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A BRIEF REVIEW ON ORGAN ON A CHIP

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ABSTRACT

Organ on a chip (OOAC) is a novel in-vitro micro-scale biomimetic platform that helps in reproducing physiological environment of human organs. This technology involves cell biology, engineering and material sciences to simulate in-vivo tissue studies. The main advantage of these chips is that they can be manufactured for a very low cost and this can allow to test the effect of a wide range of drug concentration on the efficiency of the medicine. This will allow organs on chip technology to considerably accelerate scientific investigations. Organ on a chip devices including brain, lung, heart, kidney, liver, prostate, vessel (artery), skin, bone, cartilage and more and the method of manufacturing of these models is miniaturized The chips are lined with living human cells and their tiny fluidic channels reproduce blood and/or air flow just as in the human body. Organ-on-a-chip devices can replicate key aspects of human physiology, providing insights into the studied organ function and disease pathophysiology. Moreover, these can accurately be used in drug discovery for personalized medicine.

KEYWORDS: organ-on-a-chip, microfluidics, biomimetic, cell biology, drug discovery.

INTRODUCTION

Organ-on-chip (OOC) is a concept with great interest all around the globe, due to the importance of their applications in biomedical field. Organ-on-a-chip systems emulate organ functions by incorporating multiple cell types within a three-dimensional (3D) tissue microenvironment. In addition to simulating the native cellular microenvironment by applying microfluidic engineering techniques, cell-based lab-on-chip systems allow the incorporation of bio sensing solutions to enable on-chip analysis as an alternative to strictly

endpoint based analysis routinely employed in biomedical research. As a result, organ-on-a-chip systems can reproducibly monitor human physiological and pathological processes via optical and electrical sensing strategies to identify dynamic cellular behaviour with high structural resolution. Organ-on-a-chip system design centres on three key parameters to mimic a physiologically relevant micro-niche.

(1) The specific native tissue architecture,

(2) Incorporating dynamical stimulation, and

(3) Emulating spatiotemporal biochemical concentrations. Organs-on-chips applications do not only have several advantages such as miniaturization, integration and low consumption, but also they allow researchers to accurately control the multiple parameters of a system such as chemical concentration gradient, fluid shear stress, cell patterning, tissue interface, organ-organ interaction and so on. For the past 25 years, new concepts of micro-engineering models in the early health technology assessment (HTA) stage have emerged, similar to the micro fabrication of versatile microfluidic chips. This model not only would cut cost and time in preclinical testing but would also lead to the replacement of animal subjects as a whole in the pharmacy and cosmetic industry of a 2D systems.

Organ-on-a-chip systems offer an alternative approach for nanoparticle toxicity screening that can fill the gap between the conventional pre-clinical models, specifically 2D cell culture and animal models, and human population studies. The inherent advantage of using organ-on-a-chip systems is their ability to reverse engineer native microenvironment (extracellular matrix, geometry, mechanical stiffness and flow and responses by generating high fidelity models of human tissues.

Discovery

The development of Organ Chip technology was founded on the back of the long history of cell culture research. Scientists first began finding ways to cultivate eukaryotic cells outside of an organism in the late nineteenth century, and by the early twentieth century it had become possible to maintain such cells for several months). As early as 1876 John Syer Bristowe, a British physician, coined the term ‘organoid’ to denote ‘the smallest functional organ or tissue unit’ Efforts to create artificial organs were inspired by the work of Henry Van Peters Wilson, a professor of biology and zoology at the University of North Carolina, Chapel Hill. In the early twentieth century, he discovered that if he kept individual tissue cells that he had mechanically separated from Microciona prolifera in sea water, they

naturally clumped together and fused to become new sponges. Following this, a number of other scientists generated different types of organs using organ tissues taken from different sources, including embryonic chicks and frogs.

Strengths and limitations of OoC

Since the cost of manufacturing the chips is rather cheap, it is possible to fabricate using in-house accessories without any specialized equipment many drugs and doses of drugs can be tested at the same time. This may prove helpful when a new drug is discovered, not needing test subjects and at the same time not meeting ethnic concerns. Another strong suit of the OoC concept is the close resemblance of the tissue microenvironment it replicates. When comparing the OoC with simple Petri recipient microsystems, the OoC comes out on top due to the 3D structure which is an important element of the test's reliability. Additionally, the microfluidic chips are user friendly and, in some cases, can be portable are capable to assess many physiological questions. Due to their small size multiple microfluidic systems can be integrated on one chip, saving space and money at the same time.

