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# Microfluidic Organ-On-A-Chip Models of Human organs in Drug Discovery

Shouvik Kumar Nandy[1*], Shikha Thakur[2], Sujata Saha[3], Kelsi A. Chhatrala[2], Aayushi Agarwal Bansal[2]

[1*]School of Pharmacy, Shoolini University, Solan, Himachal Pradesh, 173212, India
[2]School of Pharmaceutical, Atmiya University, Gurukul, Rajkot, Gujarat, 360005, India
[3]Burdwan Institute of Pharmacy, Purba Bardhaman, West Bengal, 713103, India

***Abstract :*** Recent years have seen a rise in interest in microfluidics phenomena as scientists have taken advantage of their special qualities to create better design options. Over the past few years, there has been an increase in interest in the application of microfluidic phenomena for tissue engineering and drug testing. Researchers have developed technologies that enable them to model the properties and functions of a wide range of organs on a microscale chip, mimicking the processes that occur in actual creatures. This article presents a logical approach to the subject and provides an overview of the latest technologies that are appropriate for organ-on-a-chip systems. The construction of synthetic or natural small tissues that can mimic physiological processes found in the human body is made possible by the use of microfluidic chips. They also maintain the tissue-specific functioning and control the microenvironments of individual cells. Advances in tissue engineering and microfabrication have allowed for the construction of organ-on-a-chips (OoCs), which have allowed researchers to conduct next-generation experiments and study human illness. Investigations into the effects of drugs on the human body are also being conducted. These abstract aims to provide an overview of the different Operating Systems (OoCs) components and help choose an OoC that is tailored to a certain application. If researchers have a greater understanding of the various components that make up OoCs, they can build applications in these sectors that are more effective and efficient.

***IndexTerms*** **- Microfluidics, organ-on-a-chip, Single- organ tissue functions, microfabrication and tissue engineering.**

## I. INTRODUCTION

Microtechnology and biology come together in the amazing technical marvel known as the organ-on-a-chip, or OoC for short (1). The convergence of organ-on-a-chip (OoC) and microfluidics technologies has transformed our ability to create sophisticated in vitro models that accurately replicate complicated physiological processes(2). The methods involved in bringing these two technologies together are the reason behind this (3). These platforms are being used more and more to study the functions of organs outside of the body for purposes including drug testing, disease modelling, and customised treatment. They are not only created to mimic the main characteristics of human organs, but also to replicate those characteristics. There is a remarkable connection between this and significant areas of human physiology and sickness (4). The term "Organs-on-Chip" (OoCs) refers to systems that are built inside of microfluidic chips (5). Real or artificial tissues are present in these systems. They are designed to control the microenvironments in which cells live and to hold onto the properties unique to different tissues so as to provide a more realistic representation of human physiology (6,7). This is done to give a more realistic representation of human physiology. Operating systems (OoCs) have drawn attention as a means of investigating medication effects on the body and human pathophysiology (8). This is due to the fact that OoCs offer a platform for carrying out next-generation experiments. This goal could be accomplished by combining the most recent developments in tissue engineering and microfabrication (9). It might be difficult for inexperienced researchers to understand what makes one OoC better suited for a certain application than another because there are nearly as many examples of OoCs as there are applications (10). The main goal of this primer is to give an introduction to the aspects of OoC that must be taken into account while creating an OoC that is specific to an application (11). This makes it feasible to do study on specific aspects of human pathophysiology and disease. The chip looks to be a small electromechanical device upon closer examination. This device uses a network of minuscule microchannels, nearly invisible to the naked eye, to handle extremely small amounts of fluid (from picoliters to millilitres) (12). The usage of microfluidic chips results in the creation of the OoC from incredibly small, individually generated tissues. This is an imitation of a few of the functions specific to different tissues that the chip can do (13). One technology that helps close the gap between different technologies is the OoC. It enables work with intricate cell cultures to be done in a more meticulously designed microenvironment that maximises the model. To circumvent animal experimentation, science must develop a compassionate in vitro substitute. It's plausible that the development of functional on-chip technology was fueled by a mix of tissue engineering and microfabrication (12). Compared to other approaches, this is more dependable and durable since it uses artificial structures to facilitate organ-like function. By using induced pluripotent stem cell (iPSC) technology, it is possible to increase the effectiveness of the organs of circulation (OoCs) personalisation process (14). Using induced pluripotent stem cells (iPSCs) derived from single donors, the procedure produces patient-specific cells that are then cultured in organs of culture (OoCs). It is therefore simpler to carry out research

