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ORGAN ON A CHIP TECHNOLOGY

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Abstract: A micro-engineered synthetic technology which replicates the makeup and functioning of living tissues is known as an "organ on a chip." Using a small system that blends technology, cell life, and biomaterial technology. A number of experimental examples using various organs, such as skin, gut, heart, liver, or airways upon chips, were successfully constructed. The United States Food and Drug Administration (FDA), which showed faith in this innovation, is working with other groups and businesses who use its contents. The Organ-on-a-Chip algorithm's theories and applications—including the creation of medical designs, drug evaluation, toxicity, pathophysiology studies, effectiveness examination, and virology—are covered by this overview. Considering the challenges posed by the present COVID-19 outbreak, it is projected that merging numerous organs-on-chip components to one body-on-chip system will prove required for detection and treatment. It is projected that demand for manufacturing organ-on-chip systems would increase quickly.

Index Terms **- Microfluid cell, FDA, COVID-19, Biomaterial.**

I. INTRODUCTION

Innovative en-vitro micro-scale synthetic system Organ in a Chip (OOAC) replicates to living tissue by integrating the study of cells, technology, and the chemical science to mimic the biological setting of living tissues [1]. While in person research on both mammals and humans is frequently utilized for investigating physical mechanisms, during the last two decades, a number of additional techniques were also investigated. These include algorithms or two-dimensional as well as three-dimensional in the laboratory modeling. In 2011, while the leader of the United States announced the start of an investigation of "an individual microchip" with US scientific companies, scientists' people around the planet became drawn to this concept. It has the advantages of unity, low usage, miniature size, and accurate regulation of variables including liquid shear pressure, organ-organ connection, and tissue-tissue interaction [2]. It was shown that a drug development technique works exceptionally well for organ-on-a-chip systems. It includes pharmacological investigation, hit to lead optimizing, identifying, examination, physiology, or toxicology investigations [3]. Since its inception in 2006, the generated a pluripotent (iPSC) method has increased in prominence as a trustworthy source of different human tissue for a variety of tissues, such the renal system, spinal column, brain, and heart. Ross Harrison is associated with creating 2-dimensional cultivation of cells and his work on the growth of neural tissue dates back to 1907. The "L" line of cells and a human HeLa cell line from an individual with cancer, each created in the latter part during the 1950s onward remain at the cutting edge of cell cultivation study today [4]. The foundation of the study of human biology, embryonic generation, illness studies, cell communication, body scans, drug development, toxicity, and drug absorption has come from two-dimensional cell cultivation from the beginning of the twentieth century [5]. However, it's not without certain drawbacks as well, such as being unable to replicate the real in vivo situation when the extracellular framework increases interactions between cells even more. The highly organized, non-monolayer units of organs communicate with others, causing one cell to physically push on next. As such, the true anatomy of the body is not accurately represented by 2D units. In two-dimensional traditions, gravitation has no impact on the cells. Additionally, 2D growth does not have divisions of living cells to assess drug effectiveness and cellular infiltration. As such, the

laboratory was unable to offer an accurate setting for the development of drugs [6]. In addition, it is generally accepted that many new drug trials encountered failures at the stage III stage of research due to cytotoxicity or ineffectiveness, and hurt the financial picture of the procedure for discovering drugs [7,8]. The 2D grown lymphocytes exhibit abnormalities with the cytoskeleton, abnormal cell shape, as well as abnormalities in their nucleus composition [9,10]. If tissues within a two-dimension growth receive exposure to identical volumes of liquids with oxygen revoked, a huge cell count has to be produced to depict tumors when oxygen levels and nutrients are significantly lower in the interior layers compared to the outermost ones [11] . The current condition of cells, wherein any cells are in various phases of their development and their cycle, is not precisely captured through 2D grown cells that are always expanding. Expansion of 2D cell cultures has been challenging. Not noting the stressful state of these cells in 2D, which has a major downside [12]. The development of 3-dimensional cell cultivation technologies accelerated in the latter half of the twentieth century. Recent developments in 3D cultured design as well as technology have made it possible to depict processes in biology accurately. Modern innovations, nevertheless, often present entirely new difficulties. There have been a lot of reviews on 2D tissue, the scientific field has been educated in 2D cell cultivation, imaging methods have been developed, screening cells through the direction of x and y is easier than doing 3D images, and conducting a 2D cultured is less inexpensive. The fact that 3D imaging increasingly mimics the natural world and makes it possible to precisely study cell-cell or cell-ECM (extracellular membrane) connections is just one of the many advantages it offers. research on the use of 3D cell cultivation to create drugs and treating cancers the increase in precision [12,13,14]. Also, 3D cell cultivation helped science become less cruel by reversing the usage of models from animals. Greater connections exist across 3D models of cells and gene transcription studies [15,16,17]. Fig. 1 shows a graphic representation of an organ-on-a-chip method, a 2D culture of cells, and a three-dimensional cell culture. There are various 3D cell culture techniques that fall into the scaffold based or scaffold-free categories. Organoids, philic glass fibre, hydrogel-based assistance, polyamide solid material-based assistance, and hydrophilic glass fibre are some examples of the scaffold-based designs, all having specific uses, benefits, and drawbacks. Such non-scaffold-based methods include levitation using magnets, dangling dropping microplates, and ellipsoid plates using extremely low adhesion coatings; all offer advantages and disadvantages [18].

