Research of Organ-on-a-chip and its application

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Abstract. Material selection for Organ-on-a-Chip fabrication is a complex process, necessitating careful consideration of multiple factors. This comprehensive assessment involves detailed scrutiny of five materials—PDMS, glass, silicon, hydrogel, and PMMA—each accompanied by an intricate exploration of their specific properties. Moreover, thoroughly evaluating the associated costs contributes to the decision-making process, ensuring optimal material choices aligned with the intended applications. Furthermore, this discourse extends to an in-depth discussion of distinct organoids, including lung, liver, kidney, and skin chips. This comprehensive analysis delves into the principles underpinning their functionality, the intricate structures replicating organ features, and a forward-looking evaluation of their development prospects. By delving into the essence of each organoid, a holistic understanding of their potential in revolutionizing disease modeling, drug testing, and personalized medicine is elucidated. The narrative culminates in the introduction of the groundbreaking combined multi-organic chip system. This integration of various organoid models represents a significant stride towards emulating the interconnectedness of organs within the human body. This futuristic approach lays the foundation for a dynamic and intricate system that provides a holistic view of complex physiological interaction.

1 Introduction

An organ chip stands as a remarkable feat of engineering, a product of precision nano processing technology meticulously designed to replicate the intricate functions of human organs on a microscale. This extraordinary microsystem comprises an array of elements, including micro vessels, microtubules, and cells, intricately woven together to achieve a remarkably high level of complexity and functionality [1]. At its core, the organ chip represents a testament to our ability to capture the essence of biological processes and faithfully reproduce them in a controlled and reproducible manner. This technological marvel holds immense promise across a wide spectrum of applications. In biomedicine, organ chips offer a transformative platform for studying disease mechanisms, drug interactions, and cellular responses with unprecedented precision and relevance [1]. The significance of organ chips extends into drug development, where these miniature organ replicas provide a sophisticated environment for testing potential therapeutics, leading to more accurate drug efficacy and toxicity predictions, Furthermore, the insights gained from these microsystems elevate the potential for health management through personalized medicine, allowing tailored interventions and treatment strategies. As the boundaries of scientific exploration continue to expand, the organ chip emerges as a beacon of innovation that bridges the gap between biology and technology. With its potential to revolutionize medical research, reshape drug development paradigms, and enhance our understanding of human health, the organ chip embodies the epitome of interdisciplinary collaboration, holding the promise of ushering in a new era of precision medicine and transformative advancements in healthcare [2]. The choice of chip materials and familiarization with the structure and principles of the various organ chips are also important, as choosing the right material for the chip can effectively improve safety, comfort, and efficiency. Familiarizing yourself with the principles of the various types of microchips will enable you to find out more about them in the main body of the following article.

2 Micro organ chip material selection

2.1. Polydimethylsiloxanes (PDMS)

PDMS, the most common material in organ chip fabrication, comprises a prepolymer and curing agent. They blend in specific proportions and solidify with elasticity upon heating or at room temperature. Key advantages include non-toxicity, chemical inertness, optical clarity, flexibility, and gas permeability [3]. These traits, coupled with ease of use and cost-effectiveness, make it a prevalent choice for organ chip creation. However, PDMS's hydrophobic surface necessitates modification for cell adhesion. A biocompatible fibronectin layer or hydrogel material is commonly applied to foster cell growth. Alternatively, PDMS can be combined with other materials, such as machining microfluidic structures and covering a glass sheet. PDMS

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provides microfluidic structures for flow in this approach, while cells grow on the glass surface, sidestepping PDMS's biocompatibility issue [4]. PDMS's downside is its high absorption rate for small molecules, including drugs. This must be considered in drug screening using PDMS-based organ chips.

2.2 Glass and silicon materials

Glass and silicon materials are extensively employed in crafting organ chips. Notably, they offer distinct advantages. Leveraging standard micro-nano-processing techniques, these materials boast high precision in processing and molding and enhanced biocompatibility which is a pivotal aspect for accurate organ replication [5]. However, their usage entails certain drawbacks. Specialized processing equipment is imperative, and the costs associated can be notably high, Moreover, silicon materials pose challenges due to their limited light transmission capabilities, making direct observation of cells or microstructures on the chip more complex. This aspect potentially restricts their application to some extent [5]. Despite these challenges, the utilization of glass and silicon materials underscores their potential to advance the precision and fidelity of organ-on-chip technology, contributing to innovative breakthroughs in biomedical research and drug development.

2.3 Polyethylene glycol diacrylate (hydrogel)

Hydrogels, valued for their strong biocompatibility, have emerged as prominent contenders in the realm of organ chip development. Their notable attributes encompass transparency, minimal toxicity, photo curability, and inherent hydrophilicity [6]. Hydrogel materials exhibit a compelling parallel to the natural extracellular matrix (ECM) in terms of their porous properties, water retention, and biomolecule diffusion. This intriguing similarity empowers hydrogels to simulate the intricate cellular growth environment found within living organisms [6]. This capability to replicate the in vivo conditions bolsters their significance in advancing organ-on-chip technology. By these attributes, hydrogels stand as a promising avenue for innovative biomedical research, offering new avenues for disease modeling, drug testing, and personalized medicine. While acknowledging the challenges they might present, the potential for hydrogels to reshape the future of organ chip technology is undeniably captivating.