on disease characteristics and treatment responses in a way that is patient-specific. Microsystem technology is the backbone of cloud computing, powering everything that happens. This product's naming is the responsibility of the integrated circuit manufacturing industry (15). This leads to the formation of lithographic pattern transfer, which enables the construction of structures in the nano- and micrometer-scale ranges. Lithographic pattern transfer is a microfabrication technique where micrometre features are transferred from a mould onto a silicone polymer, usually poly (dimethylsiloxane) (PDMS) (16). We call this process "lithographic pattern transfer." Microsystems technology is the fundamental driving force behind devices of interest with respect to their microfluidic and miniaturised actuator and sensor capabilities. Currently, it is possible to see the in vitro organ function on chips that have been specifically designed for the desired organ. To preserve and mimic the organ's function, customised chips replicate the cellular and extracellular characteristics of the organ. In turn, these characteristics are a reaction to the physical and biological mechanisms associated with the organ (17). On-chip culture devices, or OoC for short, are microfluidic culture equipment that mimic the intricate structure and operation of genuine organs. These miniature gadgets are made of a transparent, flexible polymer, and their diameter is comparable to that of a USB memory stick. These are hollow microfluidic tubes containing both human blood artery-derived cells and living human organ cells (18). The purpose of these tubes is to investigate human organs. Three-dimensional live cross-sections of human organs describe the internal workings and the potential effects of drugs on specific organs. Human organs are shown in these cross-sections in their native condition. Neither humans nor animals are involved for the sake of this conversation. Living cells and tissues are lined inside the hollow tubes to simulate the physiology of individual organs (19). This enables the simulation to be performed by the tubes. As a result, real-time investigations of the metabolic, genetic, and biochemical processes occurring in individual cells are now possible. A microfluidic cell culture method called organisms of culture (OoC) replicates the physicochemical microenvironment of human bodily tissues (20). It is a microfluidic system with controlled parameters (velocity, flow, etc.) that are similar to physiological parameters.At its core, the idea of an object of consumption is the notion of a "minime" or a customised chip. This organisation uses a method similar to a patient's to assess various medications (21). This means that the patient is not hampered in any way, and it is easy to decide whether the drug is acceptable. This makes it possible to choose the course of treatment that is most appropriate for the patient.

## II. EXPERIMENTATION:

OoC is designed to offer an in-vivo environment that leads the collection of cells to assemble as three-dimensional tissue that can duplicate one or more organ level functions (22). This is accomplished through the design of OoC. Organotypic tissue can also be cultured in this way to have its function preserved (23). The development of these systems for specific applications in drug research is provided by a variety of case studies for single-organ and multi-organ OoCs. These case studies offer insight into the development of these systems. For the purpose of modelling the pulmonary alveolus, the Wyss institute carried out Oo (24). The researchers at the institution developed a novel microfluidic model of the tiny airway of the lungs that replicates important characteristics of both asthma and chronic obstructive pulmonary disease (COPD) (25,26). This microengineered human lung small airway contributes to the research of lung inflammatory illnesses over the course of many weeks in chips coated by cells from both healthy donors and patients who are afflicted with the disease. This assists in gaining a better understanding of the processes that underlie illness, as well as screening for potential novel therapies. Kim and Ingber came up with the idea for a gadget called a gut-on-a-chip. With the use of this chio, Caco-2 cells were able to be subjected to physiological mechanical stimuli in a continuous manner (27). These stimuli included shear stress and cyclic mechanical strain, which are similar to peristalsis that occurs in life. It was shown that when these physiological conditions are present, cells that have been grown with the device are reprogrammed to undergo spontaneous three-dimensional villas morphogenesis and small intestine cell differentiation. Sandwich cultures and three-dimensional spheroid cultures are maintained as monocultures (28).