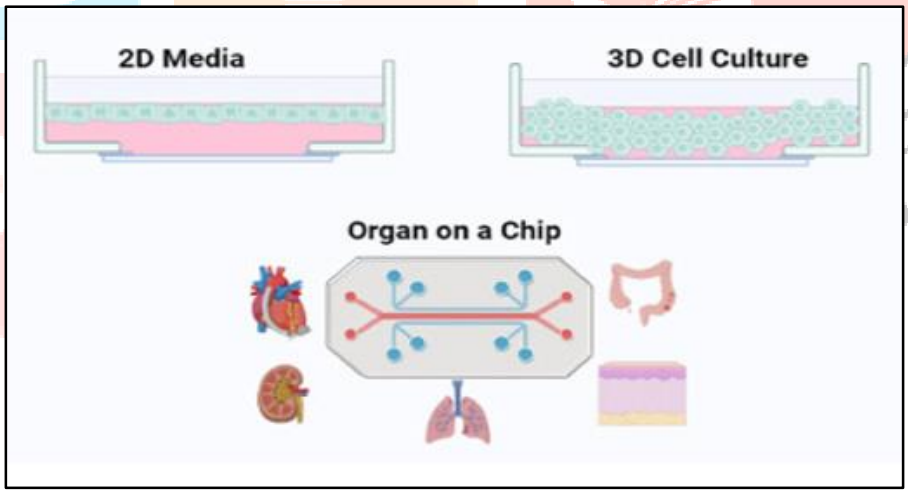


Fig 1: The two types of cell culture, the organ-on-a-chip concept, and its appearance

It can be difficult to remove 3D models using the matrices/scaffolds utilized because they could include unfavorable infections or substances produced by people [4,19]. They suffer with batch-to-batch variation, and nucleic acid and protein separation in 3D cell cultivation is much more difficult [19]. Additionally, for cytometry studies requiring individual cells, 2D cultured cell droplets are suitable. The most recent development, which replaced the use of 2D produced static cells in 3D cultivation, is its integration with tiny pumps to produce cellular-based detectors on a chip. This was followed by the development of a body on a microchip [20].

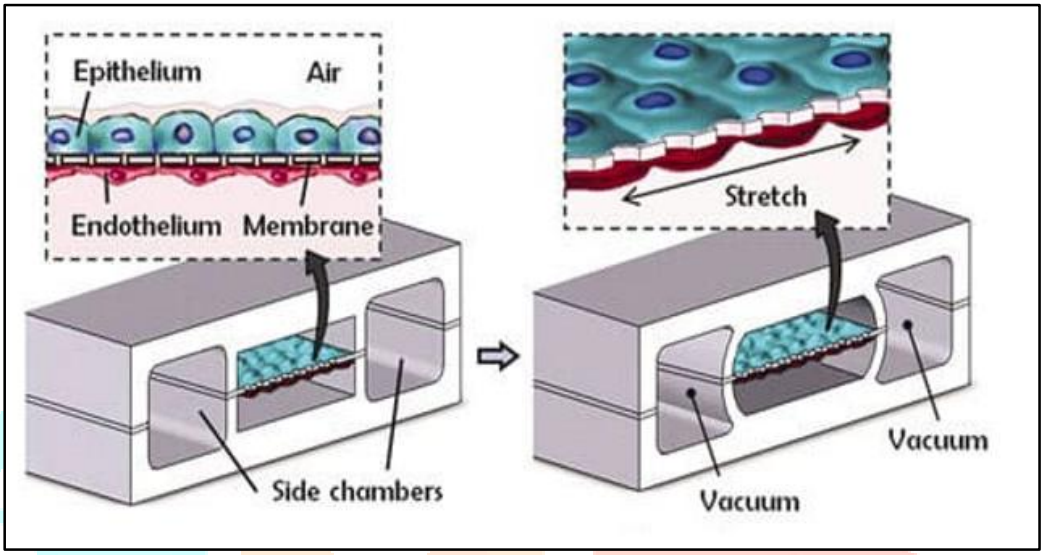
The different type of organ on a chip

Lungs on a chip

The invention of fresh lung medicines is currently a priority healthcare objective. The 3rd greatest reason for mortality globally is predicted to move from heart disease to respiratory illnesses by the end of 2020 [21,22]. In such a scenario, we might think about placing organs on chips to create novel medications. As of today, we remain unable to duplicate an entire lung in a microchip. However, [23], Huh et al. The alveoli-capillary

membrane itself, the tiniest functional element of the lungs, was properly duplicated. That organ is crucial to the evaluation of new pharmaceuticals since it acts as the human body's physical wall from the external world. This membrane was replicated using polydimethylsiloxane (PDMS), which was encased in protein for better cell adherence. On the other hand, cells of the endothelial cells that came into contact with a solution made of micronutrients in the form of blood were separated from cells of the epithelial layer in interface with the air.

Jain et al. [24] additionally carried out the study in order to as closely mimic a real lung as feasible. using blood as opposed to a nutrient fluid. The main advantage of hearts on chip over traditional cultivation of cells is that 2 unfilled small channels are placed across each micro route to simulate the contraction cycles experienced by the alveoli-capillary membranes encountered while inhaling.



