND MARKET SIZE

As Organ on a chip technology is still in its infancy stage, regulatory bodies and top pharma companies are increasingly showing interest in this technology. This technology was not specifically classified by any major regulatory body such as the United States Food and Drug Administration (U.S. FDA), the European Medicines Agency, and/or the Medicines and Healthcare Products Regulatory Agency in the United Kingdom. However, a survey showed that most developers of organ on a chip technology follow one of the following three guidelines: ISO 9001:2015, FDA 21 CFR Part 58, and FDA FD&C Act Section 507[44].

National Center for Advancing Translational Science (NCATS) USA, the USFDA, and the US Defense Advanced Research Projects Agency (DARPA) collaborated to develop organ on a chip for screening drug safety and effectiveness before approval for first in human studies[45].

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