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Your Body on a Chip: Functional Testing for Personalized Medicine

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Abstract:

Despite the well-known high prevalence of failure in drug development, recent advancements in tissue engineering and microfabrication have helped to create microphysiological systems (MPS), or "organs-on-chips," which mimic the function of human organs. These "tissue chips" might be used for toxicity and drug screening tests, which could revolutionize the early phases of the drug development process. Additionally, they may be utilized to simulate disease conditions, supplying new instruments for deciphering disease pathologies and causes and evaluating the efficacy of novel treatments. Future clinical trials on chips might be utilized to assess novel medicines in both populations and individuals, opening the door for precision medicine. Here, we'll discuss tissue chips' diverse potential and the difficulties in developing them.

INTRODUCTION

Organs-on-chips are microfluidic cell culture devices that precisely replicate the Physico-chemical microenvironment of tissues in the human body under dynamic, regulated settings (1). Therefore, the chips display tissue- and organ-level activities that are not seen in other, more straightforward in vitro cell systems. These microsystems have great potential for use in the present pharmaceutical research procedures to investigate the toxicity and efficacy routes in human tissues (2). They may also aid in creating personalized therapies and provide insight into disease processes, which bodes well for developing precision medicine (PM) (3). There is a growing understanding that in moreover to these uses in pharmaceutical and biomedical investigation, organs-on-chips can also be seen as controlled, physical representations of particular patients and can thus be used directly in the clinic to inform techniques for the treatment or prevention of disease (3). In this review, we will explain that the production of "personalized" organs-on-chips that accurately represent particular persons' genetics, physiology, and biometric factors is made possible by the regulated integration of person-specific cells, tissue samples, and culture conditions based on biometric data. We will provide samples of these customized products. Organs-on-Chip will demonstrate their potential to help create and assess treatment plans for specific patient populations or people. Introduction.

What exactly is a chip-based organ?

A bioengineered microdevice called an organ-on-a-chip, also known as a tissue chip, is typically no larger than a few square centimeters and is intended to imitate the fundamental functional unit of a human organ, such as the lung alveolus, proximal kidney tubule, or liver acinus (4). Microfluidic channels supply fluid to microfabricated chambers that mimic tissues' three-dimensional (3D) architecture and are filled with human cells. The channels enable the tissues to receive fluid perfusion. Their designed shapes and designs can mimic the biomechanical strain and shear pressures that human tissues experience in vivo. These instruments, sometimes referred to as MPS, are a part of a growing initiative by academia, the government, and the pharmaceutical industry to develop and make use of innovations that more accurately reflect human physiology and drug reactions (5-7).

Up to 60% of compounds are classified as failures owing to a lack of effectiveness, and a further 30%

pose unacceptable safety hazards from toxicity when compounds reach early clinical trials. This pressure is due to the ever-increasing costs and timetables for drug development (15 years and up to $2.8 billion) (8,9). Animals, in most circumstances, are not appropriate models for many human diseases because of the possibility that their reactions to medications may change depending on the species owing to physiologic variations (10). Therefore, the ideal models for illnesses that affect humans are based on human beings.

Models of several different organs, including the heart, liver, stomach, brain, muscle, and vasculature, have been created using tissue chips (3). Their ability to be stocked with human cells—whether from primary donors, differentiated induced pluripotent stem cells (iPSCs) from adult donors, or commercially accessible cell lines—is a significant benefit (3). Additionally, no other in vitro model has the potential to mimic hemodynamic and fluidic flow, as well as biomechanical stress. The lung-on-a-chip is one of the first and most commonly used tissue chips (11). This platform consists of two tiny chambers, one of which is filled with fluid and the other with air, and they are separated from one another by a thin membrane lined with lung cells (11). Two additional air-filled chambers are located next to the two main chambers. When a rhythmic vacuum is applied, the membrane between the two chambers stretches and relaxes, simulating the air-fluid interface of the human alveolus (11). Since then, this platform design has been adapted to simulate different systems, including gut peristalsis and the blood-brain barrier (BBB), lung infection, pulmonary edema, asthma, and chronic obstructive pulmonary disease (COPD) (12-14).