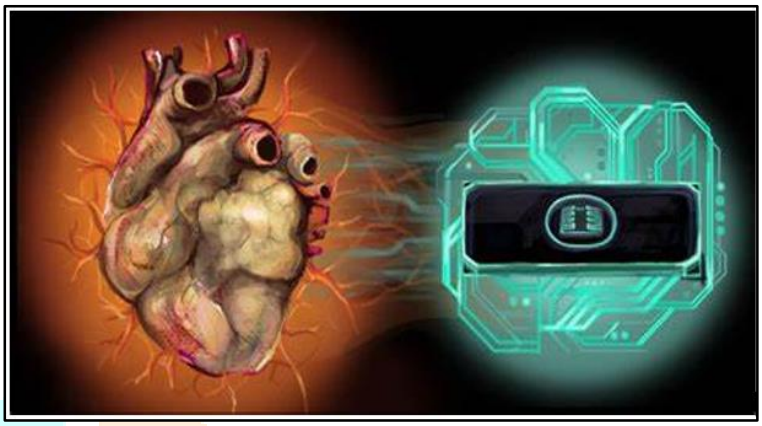
Liver on chip

During the investigation of innovative drugs, a liver-on-chip must be developed. The hepatic is the primary factor in the failure of potential medications following the laboratory testing period [25,26]. It may be possible to save a tonne of money by using livers-on-chips. The maintenance of liver cells within an incubator, nevertheless, may prove difficult [27]. It was important to learn how to replicate their habitat so they could live longer. According to Yang et al. [28] research, liver cells multiplied and their rate of metabolism rose when mixed with mesenchymal tissue cells of the human foetus. System optimization depends heavily on the ratio of both of the distinct kinds of cells. A liver-on-chip has to be created in order to investigate novel medications. They utilized Di electrophoresis to duplicate a liver's lobule, the organ's functioning unit—on a micro microchip. This lobule is made out of liver cells and cells of the endothelial system. The key advantage of the liver's function on chip is its capacity to replicate tiny aspects allowing greater accuracy investigations [26]. The liver-on-chip is necessary to multi-organ on a chip, which we will discover soon. But these continue to be improved: PDMS, which the material employed by Chen-Ta et al., has become the object of severe condemnation. It sometimes collects tiny hydrophobic compounds along with certain drugs that can have an impact on test results. The most recent discoveries of polyurethane-based polymer compounds, nevertheless, are free of this drawback. These share PDMS' attributes of transparency, biocompatibility, usability, and more, and could soon replace them [27].

Heart on a chip

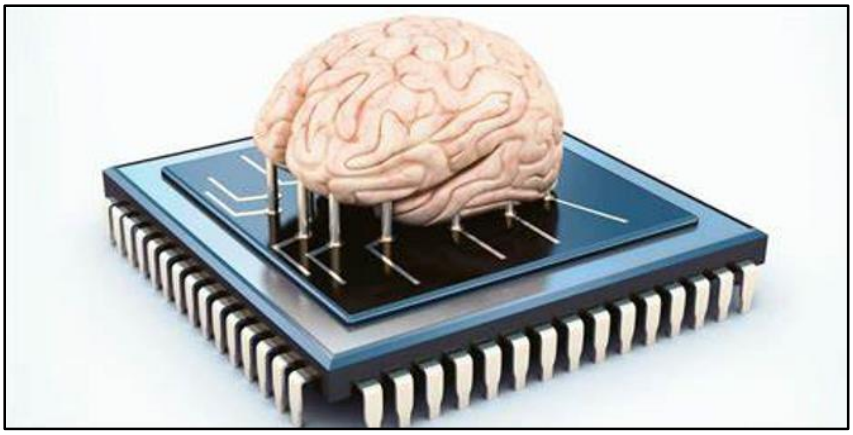
Heart on chip were created as a result of the significant disparities among animal and human cardiac cells. They aim to comprehend cardiac disorders and the cardiopulmonary effects of pharmaceutical treatments. In comparison to traditional cultivation of cells, microfluidic devices have made it feasible to obtain more relevant morphometric and electrical data [29,30]. The small devices may turn out to be the best method for examining prospective therapies for coronary artery disease. The chips may turn out to be the best method for examining prospective treatments for heart disease. Many hearts on chip are being developed at the moment for a range of purposes by various study groups [31]. It knows about how the ions of calcium are regulated by heart cells. Changes in the ions' concentrations are consequently frequently linked to arrhythmia or coronary artery disease [32,33]. Martewicz et al. [34] have shown that variations in the amount of calcium ions may be observed while cells from the heart packed in Fluo4 near a situation of hypoxia using a cardiac-on-a-chip and laser photography.

Agarwal et al. [35] investigated isoproterenol off a rat cell-based cardiac on-chip to see if it might treat arrhythmia or heart failure. Despite being conducted on other than humans' cells, the experiments show the ability of heart on chips to assess a wide range of medicine levels in doses that vary from one micron to 0.1 millimeter in diameter. The final outcome agreed using previous findings made with a real, living mouse. This instance shows the microchips' dependability as well as their additional benefits. To keep making hearts, new diseases such an ischemia cardiac have to be invented on chips. Furthermore, the poor cell attachment of PDMS is a severe defect [36]. This is always a serious issue that necessitates chip updates. Although Annabi et al. addressed the problem by coating the PDMS with a thin film of gelatin to promote cell adhesion again around.[37]



Brain on a chip

Scientists have effectively simulated a small section of the brain-blood barrier using a microchip. It protects the cerebral cortex against infection in the circulatory system stream while only permits what nutrients the brain needs to pass via serving an essential function. Some medical interventions may face difficulties because of this obstacle since it may hinder active compounds (such those used to treat Parkinson's illness disease) from getting to the mind [38]. It is essential for interacting with human tissue because, like the coronary arteries, the connection between blood and brain can be very different between people and other species. The brain-on-chip model has an advantage over existing in vivo and in vitro models due to its more accurate proportions and structure. These microfluidic devices may be used to test the velocity of an epithelial liquid [39]. It allows for the correct division and growth of neurons and mimics the circulation of blood. Brains in chips have outperformed static culture at forecasting barrier between the brain and blood porosity [40,41]. Dauth et al. [42] have also developed an that might be utilized to simulate neurological disorders in environments that are quite like those encountered in in vivo studies. Despite the fact that the barrier between the brain and blood microchip technology remains in its infancy, there are now many variations accessible [40,41]. To explore unilateral amyotrophic sclerosis, which a group of scientists, for example, developed a chip from the cells of an individual. They may use it in the years to come for trying out new drugs and it will help researchers better understand the sickness. As proof of the usefulness of this capillary chip and a device for illness study, they additionally showed the cells' activity on the chip [35]. However, the number of brains on chips can differ significantly amongst study teams [42]. If this indicates the adaptability of tissues on chips, it saves academics the time-consuming task of comparing their results to those of other groups, which would slow up their studies. It would be fascinating to develop a single, all-encompassing model at some point to represent the barrier between the bloodstream along with additional cerebral sub-organs.