The first disadvantage considered is the presence of the surface effect. Since the dimensions of the fluids are very small, the surface effects dominate the volume effect. This may reflect in poor quality of the analysis and some of the product of interest may be adsorbed. Since laminar flow is present at the intersection of multiple fluids the relevant fluids might not mix properly. Another limitation of these platforms is represented by the fact that, in some experiments, there is a need for special instruments in order to obtain reliable results.

Organs-on-a-chip design concept and key components

Design Concept

Culture systems require the control of external and internal cell environments. OOAC combined with micromachining and cell biology can control external parameters and accurately simulate physiological environments. Dynamic mechanical stress, fluid shear and concentration gradients are required on the chip. Cell patterning should also be realized to fully reflect physiological processes.

Fluid shear force

Microfluidics enables the dynamic culture of cells through micro-pump perfusion, which facilitates the administration of nutrients and timely waste discharge. The dynamic environment in which cells are located is more comparable to in vivo conditions than static

culture. In addition, fluid shear stress induces organ polarity. Importantly, OOAC exerts necessary physical pressure on the normal biological functions of endothelial cells by activating cell surface molecules and associated signalling cascades. Similarly, the incorporation of fluid into the OOAC device permits biological assessments at the single organ level. The OOAC system summarizes flow through a simple "rocker" on a chip fluid motion, or through a more complex programmable "pulsatile" format, arranged in a single loop for organization-specific configurations.

Concentration gradient

At the micro scale level, the fluid acts primarily as a laminar flow, resulting instable gradient of biochemical molecules, controlled both spatially and temporally. Various biochemical signals driven by concentration gradients exist in biological phenomena, including angiogenesis, invasion, and migration.

Microfluidics simulate complex physiological processes in the human body by altering flow velocity and channel geometry using microvalves and micro-pumps to achieve stable, three-dimensional (3D) biochemical concentration gradient.

Cell Patterning

Microfluidics control cell patterning for the construction of in vitro physiological models with complex geometries. Surface modifications, templates, and 3D printing contribute to cell patterning on the chip. The 3D printing method enables multi-scale cell patterning by permitting the formation of hydrogel scaffolds with complex channels. The advantage of 3D printing is to allow user-defined digital masks to provide versatility in cell patterns, critical for the in vitro reconstruction of the cellular microenvironment. Li et al. Developed methods to achieve rapid heterotypic cell patterning on glass chips using controlled topological manipulations. This method combines a polyvinyl acetate coating, carbon dioxide laser ablation, and continuous cell seeding techniques on a glass chip. This method enables controlled epithelial–mesenchymal interactions. In addition, mesenchymal cells with similar properties can also be patterned on glass chips. This method can be helpful for large-scale investigation and pharmaceutical testing of cutaneous epithelial–mesenchymal interaction and can also be applied to the patterning of other cells.

Key Components

The OOAC involves four key components,

(1) Microfluidics.

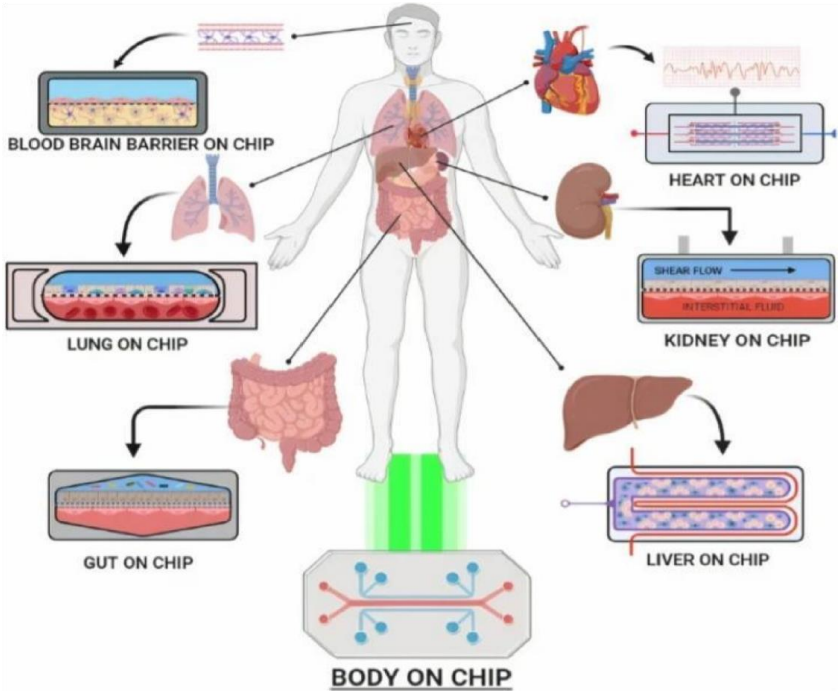
(2) Living cell tissues.