MPS platform designs vary greatly depending on the tissue they are intended to mimic. However, they all have three key design elements: 1) the cell arrangement in three dimensions to build a biologically accurate model, 2) incorporating microfluidic components for fluid exchange, and 3) tissues made up of different cell types, for as a liver chip made up of immunological, endothelial, and hepatocyte cells [3]. The capacity to represent the multicellular makeup of each human tissue in the systems and arrange the cells in scaffolds that simulate 3D tissue architecture is a significant benefit of employing MPS. Several preclinical assays for toxicity and efficacy screening can currently be performed on human cells. However, these assays frequently take place on two-dimensional (2D) monocellular layers in static cell culture plates, missing the multicellular, multidimensional, and fluid-exchange characteristics of tissues in vivo (15). Additionally, current developments in iPSC technology enable the production of a range of organ tissues from a single person's skin fibroblasts, adipose tissue, and blood cells, enabling the production of different organ tissue types from the same donor (15).

The accuracy of treatments is improved by using health data in precision medicine

The idea of precision medicine, in which each individual would receive customized treatment for the promotion, maintenance, and restoration of their health, is becoming more and more significant in medicine, toxicology, pharmacology, and biomedical science as a result of the growing recognition (16). Due to the current lack of "precision" in medicine, many patients receive treatments that are not in their best interests,

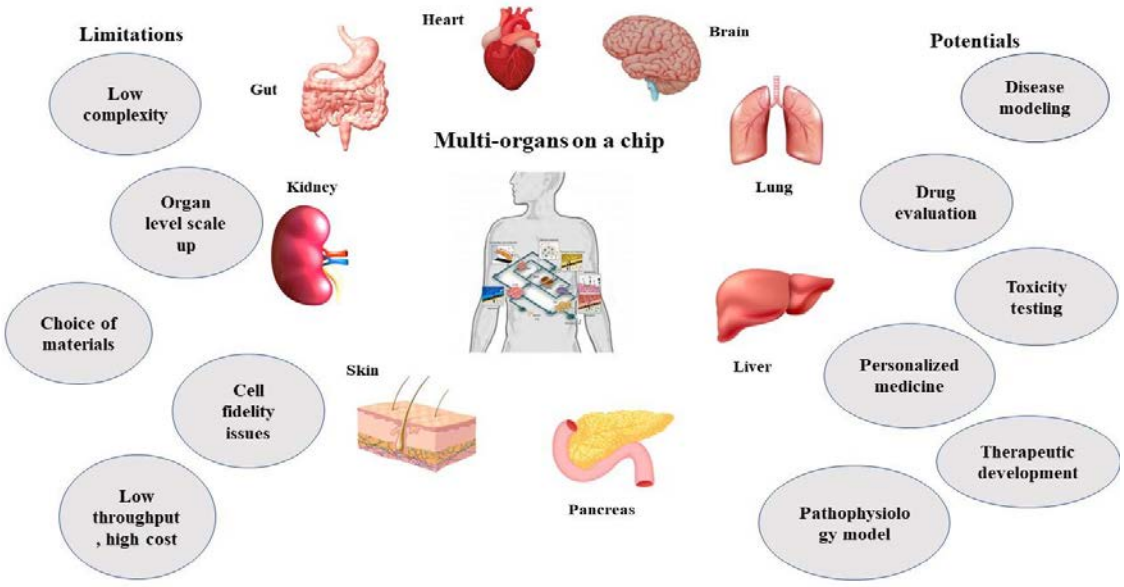

Fig 1. Several effective organ-on-a-chip applications and their accompanying functionalities. Preclinical to clinical translational precision biomedical applications are made possible by the organ-on-a-chip.

which results in ineffective healthcare (16). For example, for some medications with the most significant sales worldwide, the total number of users required for just one person to benefit from a drug's benefits ranges from 5 to 50 (16). Even more concerningly, several people are subjected to medical procedures that harm their health (17). Due to negative drug responses, millions of individuals are hospitalized annually, resulting in tens of thousands of fatalities (17). By creating techniques that can make therapy more accurate, hazardous and useless remedies can be avoided, potentially enhancing patient quality of life and lowering healthcare costs.