Gut on chip

The last tissue discussed is the gastrointestinal tract on a semiconductor, and it has especially one unique application. Kim et al. developed a two-layer gut-on-chip system that is comparable from the lung-on-chip we talked about before. Similarly, to a lung on a microchip, the use of microfluidic components in this application was essential since it made it possible to replicate mechanical stress and peristaltic motion [43]. At a Wired Health event in May 2016, Gerald Hamilton (President & CSO of Imitate and the other author in the Kim et al. paper) presented a use case for this gut-on-chip [35]. They developed a stomach on an implant using stem cells that came from an individual who suffered from digestive issues in order to study how it reacted to different diets and modern therapies. This instance demonstrates how individualized care might seem with organs on chips. Since the gastrointestinal tract is a vital organ for absorbing drugs, such knowledge would help us comprehend these issues more fully and improve research.

Intestine on chip

The design of an organ-on-a-chip is essential for drug testing. Oral medications are primarily taken in the tiny intestines, where they then permeate throughout both barriers—the mucus layer and the epithelial cells that are part of the gastrointestinal wall. A number of factors must be taken into account when creating a complex model of a colon on a chip, such the biological composition (mainly intestinal cells and goblet cell), structural elements (villi plus mucous), and the dynamic components (intestinal actions, known as peristalsis). Kimura et al. created an intestinal model with two separate circuits and a semipermeable barrier [44]. wherein cells get introduced and developed. At Harvard University's Wyss Institute, an identical approach was employed to build a "gut-on-a-chip" that also regularly expands to mimic the peristaltic activity of the intestines. Furthermore, within this particular organ on chip, the researchers were capable of growing regular gut microbes [45].

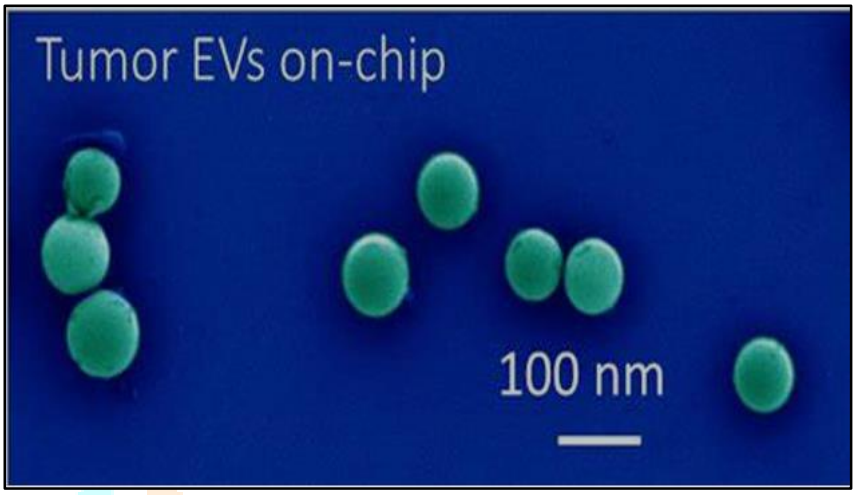
Muscle on chip

The muscles of the skeleton are crucial in diabetic because they play a substantial role in glucose regulation. On-chip muscle models require structural parts (myotube orientation and assembling into sarcomeres) in order to produce contractions in the muscle. Myotube orientation on a chip was achieved via rigidity or platform imprinting. Kaji et al. [46] utilized a tiny transistor array to manually regulate each myotube in order to demonstrate the correlation among glucose absorption and myotube contraction.

Tumor on chip

As a consequence of the efficacy of organs, researchers have started to make tumors on chips. The goal is to recreate the microcosm where tumor cells communicate on a both chemical and physical level. It will then be possible to study the length of time malignant cells live and proliferate. Compared with other chips, study on reproducing tumor habitats is progressing much more swiftly; multiple articles have been published on this subject [43,47].

Numerous tumors on chips were produced in order to assess new treatments at different doses [37]. Kim et al. [48] developed an independent, configurable system to determine the appropriate concentration. Their method's efficacy was established by administering doxorubicin and mitoxantrone together to cells called PC3 (prostate cells with cancer). The importance of such tumors on chips in studies on cancer will be covered in greater detail with examples in the part that follows as they are especially fascinating when linked to various organs.



Kidney on chip

The strain experienced by the cells in the kidney is far lower than that of endothelial or cells in the lungs. The original Kidney on its chip design consisted of two separate compartments: 1 represented the interstitial cavity, while another essentially represented the bladder tract and housed flow of fluid. Rat cells with tubes were utilized in the device [49]. A fluid kidney-on-a-chip device was developed in the year 2013, according to Jang et al. Numerous basic cilia, which the production of sodium-potassium Exchanger and the aquaporin 1, protein intake, and reabsorbed glucose might all be clearly shown in the framework [50]. The microchips have been effectively employed in nephrotoxicity caused by drugs study [51]. The effects of the medication's gentamicin as sildenafil A, and cisplatin on permeability of membranes and drug-induced cytotoxicity were investigated [52]. In a single investigation, adult humans the podocytes created from humanity inspired embryonic cells that might mimic albuminuria brought on by Adriamycin [53]. were utilized to measure the function of the glomerular system. In certain organ-on-a-chip models, the kidney has also been implemented; more information is provided below. A type of renal visceral epithelium known as a podocyte controls the dimension and weight of plasma proteins, acting as an obstacle to them. A podocyte damage may lead to proteinuria. Podocytes on a microchip have been the subject of studies, however the method is challenging since complicated culture is required [54].