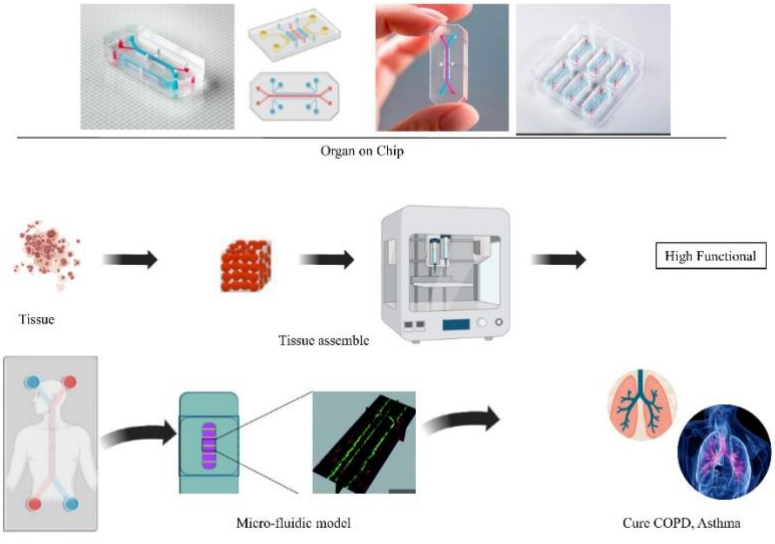


Fig 2- *In vivo* Experiment

## III. EASE SINGLE- ORGAN TISSUE FUNCTIONS

The liver's cell source and the cultural makeup of the liver's OoC account for the device's capacity to mimic some of the liver's functions. In-vitro liver models should be able to express both Phase I and Phase II metabolising enzymes (ex-CYP450, UGT, and

GST), as well as biliary excretory activity and albumin synthesis (2). The levels of albumin secretion and CYP 450 activity should be similar to those of recently cryopreserved human primary hepatocytes (29). Hepatocyte monocultures in 3D spherical and sandwich cultures maintain metabolic and synthesis functions for a duration of 3–7 days. They perform hepatocyte ventricular depolarization and biliary excretory activities. It is necessary to co-culture non-parenchyma liver cells, such as hepatocytes, granulocytes, and liver capillary endothelial cells, in order to enhance bile excretion and sustain metabolic and synthetic activities for a longer duration (about 14 days) (30,31). Because non-alcoholic fatty liver disease and liver cancer include inflammation and fibrosis processes, these OoCs are helpful in simulating liver disorders and in predicting liver-specific functions that are critical for predicting human responses in preclinical testing (32,33).

The OoC model was used to study pancreatic cancer (32). Transparent, pliable plastic chips with integrated microfluidic channels were utilised by the scientists. To simulate the behaviour of the disease, they used human endothelial cells in the adjacent channel and pancreatic cancer cells produced from mice in the first (34). The analysis of the chip revealed the behaviour of the cells. Mouse cells were used in the prior experiment, but human cells were used instead. This demonstrates that the illness acts the same manner in all species. This suggests that any drug that benefits test subjects such as mice will presumably benefit humans as well (35). It was found that administering the experimental treatment to the chip's cells prevented the cancer cells from spreading (36).