Linking an individual's health-related data to functional results in their response to specific therapies is the main difficulty in precision medicine. To determine which patients respond to which therapies, the typical method is to employ patient-specific data gathered from genomics, transcriptomics, imaging, biomarkers, and biometrics, followed by longitudinal studies using statistical and computational analysis. This strategy is thriving and has produced outstanding instances of precision medicine, such as choosing person-specific therapies for cancer and lung disease, which may be used in practice (18, 19).

Body-on-a-chip: multi organ system application

Clinical tests using chips for different patient subgroups

A benefit of an organ-on-a-chip is that it may be filled with human cells, either from the central organ or from iPSC sources. This enables the creation of an in vitro genotype model for a particular person. Particularly in multiorgan systems, as mentioned above, utilizing an individual's cells in MPS platforms enables secure and reusable techniques for researching disease causes, medication toxicity and effectiveness, off-target side effects, metabolic drug profiles, and more. Before a therapeutic is approved for use in a "first-in-human" clinical trial, these data and outcomes must be carefully described to minimize risk to any volunteer or patient. These data and results are essential for supplying information on the likely effects of drugs and therapeutics during development. However, some patient groups may not be eligible for clinical studies. For instance, individuals with certain aggressive tumors may need more time to engage in clinical trials before the disease progresses too far to get therapies or benefit from them.

Moreover, for patients with uncommon diseases, where a "one-size-fits-all" medication development procedure seldom helps distinct familial genetic variations, the availability of clinical trials and the difficulties of going to a facility where they can participate may rule out the possibility entirely. All patients may not even be able to sign up for a given experiment because of eligibility limitations, especially if they have already participated in studies. From a broad perspective, the idea of "clinical trials on chips"