Skin on chip

Artificial juvenile stem cells (iPSC) or readily accessible rebuilt tissue from the skin (EpidermFT, Episkin) were the origins of cutaneous cell types [55]. The skin's dispersion testing, toxicity research, effectiveness testing, healing of wounds, inflammatory processes, restoration, aging, and stress fracture studies have all made use of skin-on-a-chip systems [56]. Kim et al. studied the anti-aging capabilities of turmeric and Q10 coenzymes utilizing a pump-less skin-on-a-chip system [57,58]. Skin-on-a-chip technique was created by Wufuer et al. to study the structural as well as functional features of the skin. In the model, TNF- was utilized to imitate skin edema and inflamed whilst levels of cytokines were examined. The structure of which is depicted in Figure, was utilized to research the steroids drug dexamethasone's anti-inflammatory abilities [59].

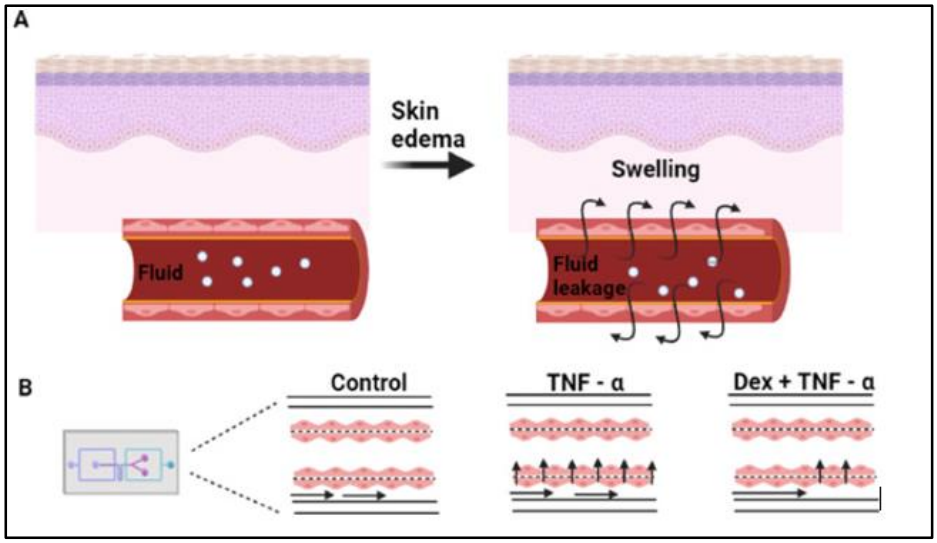
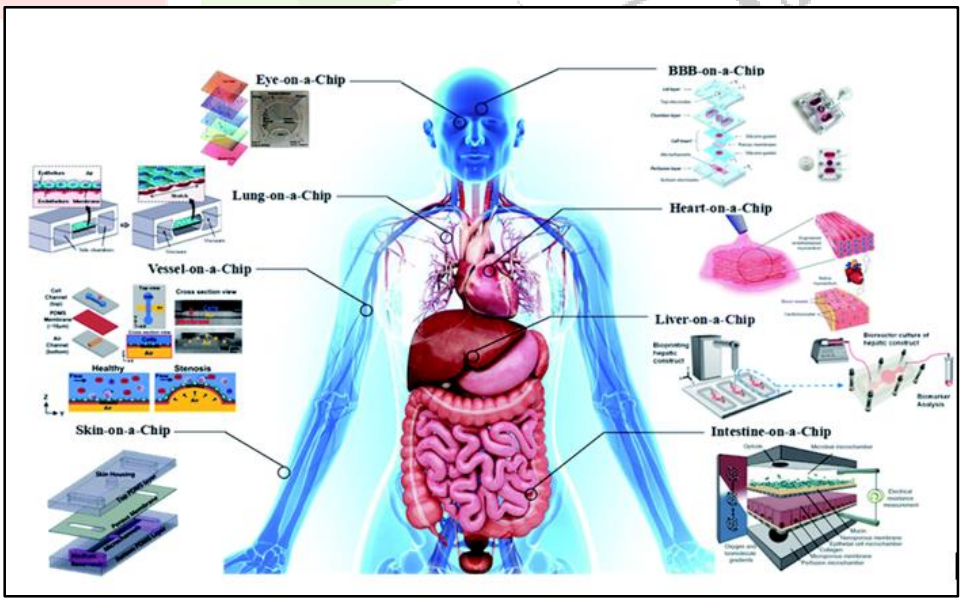


Fig (A) Diagram of the human epidermal edema method, (B) TNF-induced inflammatory destroys junctions that are tight, causing blood leakage and dexamethasone effectiveness testing [59].

Utilizing an organ-on-a-chip system, Sriram et al. investigated the impact for the fibrin-based skin material on barriers performance and squamous development [60]. Several studies have examined the efflux transporter's function, permeation, and relationship with drugs in relation to epidermal layer dispersion investigations [61,62].

Multi organ on chips

It is crucial to link all of the tissues in a multi-organs-on-chips structure in hopes of either permanently substitute the use of animals or to generalise personalised treatment, especially if developing hearts on chips and tumours on chips have proven beneficial in evaluating particular treatments. When developing a novel medication, it's crucial to make sure that it won't affect the body as a whole. For example, the major organ is frequently linked to a liver on a chip during drug testing in order to assess the drug's hepatotoxicity [37]. His is the circumstance as described in the paper by Midwood et al. [63]. These multi-organ systems have rendered it feasible to evaluate four tumour therapies' efficacies, as well as metabolic and uptake [64]. Imura et al. sought to comprehend the movement of samples tested in the arrangement. breast cancerous cells mixed with intestinal and cells found in the liver. A decade later, they improved it by adding acid from the stomach to simulate the gastrointestinal absorption of an oral drug [65].