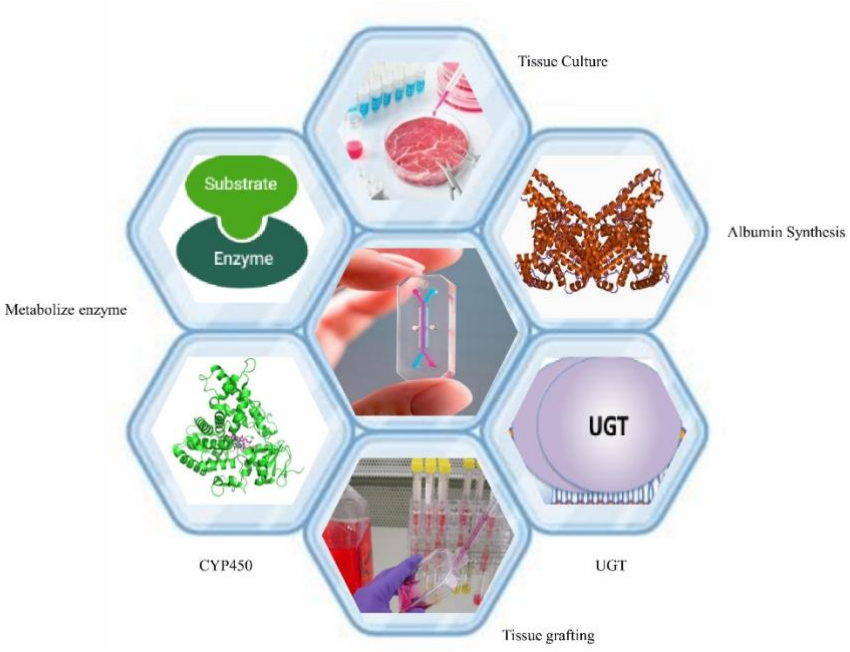


Fig 3- Function of Ooc

## IV. HEART

Cardiovascular diseases are a significant global health concern, affecting the heart and blood arteries. Current research relies on ex vivo rodent and in vitro human cell culture models, but these models have limitations (37). Animal models often fail to replicate human reactions, and traditional cell models fail to consider in vivo environments, intercellular communication, and tissue interactions (38). The convergence of microfabrication and tissue engineering has led to the development of organ-on-a-chip technologies, which combine microfluidic chips, cells, and extracellular matrix to mimic physiological processes in specific anatomical areas. This method is considered a promising bridge between in vivo and 2D or 3D cell culture models. The advancement of vessel-on-a-chip and heart-on-a-chip technologies could provide crucial insights for future cardiovascular disease research (39).

## V. BLOOD BRAIN BARRIER AND NERVOUS TISSUES:

The BBB maintains homeostasis while shielding the brain. CNS-affecting drugs need to overcome this obstacle (40). The BBB OoCs are split into two compartments by a thin membrane. The vasculature's compartment is lined with brain endothelial cells. The brain compartment is composed of astrocytes and pericytes (41).

## VI. SPINAL CORD OOC

Blood-spinal cord barrier simulations are performed using BBB chips. Spinal cord OoCs contain cells that can differentiate into spinal motor neurons, such as spinal neural progenitor cells derived from iPSCs (42). The technique used to produce the brain on a chip is called ultrasteplithography. The soma and axon are separated by this. BoC approved studies on axons, their regeneration, and the use of different drugs to treat them (43). The models that are created are used to study neurodegenerative diseases, understand behaviour, and ascertain the impact on brain cells. Using a patient's cells, researchers developed a chip to investigate lateral amyotrophic sclerosis. This method improved our understanding of the condition. This method could be used to test new drugs. They observed that the neurons on the device were firing. This concluded that investigating the problem with a microfluidic chip was relevant (44).

## VII. CONCEPTUALIZATION AND DESIGN

Biological authenticity can be achieved in single-organ systems. This allows evaluation of the response of a specific organ to a drug or combination of drugs. Multi-organ systems investigate possible relationships between one organ and a minimum of one additional organ (45). This occurs through the interchange of soluble signalling molecules, or metabolites. In this case, human or animal features are simulated by the use of micro scale culture (4). Systems with a body-on-a-chip are multi-OoC systems. This mimics the typical systemic response of the body. Only the necessary functions of the system—which provide a good model for the physiological process—are taken into consideration when making this selection. Single-OoCs are more biologically realistic representations of an organ, while multi-OoCs are less accurate tissue models that focus on the linkages between organ systems in the developed OoC systems. The top and bottom approaches control the formation of functional tissues inside the OoC (46). The top-down method, sometimes referred to as the organotypic approach, makes use of primary tissue such as organ slices from a biopsy or artificial tissues such as prefabricated organoids that are included into the OoC system. A bottom-up approach is used to extract isolated cells from primary, immortalised lines, or sources produced from stem cells. This is being raised in an initially empty microfluidic environment. This promotes the cells' transformation into a functional neotissue. This organises and supports the cells of the OoC (47). Routing fluids, like culture medium, link tissue components in a manner that mimics in vivo connection. OoC benefits from microfluid control. This is limited geometrically to very small volumes of fluid in the nanoliter region (48). The liquids are held within minuscule conduits that range in size from tens to hundreds of micrometres. Subsequently, this technology may make it possible to develop personalised medicine methods that effectively cure individual patients by using their own cells (49).