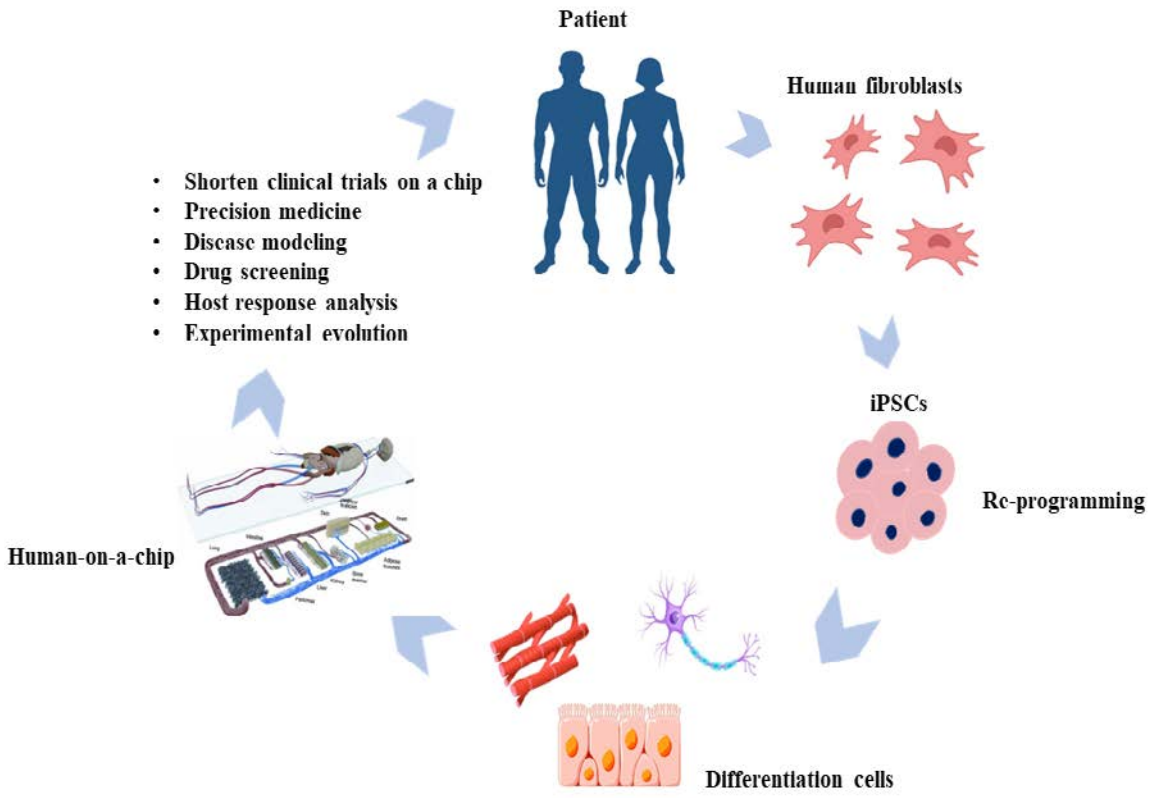

Fig2. Potential applications for tissue chip technology.

may be beneficial for particular patient subgroups, and modeling organs or humans on a chip would enable the monitoring of known toxicity profiles, for example, or the quantification of the efficacy of an experimental drug in vitro before administration to a patien.

Drug screening and testing

Studying the reactions of various organs and tissues to the administration of specific medications is essential in medicine, as we have covered throughout this paper. Several instances illustrate this idea (20). One typical chemotherapy drug is 5-FU, used to treat colorectal cancer. Unfortunately, 5-FU can have various adverse effects on patients, including intestinal cell destruction. Many prodrugs, including tegafur, have been developed to decrease toxicity. Tegafur and other prodrugs are inert when supplied; they only become active during metabolism, typically carried out by hepatocytes in the liver. Without using a metabolically active liver organoid, data from in vitro prodrug drug trials are probably utterly worthless. By creating a platform with a liver and other organoids or tumors, it would be possible to analyze the effects of the activated drug on the downstream tissues or tumors once the prodrug is metabolized (20).

Disease modeling

By simulating disease conditions on MPS, new perspectives on pathologies and therapeutic options are made possible. Using primary or induced stem cell sources or genetic techniques to create a disease phenotype that can be investigated in vitro against an isogenic background, diseases might be mimicked from patient donors.

Using tissue chips to study disease processes

Tissue chips have recently been used to represent various disease conditions. For example, when cultivated in 2D instead of 3D, malignant tumor cells exhibit various phenotypes. The microenvironment in which they are grown is a significant factor in determining their behaviors, including development and dissemination (21). The liver is an important site of metastasis for many carcinomas and a binding site for drug metabolism, making it an essential target for MPS cancer modeling. Metastatic spread is a significant cause of cancer-related mortality. According to Clark et al., human liver tissues are cultivated for many weeks in a liver bioreactor that can be seeded with carcinoma cells that multiply and form tiny tumors. Notably, the system demonstrated that some cancerous cells entered a dormant state within the systems when used to investigate the metastatic growth of breast cancer. As microtumors can lay dormant for many years before starting to grow again, this is a severe issue for human populations (22-24).

Tissue chips can be used to discover more about viral and bacterial infections. For instance, a "gut-on-a-chip" platform was recently utilized to show how human Caco2 intestinal cells react to infection with enterovirus coxsackievirus B1 in a two-chamber device similar in design to the lung-on-a-chip. Understanding the mechanisms of action of enteroviruses was made possible by the authors' demonstration of a viral entrance, replication, and inflammatory cytokine production in the epithelium. These two last examples show how data from MPS were verified against well-known clinical outcomes. It is a crucial step for the field since it demonstrates the value of platforms for understanding disease pathophysiology and developing new treatments (25-27).