As shown by the prior instance, tumours on chip can be used to evaluate the efficacy of treatments for cancer. Yet, those multi-organ combinations have additional uses as well. For example, researchers have used an excellent quality lens to enable the observation of live cancer of the breast cells that have metastasized in fractures [66]. The technique was also used by Xu et al. to monitor cancer of the lungs spread [67]. As we mentioned above, the development of multi-organs on chip has allowed for the testing of already approved

pharmaceuticals and the advancement of anti-cancer studies. Before they may entirely substitute testing on animals in the development of innovative medications, there is still quite a way to go.

Organ on a chip system: Regulatory authorities and market size

Despite the fact the tissue on an electronic device innovation remains in its early days, well-known pharmaceutical businesses and governmental organizations are showing growing curiosity in it. The European Pharmaceuticals Agency, the United States of America the FDA (U.S. FDA), or perhaps the Pharmaceuticals and Health Devices Regulation Authority in the Kingdom of England have not yet given organ-on-a-chip technology a specific categorization. Based on a questionnaire, the vast majority of companies that manufacture organs on chips adhere to one among all three main requirements: the standards ISO 9001 the Food and Drug Administration, the provisions of 21 CFR Parts [58], or the Food and Drug Administration FD&C Act Sections 507 [68]. The US FDA and Model Inc. (Boston, MA) reached an agreement in 2017 for the latter's organs-on-chips innovation (CFSAN) to be assessed by the FDA's Centre of Food Security and Nutritional Nutrition. The objective of the study is to understand the way this science may be utilized to predict the harmful effects that specific potential chemicals could have on the health of humans [69]. The Food and Drug Administration provides funds to the Harvard College Wyss Centre for in biology Inspired Engineering to develop acute electromagnetic sickness (ARS) remedies. Multiple organs are impacted by ARS illness after being subjected to high radiation levels. The center will produce organs-on-chips models that mimic radiation harm to the pulmonary, digestion, and blood vessels in order to explore potential preventative measures for its medication [70]. In the last month of 2018 onboard the global space station, a cooperative research utilizing cell chips was scheduled by the National Centre of Advanced Translational Science (NCATS) of the National Institutes for Health, or NIH, with the Institute of Progress in Technologies in Space, in partnership with NASA. The objective was to comprehend how sickness and wellness among people are affected by space. These chips are thought to behave comparable to the way an astronaut's body could undergo such a quick change [71]. The endeavors used chips that imitated the barrier between the blood and the brain, the kidneys, lymph nodes, lung capacity, and tissue to send out their initial mission in May 2019. Studies were conducted on chip that mimicked gut and cardiac organs the next year. In the last month of 2020, investigation focusing on reversing heart tissue damage, muscular waste, and rheumatism avoidance after joint trauma was initiated. As it commenced in May of 2021, the following journey of an endeavor that started in May 2019 was centered on comprehending renal stones production and the effect of gravitation on kidney activity. The market for organs on chips is predicted to be worth USD 41 million dollars in 2020 and USD 303.6 million in 2026. Over the following seven decades, the liver industry will expand at a compound annual growth rate (CAGR) of 35.4%, whereas the renal industry will expand at a the CAGR of 36.1 percent. Increasing medical devices with organ-on-chip producer cooperation to speed identification of drugs and an eye on alternatives to testing with animal paradigms are the main forces behind the growth of organ-on-a-chip technologies. Although the Asia-Pacific region (China, India, and Japan) is predicted to see a rapid expansion rate throughout the forecast time frame, the North American region is likely to hold the majority of the market [72]. It is an overview of a few of the top companies working on organ-on-a-chip innovation [73].

Table: Major companies developing organ on chip models.

Organization	Nation	Region
Emulate	United State	Blood barrier on chip, intestines-on-chip, and even the airways and stomach are embedded in chips
Mimetas	Netherlands	renal intestine, cancer, and numerous other organs
Elvesys	Nation of France	Microfluidic device
AxoSim	United State	seeks to create specialised microfluidic devices to combat
Tara Bio System	United State	aims to create a heart-on-a-chip
Nortis Bio	United State	renal on a chip
Bio IVT	United State	There are well-established designs, such as the islet cells of pancreas and the epithelium that covers the airway of the lung.
AlveoliX	Swiss Nation	a chip with human beings' lung

A system that assesses the stage of development of an innovation is its technical ready straight, formerly referred to the European Mission 2020 technologies. Articles with peer review explain how this kind of equipment is used in an operational setting (TRL 7), in addition to how it might be applied in preclinical research [68].