(3) Stimulation or drug delivery; and.

(4) Sensing.

The microfluidic component refers to the use of microfluidics to deliver target cells to a pre-designated location and includes a system of culture fluid input and waste liquid discharge during the culture process. Typically, this component is characterized by miniaturization, integration, and automation. The living cell tissue component refers to components that spatially align a particular cell type in the case of 2D or 3D systems. The 3D arrangements are typically created by the addition of biocompatible materials such as hydrogels. These materials can prevent mechanical damage and shape three-dimensional arrangements. Although the 3D tissue structure more accurately simulates the in vivo situation compared to 2D models, due to the limitations of technology and cost and the assembly of extracellular matrix and the presenting and formation of vasculature, living cell in organ tissues are still mostly cultivated in 2D. For certain tissues, physical or chemical signals are required to simulate the physiological microenvironment, which promotes micro tissue maturation and function. For example, electrical stimulation can help myocardial tissue maturation. Different signal stimuli can be derived from for drug screening approaches. The sensing component for detecting and compiling data can be an embedded sensing output component or a transparent chip based visual function evaluation system. Peel et al. used automated systems to image multicellular OOACs, producing detailed cell phenotypes and statistical models for measurements developed a cell system to monitor cells in a 3D microfluidic setting. These assays featured time-lapse imaging microscopy to assess cellular electrical activity through quality control. A meaningful human-on-chip cell model cannot be described and accessed without micro sensors-mediated reading of the metabolic state at characteristic points in the system.

Types of OOC



Liver-Maintains physiologic properties; Great regenerative properties.

Breast Tissue -Mainly used in cancer study and treatment, difficulty to treat.

Lungs- Bad regenerative properties; Successful replication of functionality by modifying the pressure.

Brain-Complex due to functionality; Differs from person to person, Can be recreated by separating the soma and axons.

Blood-Multiple cell types, OoC uses all cell types; Need for small chambers.

Lungs on a chip

A lung alveolus chip lined with primary human lung alveolar epithelium interfaced with primary pulmonary micro vascular endothelial cells has been used to model pulmonary thrombosis by flowing human whole blood through its vascular channel. This approach enabled quantitative analysis of organ-level contributions to inflammation-induced thrombosis, and recapitulated complex responses, including platelet–endothelial dynamics within individual thrombi that were nearly identical to those visualized within thrombi that formed in vivo. Analysis of thrombosis formation on-chip induced by lipopolysaccharide endotoxin also revealed that it acts indirectly by stimulating the alveolar epithelium to produce other inflammatory molecules that induce endothelium activation, such as IL-6, rather than acting directly on endothelium.

Healthy and diseased human lung airways have been modelled by populating chips with primary bronchial or bronchiolar epithelial cells obtained from healthy donors or patients with chronic obstructive pulmonary disease (COPD) and culturing them under an air–liquid interface. Chips lined with COPD epithelial cells exhibited selective cytokine hyper secretion, increased neutrophil recruitment and mimicked clinical exacerbation by exposure to viral and bacterial infections as well as cigarette smoke. Transcriptomic profiles of healthy airway chips exposed to cigarette smoke closely resembled those obtained in past clinical studies. In addition, models of the asthmatic lung airway were developed by exposing healthy airway chips to IL-13, which induced goblet cell hyperplasia, inflammatory cytokine secretion and endothelial activation, while reducing cilia beating frequency, all of which are observed in asthmatic patients. The IL-13-stimulated airway chips also recruited increased numbers of circulating neutrophils under flow, which could be inhibited by administering an anti-inflammatory drug (bromodomain-containing protein 4 inhibitor), and this recruitment response was greater than observed in a static Tran swell micro physiological system.