Patients with rare diseases could benefit from tissue chip technology

Fewer than 5% of the over 7000 currently known rare diseases have viable pharmacological therapy, which makes treating people with rare diseases extremely difficult for various reasons (28). However, MPS technology may not only improve comprehension of several understudied illnesses but also offer platforms for evaluating repurposed current medications and new drug screening techniques for therapies that are already on the market (29). The use of a cardiac MPS to represent the uncommon illness Barth syndrome, which results in immunological deficiencies and cardiac and skeletal myopathy owing to a mutation in the TAZ gene, is one of the most well-known applications of MPS platforms to date (30, 31). Wang and colleagues used 'muscular thin films' (MTFs) of cardiac tissue on elastomeric thin films that 'twitch' in a measurable way as tissue contracts (30). The group created induced pluripotent stem cells (iPSCs) from two individuals with Barth syndrome, differentiated the cells into cardiomyocytes, and then implanted and cultivated the cardiomyocytes on the MTFs (30). The resultant MTFs exhibited decreased peak and twitch stress, which was consistent with the condition's pathophysiology. The scientists then demonstrated the effectiveness of gene editing methods on MPS by "rescuing" a normal phenotype in the tissue by introducing TAZ RNA (30). Several rare diseases, including Hutchinson-Gilford progeria syndrome, hereditary hemorrhagic telangiectasia (HHT), Rett syndrome, and Alpers-Huttenlocher syndrome, are currently being modeled in MPS platforms, to the authors' knowledge (32).

Tissue-based chips for precision medicine and clinical trials

MPS in illness research can advance our knowledge of a broad spectrum of diseases and pave the way for potentially game-changing discoveries about the causes and therapies of illness. The National

Institutes of Health (NIH) in the US are funding a program expressly for using the chips for disease modeling with an investment of around $75 M over the following five years. In other words, MPS might be helpful tools for efforts in precision medicine. In the future, the possibility of filling MPS with primary or iPS cells from patients provides opportunities for therapies that are personalized to an individual. Chips might be utilized to simulate patient-specific tissues for therapy evaluation. To represent pharmacogenetic variability within populations, tissues with known genetic polymorphisms might also be included in chips. Furthering this idea, tissue chips allow for population-wide variation by modeling genetic and environmental characteristics, such as gender and exposure to toxins or infectious agents. Together, these opportunities pave the door for clinical trials on chips in the future, allowing for testing both new and existing medications on MPS. It might speed up the medication development process by precisely simulating population variance throughout preclinical and early clinical trial stages, lowering the attrition rate of potential treatments (33-35).

What kind of cells is suitable for tissue chips?

Cell sourcing is one problem that the profession is now confronting. Currently, researchers have access to primary tissues from donors, commercially accessible immortalized cell lines, and iPSC sources (from both commercial and donor sources) (36). There are benefits and drawbacks to each of them. For instance, readily accessible cell lines from the marketplace make it easier for researchers to do their work. Nevertheless, because of their prolonged culture, these immortalized lines could have experienced considerable genetic or epigenetic drift (37). For MPS seeding, primary tissues from donors are preferred, especially for rare disorders. They may only be accessible in small quantities or from populations with diseases, and they are challenging to acquire from trim population levels. Depending on how long it takes after death for tissues to become accessible, it may be brutal or immoral to obtain healthy tissues, or they may come from compromised dead donors. Additionally, some tissues are challenging to get from donors (i.e., nervous system tissue) (38).