Micro-engineered chip devices

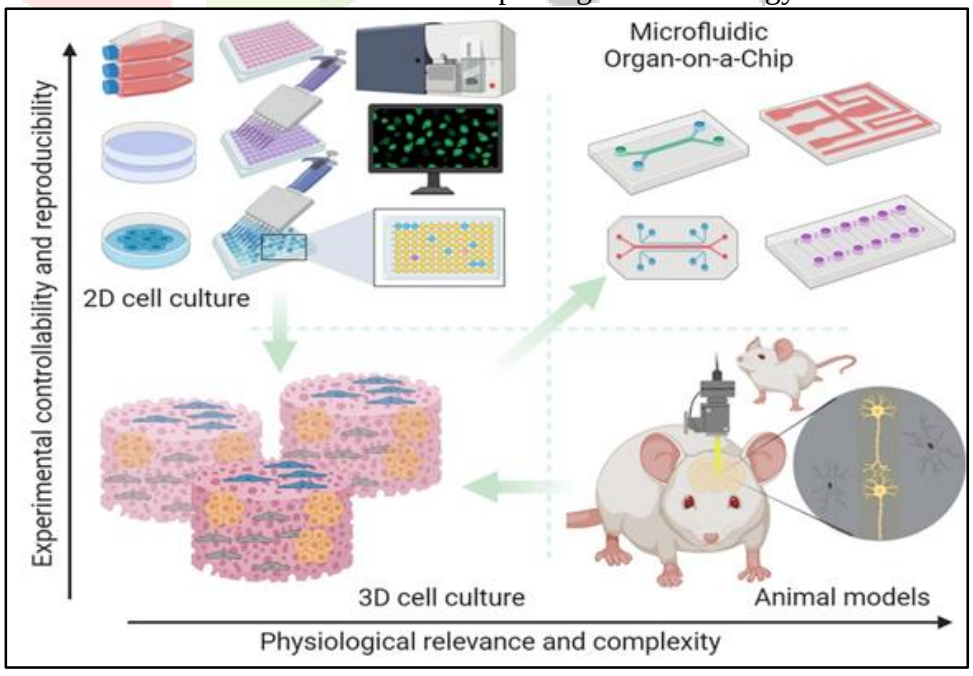
This lists a number of popular techniques, microarchitectures, and substances used in the production of microchips [74,75,76].

Micro-fabrication method	Materials	Types of microarchitectures
Photolithography, Soft microfluidic devices	Polydimethylsiloxane (PDMS)	Single layer
Lithographic, 3D printing	Hydrogels, Gelatine, meth acryloyl	3D Priting
Compartmentalised		
Computerised notation, Vascular networks	Polyamides, Polymethylacryate	Microfluidic

Almost all of the body's systems have a multimodular structure and are composed of living organisms that carry out particular bodily processes, like absorbing in the intestinal villi, or synthesis in the liver, among others, and exchange of gases in the pulmonary alveoli [77]. Induced pluripotent cell stem cells (iPSCs), adult neural stem cells (ASCs), and stem cells from embryos (ESCs) are the most widely used sources of living tissue for diverse organs on chip concepts [1].

Organ-on-chip in microfluidics: A new approach to medication development

The healthcare sector continues to be looking for a successful and efficient scientific and technological (R and D; also, terminology) system for developing drugs. Yet, the present laboratory sites for multifaceted (2D) or 3D cultivation of cells and in live testing on animals are still not enough for an accurate and efficient preclinical assessment of medication effectiveness and safety prior to clinical studies can be authorised to be conducted on people [78,79]. However, due to differences between human organs and those of livestock, the reliability and precision of outcomes from animal research are impaired. Currently, rodent studies remain the gold-standard method for the early verification of drugs in the field of pharmaceuticals [80,81]. Approximately forty percent of newly developed drugs fail to advance even after passing preliminary evaluations using animals as models because of variable reactivity and unanticipated effects for humans [82]. The creation of drugs involves assessing the biological and toxicological impacts of numerous compounds and their analogues in order to identify the most effective and secure treatment options. Low-throughput in vivo studies on animals has a number of disadvantages, which contribute significantly to the longer drug creation time and greater research costs. To expedite the discovery of new therapies and vaccinations for urgent situations, such as COVID-19 pandemic, rapid drug testing systems are essential [83]. Furthermore, while cells grown in vitro in Petri plates can be used for fundamental drug discovery and evaluation, these cell cultures frequently fail to replicate the biological function and tissues micro architecture present in vivo. New tissues models with synthetic human physiology are urgently required to fill the divide among animal research and clinical experiments using human participants in the drug's discovery process [84]. Animal testing will no longer be used in drug studies and personalised medicine thanks to recent advancements in "Organ-on-a-Chip" the internet, which replicates the anatomy and operations of human tissues on a microchip using this technology [85].



General fabrication process of Organ-on-Chip devices

Organ-on-a-Chip is a capillary culturing device constructed from polydimethylsiloxane (PDMS) with soft printing. Since Whiteside's group created the PDMS-based replication modelling approach (soft patterning), PDMS polymers has been a commonly used building block in tiny pumps due to its excellent flexibility, gas permeation, optical openness, and biocompatibility [86-89]. Typically, master moulds of the planned structure's components are initially made using photolithography-based production techniques. Each of the layers of the capillary device are then made via soft lithography, which copies the micro-size characteristics of photolithographic moulds into the PDMS slabs. Then, utilising gas plasma assisted connection, these tiles are put together with slides of glass. Thus, the PDMS-based microfluidic devices enable long-term cultivation of cells, immediate form images, and tracking of Organ-on-a-Chip operations [88-89]. Organ-on-a-Identical approaches are commonly followed during chip production, although a variety of building layouts can be created to precisely match the characteristics of different tissue and organs.

Single and multiple organs on a chip system

Beginning in the first decade of the 2000s, scientists' efforts to use various microfluidic instruments and lab-on-a-chip technologies to allow regulated and organotypic cell development for vitro metabolic and pharmacological studies gave rise to the concept of an Organ-on-a-Chip technology [88,89]. As the Ingber team at the Harvard School of Medicine released a Lung-on-a-Chip concept in 2010, it expanded on Huh's initial research from the Takayama group. The scientific and technological sectors were very interested in this arrangement, and it was thought by many to have contributed to the beginning of the Organ-on-a-Chip revolution [90,91]. By combining pulmonary blood vessel and alveolar tissues on both sides of a membrane with holes in the channels made up of micro of the Lung-on-a-Chip, investigators can examine respiration processes that take place at the alveoli capillary connect of the lungs of a in addition to the impact of the natural world on pulmonary cells in vitro [83]. This method provides a synthetic framework to comprehend the causes of illness causing different lung or bronchial disorders, like CO because then, numerous single-organ chips were established for following the progression of illness, such as the liver chips [81,82,93], renal chips [94,95], the digestive tract chips [96,97], heart chips [98-102], the intestinal tract and stomach chips [103-105], the brain-blood barrier (BBB) chips. The chips are [106,107], and cartilage and blood vessel chips [108-110]. Such single-organ microchip tests can be used as a reliable standard for clinical studies at the preclinical study stage by assisting in the identification of significant biological pathways and evaluating drug effectiveness and toxicology in the targeted organs.