Liver on a chip

Multiple liver chip designs have been developed and used to model drug metabolism, drug–drug interactions, hepatotoxicity, inflammation and infection. A microfluidic liver chip with the multiwall bioreactor design lined by primary human hepatocytes and Kupffer cells replicated breakdown of the glucocorticoid hydrocortisone to phase I and phase II metabolites, and the intrinsic clearance values measured on-chip correlated with human data. A similar liver chip system was used to show that sustained stimulation of inflammation by IL-6 suppresses cytochrome P450 3A4 isoform (CYP3A4) activity, increases Creative protein secretion and decreases shedding of soluble IL-6 receptor. Treatment with a therapeutic anti-IL-6 receptor monoclonal antibody (tocilizumab) that is used to treat rheumatoid arthritis modulated CYP3A4 enzyme activities and altered metabolism of the small-molecule CYP3A4 substrate simvastatin hydroxyl acid in this model, thus replicating the drug–drug interactions observed in patients, which was not possible using static 2D culture models.

Heart on a chip

A heart chip was developed by culturing human iPS-cell-derived cardiomyocytes on flexible ECM gels overlaid on multielectrode arrays in a single channel microfluidic device, which supported laminar cardiac tissue formation and enabled recording of tissue-level

electrophysiological responses in real time. This chip mimicked the difference in safety profiles between the cardio toxic pro-drug terfenadine and its non-toxic metabolite fexofenadine seen in patients. Another heart chip created by combining micro fabrication and 3D printing that contains human iPS-cell-derived cardiomyocytes interfaced with endothelial cells reproduced the toxic effects of the cancer drug doxorubicin on heart myocardium observed clinically.

Kidney on a chip

Kidney chips lined by human renal tubular or glomerular cells have been used for studies on drug and molecule transport, reabsorption and toxicity as well as disease modelling. For example, a two-channel kidney chip lined by primary proximal tubular epithelium that expressed high P-glycoprotein efflux transporter activity replicated a transporter-specific cisplatin toxicity that is observed in patients but not in static 2D cultures or animal models. Albumin reabsorption and cyclosporine toxicity were also recapitulated in a 3D-printed kidney chip containing human proximal tubular epithelium deposited within tiny cylindrical structures surrounded by a thick ECM gel. This approach was extended further by printing closely apposed kidney tubules and vessels lined by proximal tubular epithelium and kidney endothelium within an ECM gel, which exhibited active reabsorption via tubular–vascular exchange of solutes similar to that observed in vivo. Hyperglycaemia-induced endothelial cell dysfunction was replicated in this model, as well as its reversal by administration of a glucose transport inhibitor drug. Moreover, a kidney distal tubule chip was used to explore pathogenesis of Pseudo rabies virus-induced renal dysfunctions. Virus infection resulted in altered sodium reabsorption, disruption of the reabsorption barrier and changes in microvilli, which may contribute to the serum electrolyte abnormalities observed in virus-infected patients.

Use of a human kidney glomerulus chip containing closely opposed layers of immortalized kidney podocytes and glomerular endothelial cells revealed that glomerular mechanical forces play a crucial part in cell damage that leads to increased glomerular leakage, as observed in patients with hypertensive nephropathy. Another glomerulus chip lined by human iPS-cell derived podocytes interfaced with glomerular endothelium reconstituted in vivo levels of urinary clearance and mimicked the toxic effects of the anticancer drug Adriamycin on kidney podocytes. More recently, a personalized version of this chip was developed using both human iPS-cell-derived kidney glomerular endothelial cells and podocytes from a single

patient. In addition, the renal effects of autoimmunity have been studied using a human kidney glomerulus chip that recapitulates the perm selectivity of the glomerulus. When exposed to patient sera containing anti-podocyte autoantibodies, the chips developed albuminuria proportional to patients' proteinuria, and this phenomenon was not seen using sera from healthy controls or individuals with primary podocyte defects.

Brain on a chip

Transport across the brain endothelium, and this clinical phenotype could be replicated on-chip. In a recent study, the human neurovascular unit was modelled in a microfluidic chip containing a perfused channel lined by endothelium interfaced with pericytes adjacent to a 3D ECM gel containing astrocytes and neurons derived by in situ differentiation of human neural stem cells91. This chip was used to model brain infection by the fungus Cryptococcus neoformans and revealed that clusters of the fungal cells penetrate the BBB without altering tight junctions, suggesting a transcytosis-mediated mechanism as well as providing a test bed in which to develop novel therapeutics.