Stem cells, significantly induced pluripotent ones, are the most promising cell sources for MPS platforms. Reprogramming different tissue types from skin fibroblasts or blood cells (to form iPSCs) offers exceptional prospects and numerous advantages over primary cells (39). Technological advancements now provide renewable cell sources for several tissues. First, many tissue types may be produced by people, and they are known as isogenic tissues since they all have the same genetic makeup (40). Another benefit is that with the development of gene editing methods like CRISPR, the production and genetic treatment of tissues for monogenic or Mendelian illnesses is achievable in ways that were before unimaginable. Last but not least, the development of iPSCs offers hope for validating other population-wide investigations like genome-wide association studies (GWAS) (41).

What materials use to create MPS?

The materials used to make chips offer great design flexibility, but they also significantly impact functioning. Since it is transparent and flexible, polydimethylsiloxane (PDMS) is the perfect material for MPS creation (42). It is also inexpensive and straightforward to work within the lab (for example, through soft lithography). However, it is gas permeable and absorbs hydrophobic medicines as well. It might reduce the amount of medication that reaches tissues or pollute nearby microfluidic channels or cell-containing chambers (42).

Additionally, the hydrophobicity of the substance has been linked to poor cell adhesion in MPS devices, which might cause cell aggregation and obstruct fluidic flow. Researchers in a variety of methods have addressed this problem. These include plasma treating or coating the PDMS with proteins to limit cell attachment and medication loss and oxidizing it to produce a barrier layer of silicon dioxide on the surface (43, 44,45).

Outlook

The idea of customized organs-on-chips is anticipated to go from its current stage of academic proof-of-concept investigations to confirmation in the field of precision medicine during the next several years (46). Suppose personalized organs-on-chips can be shown to be helpful in guiding personalized treatment and preventative efforts. In that case, they are expected to become a crucial component of more extensive medical advancements toward a more predictive, preventive, personalized, and participative field. A more thorough understanding of disease mechanisms will result from a customized organ-on-chip that includes a disease-related parameter determined by observational studies, followed by an experimental functional comparison with matched, person-specific control organs-on-chips (46). This comparative analysis could then lead to the discovery of new drug targets and biomarkers. Finally, because organ-on-chip systems are dynamic, it may be feasible to create organs-on-chips whose cell culture settings may be changed under precise control when more recent or updated health information becomes available. This might be crucial for evaluating how well lifestyle modifications for prevention work (46).

Key challenges

Because organs-on-chips are helpful in the preclinical clinical domains, MPS technology offers significant promise for PM initiatives. However, before the tools can fully realize their promise, there are still issues to be solved, as with every new technology. An NIH-funded industry that has established two Tissue Chip Testing Centers for platform validation initiatives is tackling some of these difficulties, including technology transfer across laboratories and the validation of assay results from chips. The necessity for dependable, mature cell sources to fill the chips and the development of platform accessibility to a larger population are the two more significant problems. Individualized chips can be made for each person using iPS-derived cells for cell sources. However, not every tissue in the body presently has a differentiation pathway.

According to our predictions, highly complex single- or multiorgan systems should continue to be helpful in examining disease pathologies and drug mechanisms. However, human training and implementation costs for these sophisticated systems are higher. The physical challenges of scaling organs and tissues appropriately, perfusing tissues with the proper blood mimic to supply tissue-specific nutrients, and linking organs with functional vascularization while utilizing the appropriate type of endothelial cell are among the technical challenges facing the linkage of systems.

CONCLUSION

As instruments for modeling disease pathologies and profiling pharmacological and therapeutic effects in vitro, tissue chips provide previously unheard-of chances to comprehend disease processes and treatment effects. By creating "subpopulations-on-chips" and, eventually, "you-on-a-chip," these technologies will support PM efforts in various ways. The field of PM is still in its infancy. Nevertheless, if patient populations are modeled ex vivo or therapies are evaluated in people with particular genetic variants and genotypes, the ability to employ tissue chips to mimic organ systems in specific individuals will probably entail more awareness in the coming years. This intriguing and quickly developing subject has much promise to help biomedical researchers and the pharmaceutical industry understand how to cure some of the most common and difficult-to-treat ailments of our day.

Conflict of interest

There are no conflicts of interest to declare.

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