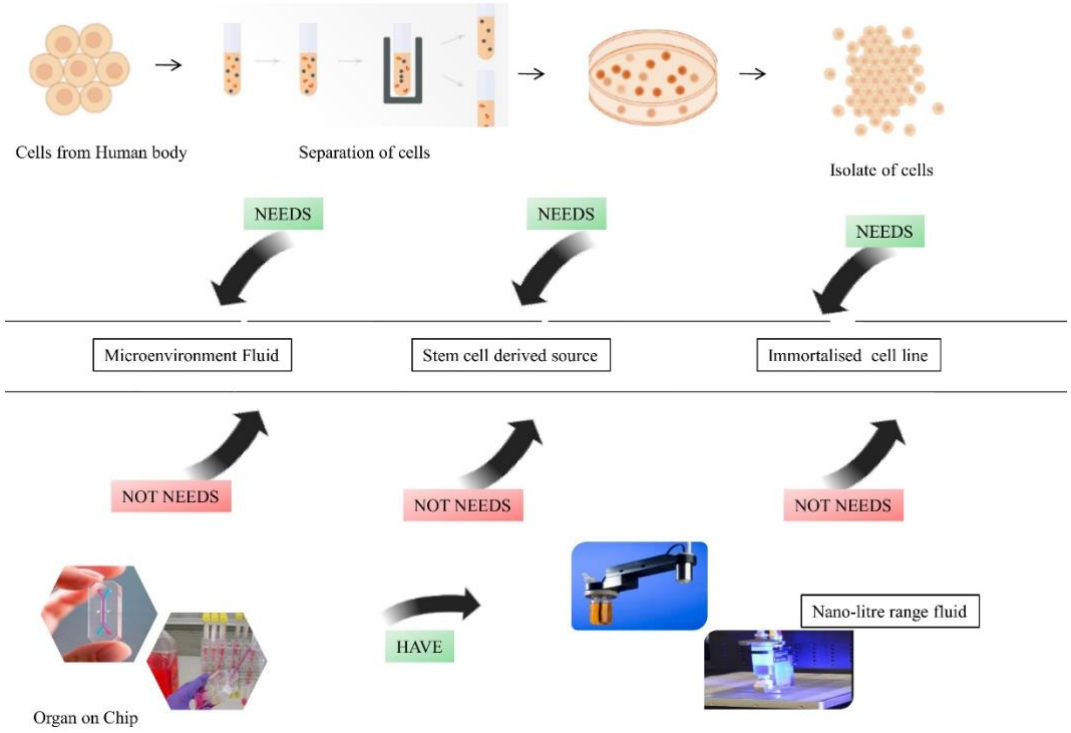


Fig 4- Conceptualization and design of Ooc and normal isolated cells

## VIII. OOC DEVICE ARCHITECTURE:

Two types of OoC device architectural differences can be distinguished. First is the solid organ chip. Tissue masses of 3D-cultured cells are interacting with the selective media and one another in this instance. Micro-pillar and microwell clusters, which are utilised in the OoCs of the liver, tumour, heart, and fatty tissue, are two examples (50). Barrier tissue chips are present in the second one. In this case, the device's design promotes the cells' spontaneous formation of an interstitial fluid barrier. This allows only specific operations to cross the barrier. The most common targets for these structures are the OoCs of the skin, lungs, and stomach. Solid-organ chips: The mesenchymal or parenchymal organ tissues are comparable to these Organ-on-a-Chip systems (51). The liver, pancreas, tumour, bone, and cartilage are a few examples. When cells are grown as a three-dimensional (3D) tissue mass or submerged in an extracellular matrix (ECM) analogue, they can interact with the culture substrate, the medium, and each other directly in a defined manner. Barrier tissue chips are organ-on-a-chip structures that mimic the gut, vascular endothelium, corneal, and epidermal tissues, among other tissues' endothelium and epithelium. This role acts as a living barrier to regulate the active and/or passive migration of molecules. Cells are frequently attached to the porous surface dividing two separate compartments (52).

## IX. Material used in OoC:

The material selection is influenced by the final device's functionality, microfabrication, readouts, and biocompatibility. A multitude of material combinations are used in the construction of a conventional OoC device. silicon rubber, such as the silicon and carbon-based synthetic polymer poly (dimethylsiloxane, or PDMS) (53). Throughout the production process, liquid PDMS is mixed with a material that facilitates PDMS solidification. Subsequently, the slurry is formed into the desired shape by placing it within a mould. The materials used are glass, thermoplastics such PS, poly (methyl methacrylate), polycarbonate, or cyclic olefin copolymer (COC), and glass. Because PDMS is transparent, users can see through it. The material used in OoC shouldn't have an effect on the cellular microenvironment. It needs to maintain a strong, fluid link. The human OoC is a microfluidic device lined

with human live cells that is used for drug discovery, sickness modelling, and customised therapy (54).