Eye on a chip

An eye chip that reconstituted the outer retinal–choroid barrier containing human retinal pigmented epithelium adjacent to a perfusable 3D blood vessel network was able to recreate the choroid neovascularization associated with wet macular degeneration by demonstrating penetration of the retinal pigmented epithelial monolayer by antigenic sprouts that extended from pre-existing choroid vessels. This pathological angiogenesis was inhibited by the monoclonal therapeutic antibody bevacizumab, which is used clinically for this condition.

Furthermore, a retina chip was developed containing more than seven different retinal cell types, all derived from human iPS cells, which provided vascular perfusion and recapitulated interactions of mature photoreceptor segments with retinal pigmented epithelium. In addition to mimicking the formation of outer segment-like structures and establishing in vivo-like physiological processes of the eye (for example, outer segment phagocytosis and calcium dynamics), this organ chip reproduced the clinical retinopathy toxicities of chloroquine and gentamicin.

Blood vessels on a chip

Patient-derived renal cell carcinoma cells from multiple donors that exhibited patient-specific patterns of antigenic factor production. A similarly vascularized tumour chip revealed that

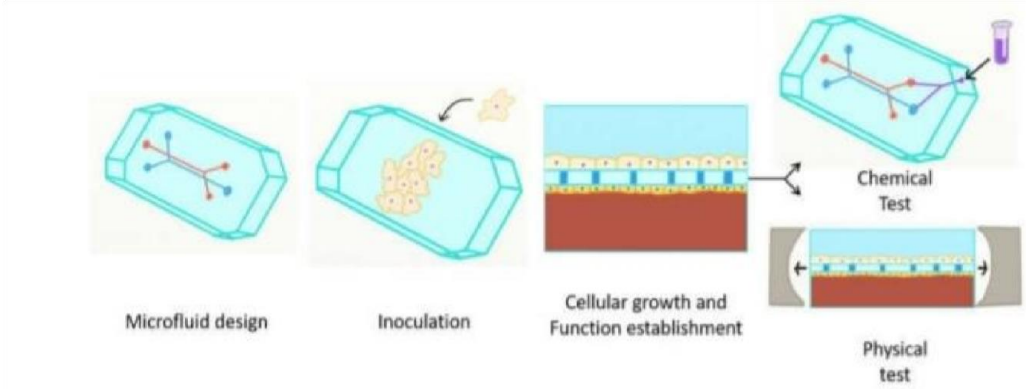
gene expression, tumour heterogeneity and therapeutic responses observed on-chip more closely model colorectal tumour clinic pathology than do current standard drug screening modalities, including 2D cultures and 3D spheroids. A three channel microfluidic device that mimics the vascular–tissue– lymphatic interface has also been developed to study lymph angiogenesis associated with cancer metastasis.

METHODS

In the beginning, microfluidics was implemented by industrial processes such as gas Chromatography and printing machines to handle small volumes to perform fast analysis with high Precision. Later, lithography from microelectronics was adapted to construct devices with medical Potentialities using various types of biocompatible materials. Verpoorte and De Rooij reviewed Developments that have emerged from the increasing interaction between the microelectromechanical Systems (MEMS) and microfluidics worlds. The incorporation of MEMS techniques to fluidic device Fabrication using photo-sensible polymers allows producing moulds by shading patterns with UV Light. This mould is then used to cast the pattern using a biocompatible polymer. The principal Characteristics of polydimethylsiloxane (PDMS) are transparency, flexibility, biocompatible, gas Permeable, etc. Through the high attention attracted towards microfluidics in the last two decades Led to the development of novel fabrication processes and the use of other materials. Despite The significant involvement of physics, the integration of other research areas such as chemistry, Biology, and medicine to labs-on-a-chip confronted researchers with new problems which made them Develop new microfluidic platforms. Replica moulding, along with procedures such as micro-contact Printing, casting, injection moulding, and embossing, encompass the techniques for manipulating Elastomeric structures. Some of the first approaches have used micro-contact printing, replica Moulding, micro-transfer moulding, micro-moulding in the capillary, solvent assisted micromolding, Phase-shifting edge lithography, Nano-transfer printing, decal transfer lithography, and nano-skiving. Since most techniques use polymeric or organic matter known by physics as soft matter, all together These techniques are known as soft lithography. Soft-lithography is a rapid prototyping technique Applied to generate micro and nanostructures. Generally, a low-cost polymer is used to build the desired pattern. Cell culture refers to the cell growth and maintenance of influencing parameters in a controlled Environment. In cell related experimental biological research at large, and cell culture technology, In particular, in vitro cell culture models are considered the backbone of the field. Based on Collected works evidence, several traditional approaches, i.e.