Multi-organ circuits have lately acquired popular to enable more detailed investigations, whereas single-organ chips focus on replicating the operations of just one organ [111,112]. These chips combine numerous organ units into a single unit, including the renal compartment for medication clearance, the liver's sector for drug processing, and the intestinal region for drug absorption. For example, Pires de Mello et al. [111] created a three-organ model consisting of the cardiovascular system, the liver, and epidermis to study the impact of immediate and long-term drug treatment on the workings of the cardiovascular system and hepatic. likewise, a four-organ chip featuring divisions for the gastrointestinal tract, liver function. the epidermis and renal that are progressively linked in addition to maintaining balance across the multiple organ divisions was created for evaluating the systemic effects of medication options [12]. A more advanced model, called "Body-on-a-Chip" or "Human-on-a-Chip," has been created to reproduce the entire physique's biology using one device for drug pharmacokinetics and it studies [13,14,15]. Miller or Shuler [16], developed an experimental organ model with different types of cells that matched the primary parenchymal systems and functional boundary layers of people in order to provide a physical foundation. This technology made it possible for scientists to look at how human organs respond to pharmacological challenges. Without a doubt, the Human-on-a-Chip innovation has an opportunity to transform the chemical sector by serving as an alternate system for modelling that can substitute animal specimens in drug development. Due to the intricacy of the human system, various technological problems must be tackled.

The final hurdle for a massive amount's adoption of organs on chips

To calculate the proportional sizes of every organ on chip

If one is monitoring the efficacy of a medication or researching the links amongst organs, the distance between each of the simulations is crucial for connecting organs on chip. Any pharmaceutical residues that travel via the lung are unlikely to impact a millimetric liver coupled to a micrometric pulmonary. If we comprehend the connection with organ dimensions, we can create simulations which can be more precise in relation to the human being than the present animal models. Getting the right size on the model in question is really difficult, though. Should we take organ size into account? Organ dimensions? Flow of liquid? A novel solution to this issue is to make tissues sufficiently big to fulfil their main purpose, as proposed from Wikswo et al. [117].

To calculate the amount of fluid present inside the chips

Because normal human anatomy has five litres of blood, we might assume that a micro human would have a blood volume of 5 microliters [117]. The results of the experiment could be impacted by a high volume of fluid dilating the drug or hormones generated by all of the organs. Its 5-microliter sum creates a few issues, though. We have to be able to create micro devices such as valves and pumps with the correct dimensions to handle such minute amounts. Microfluidic chips must also be reasonably priced since they will need to be produced in mass quantities in order to support multiple studies at various levels.

To develop a universal blood replacement

While organs on chips could substitute for blood, we also need to discover an affordable substitute that is accessible to everyone [117]. Plasma ought to be able to supply water and keep dozens of various kinds of cells living for as long as is practical in addition to delivering oxygen, protein molecules, vitamins and minerals, and other substances that are necessary for regular bodily functions (such as metabolism). Jain et al. [24] 2017 were able to successfully substitute blood (recalcified citrated entire plasma) for the culture environment in a chip-based lung via the division of endothelial cells in the vascular system. The application of recalcified citrated plasma in thrombus investigations, according to Rajwal (2004), is relevant in a different context [117]. Nevertheless, not all organs need identical things. When serum would prevent cells from dividing, it was occasionally difficult to use it. In these conditions, it is necessary to give peptides to preserve chemical equilibrium [118]. Zhang et al. [119] created a blood replacement for four distinct cell types: liver function. pulmonary, renal and cells in the fat. They were able to do this by giving every kind of cell a special environment and by including extras that improved physiological processes (such as the development factor). One option might be to add materials to the medium that are poisonous for certain organs but essential for another to operate properly. We would also need to know how to prevent hazardous substances from reaching one organ and exiting another [120].

II.CONCLUSION

As the above investigation illustrated, pharmaceutical companies would be able to conserve both time and cash by using organs on chips in an organized manner, as well as reducing the number of animals employed for clinical testing. The chips could also become effective research acceleration since they could make it possible to run numerous studies quickly at the beginning of the research process. Even if the use of the organ on chip innovation has been frequently shown and a few of these are even already being used, we remain quite a way from constructing an actual human being on a chip. Since linking the organs is now too difficult, further study in this field is not possible absent considerable advances in the study of biology. In the meanwhile, these fragments can still be used to determine which medication ought to be examined first. Once the last few issues are fixed, this sort of equipment might help with the deployment of tailored medicine. Depending on their embryonic stem cells, everyone may receive the correct therapy in the correct amount. The majority of currently available systems on a chip models limit themselves to a handful of organs. It is crucial to combine these models to create a single device that replicates all of the main organs since each organ model on a chip symbolizes an element of a larger puzzle. As we approach a body-on-a-chip, it's critical to take into account inter-organ expanding, common material including its circulation percentage, and the interconnected functioning of many organs. Even though this kind of technology can replicate major organs, many other organs, like fat cells, the eyeball, and the womb, just to name a few, have received very little study focus.

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