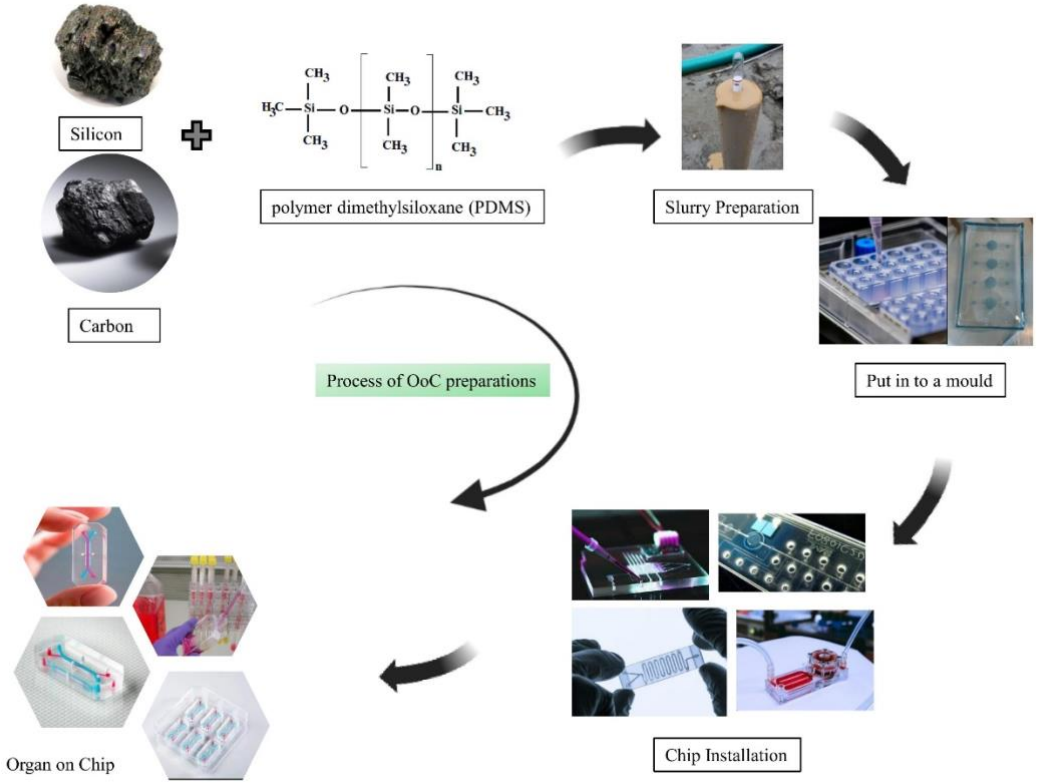


Fig 5- Ooc preparation

**X. MICRO FABRICATION:**

Chips on OoC were made using the first manufacturing process. This is a better method of photolithographic etching, which is used to create microchips for computers. Proteins and cells can be patterned using photolithography technology (55). Another method for creating micro fluidic culture systems is soft lithography. This is a substitute method for photolithography. It patterns surfaces that are required in biology. Patterns etched into silicon chips can be replicated in more flexible and biocompatible materials via soft lithography. In order to create this unique chip, a liquid polymer, such as poly-dimethylsiloxane (PDMS), is poured onto an etched silicon substrate created using soft lithography technology (17,56). This polymerizes into an optically transparent material that resembles rubber, forming a "stamp." Next, the polymer block's two ends are opened in order to fill the fluids. The ECM substrate is adhered to by the cells that flow into the channel, and culture media is then constantly infused into the channel. Systems for PDMS culturing exhibit optical clarity. It enables high-resolution optical imaging of cell responses to external stimuli in real time (57).

**XI. CONCLUSION:**

There have been a great number of novel discoveries made in the process of drug discovery as a result of the developments in OoC. This method is useful in the research of disease as well as in the testing of drugs because it takes into account the intricate interactions that occur between various cell types and their surrounding environment. Single organs of consciousness have been developed for virtually all organs. A number of different OoC devices are currently being investigated. The monitoring of the physiological indicators is made possible by the incorporation of sensors into the chips. In addition to the potential adverse effects that may be seen in other organs, it has been discovered that medications that are effective in treating a particular disease can also aid in the recovery of other organs23. It is through this method of work in OoC that rapid progress in drug discovery is made possible, as well as through the assistance of preclinical research and the testing of therapies.

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