(1) culture in the flasks.
(2) culture in the Disflask
(3) Well-plates, etc.

Have been developed and have gone through heuristic optimization. The modern cell culture techniques such as microfluidics-based cell culture approach offer unique Potentialities to culture, maintain, and analyse the cultures in a more sophisticated manner at Micro-level. These interactions are not easily replicated or controlled in the traditional cell culture Layouts. As compared to the traditional cell culture methods, microfluidics-based cell culture Approach reveals a clear understanding of an interplay between cell culture parameters and the micro environmental elements which traditional cell culture methods fails to demonstrate on their Own. Furthermore, it is also believed that the controlled operational conditions at microenvironmental Level by microfluidic approach will further accelerate and advance the cell culture technology. With a variety of cost and resource benefits such as reduced consumption of reagents, smaller volume, And reduced contamination risk, microfluidics-based cell culture offers a unique platform for efficient High throughput experimentation. The microfluidics-based cell culture approach has several Advantages over traditional or macroscopic cell culture.



Applications of OOAC

Organ/Disease Modelling

In vitro modelling of disease pathways associated with several organs/organ systems has innumerable potential applications: analysis of organ anatomy, function, in-depth etiology of disease, the development of reliable diagnostics, and effective and well-tolerated therapeutic agents. Multiple organ models.

Pharmacology

A drug development process begins with early laboratory-based discovery stages and ends in the final marketing and surveillance once released to the industry. It involves five basic steps:

(i) drug discovery and development.

(ii) preclinical research.

(iii) clinical develop stp.

(iv) FDA review and approval.

(v) safety monitoring post-release.

This whole process takes a minimum of 10–15 years. If the investigated drug is not effective, incompatible with human metabolism, or has serious or fatal side effects, it results in substantial losses to both pharmaceutical and biotechnology companies. The rapid and accurate evaluation of drug efficiency as well as the impact of novel therapeutics on target sites and associated organs can be effectively monitored with OOAC models. In 2018, Seo and co-workers effectively engineered a blinking human eye to assess cornea therapeutic drugs to ward off dry eye disease. With this experiment, they identified novel mechanobiology aspects of the ocular surface.

Personalised Medicine

The expansion of precision medicine into other diseases, such as HIV/AIDs, hepatitis B, and other chronic conditions, will revolutionize patient care. Precision medicine will allow for the development of highly efficacious and personalized therapy, based on a patient's health history and genetic profile. Using health data and patient samples, the personalization of OOAC can be performed. Sample acquisition can be easily obtained via blood, urine, stool, and/or biopsy samples. Benam and co-workers formed a breathing airway-on-a-chip to study the pathophysiology of COPD and asthma.

Dentistry

According to a WHO report on 23 December 2020, more than 3.5 billion People suffer from oral diseases, a condition that has not improved from 1990 to 2017. Untreated dental caries in permanent teeth is the most dominant condition, affecting 2.3 billion people.Cristaine and co-workers developed an organ-on-a chip model system that links cells cultured on a dent in wall inside a microfluidic device that duplicates some of the structures and functions of the dentin–pulp interface. The tooth on-a-chip is made of moulded PDMS consisting of two chambers separated by a dent in fragment. To capture pulp cell responses to dental materials

on-chip, stem cells from the apical papilla (SCAPs) were cultured in an odontogenic medium, seeded onto the dentin surface and observed under live-cell microscopy. Standard dental materials used clinically were tested for cytotoxicity, cell morphology, and metabolic activity on-chip and compared against standardized off-chip controls.

CONCLUSION

In this article we have discussed about the detailed information about organ -a- chip concept including its types of OOAC and the method of fabrication of organ on a chip by microfluidics method and various applications of organ on a chip are elucidated and the strengths and limitations of organ on a chip (OOC) and its Discovery explained in detail. This review showed us the importance of organs on chip technology for the future of medicine: systematic use of organs on chips would help the pharmaceutical industry save time and money, and would limit the breeding of animals destined to clinical testing as well. The chips could also become formidable research accelerators, since they could allow to conduct many trials, much more rapidly, early in the research process. Although the use of the organs on chip technology was proven again and again, some of them already being used today in some cases, we are still far from making a proper human on chip.

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