2.4 Polymethyl methacrylate (PMMA)

PMMA material is favored for chip fabrication due to its benefits. These encompass excellent light transmission, affordability, and ease of molding. Its lightweight construction and low density add to its appeal [7]. Another merit is PMMA's strong electrical insulation, enabling the application of high electric fields for functions like liquid propulsion and separation within chips. This material holds promise for various applications [7]. Its transparency aids optical observation, while its fabrication ease and suitability make it significant for microfluidic systems and organ chips. In diverse fields, from diagnostics to research, PMMA is poised to shape the future of miniaturized technology. As Table.1 shown below which summarized properties of each material.

Table.1. Summary of each property of the materials

Material	Biocompatibility	Hydrophilia	Light-admitting quality	Cost	Permeability	Processing temperature
PDMS	Good	Hydrophobic	Good	Low	Good	Low
Glass	Good	Hydrophilic	Good	Medium	Bad	High
Silicon	Medium	Adjustable	Bad	High	Bad	High
Hydrogel	Good	Hydrophilic	Good	Medium	Good	Low
PMMA	Good	Adjustable	Good	Medium	Medium	Medium

3 Organ chip refinement types and detailed introduction of them

3.1 Micro lung tissue microarray and evaluation

With the ever-changing times, the development of micro lung chips is becoming more and more sophisticated. The scientists and researchers have innovated a wide variety of microfluidic-based custom chips that can be used to explore the physiology of the lungs, and even some that can assist the lungs in breathing and ventilating, or in monitoring the well-being situation of the lungs. Huh et al. working group, as the Fig 1 shown below, they created a form of microchip with two compartments, one upper and one lower, and cultivated human alveolar epithelial cells and pulmonary microvascular endothelial cells in the upper and lower compartments, respectively, the upper and the lower compartments were also separated by microporous polydimethylsiloxane (PDMS) membranes with extracellular matrix attached to it [8]. To simulate the alveolar-capillary structure, air was introduced into the upper channel and fluid was introduced into the lower channel to form an air-liquid interface to simulate the real alveolar structure [8]. At the same time, Huh performed cyclic vacuum pumping in the upper air cavity to simulate the contraction and expansion of the alveoli caused by respiratory movements [8]. Using this device, scientists

have also studied many malady types, such as nanotoxicology, pulmonary edema, inflammatory damage, etc., validating its brilliant bionic capabilities.

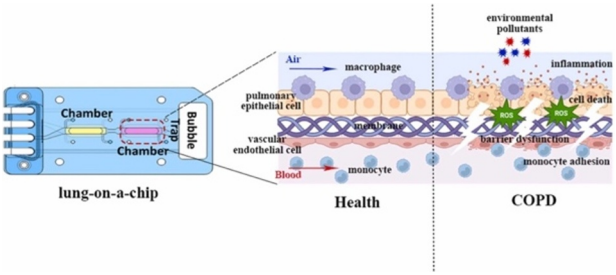

Fig. 1. Detailed structure of Micro lung chips [9]

The figure 1 shows that the microstructure of the micro lung chip consists of two chambers, each with upper and lower channels, the upper channel has air flowing through it and macrophages attached to pulmonary epithelial cells, and the lower channel has blood and monocyte flowing through it, as well as vascular endothelial cells on the membrane. The two layers are separated by membrane.
Miniature lung microarrays have advantages and disadvantages compared to traditional animal models, with animal models being the most widely used for drug toxicology and in vivo metabolism studies, and at a relatively low cost. However, animal models cannot well imitate the real mechanism of human organs, and society has criticized some ethical issues [10]. On the contrary, lung microarrays can realistically reproduce the microenvironment of human lungs. They can be used to research the structure and function of lungs, disease mechanisms, and drug discovery and development at both the macro and microscopic levels [11]. It has a bright future, and when the technology is mature, it will be more convenient for drug development and disease research and is expected to become a mainstream model for scientific research.

3.2 Microarray of liver tissue and assessment

The liver is a vital detoxification organ and is crucial for pharmacokinetic and toxicity testing of drugs. To better study and explore the liver, it is essential to create precise and reproducible models that can depict its structure, potential for regeneration, and reaction to injury [12]. Back in 2006, the most original miniature liver-on-a-chip was created, it is made of a matrix of 64 (8×8) microfluidic wells co-cultured with rat hepatocytes and 3T3-J2 fibroblasts, and two microfluidic perfusion networks were utilized to provide a separate, continuous supply of cell culture medium and oxygen for the co-culture [13].

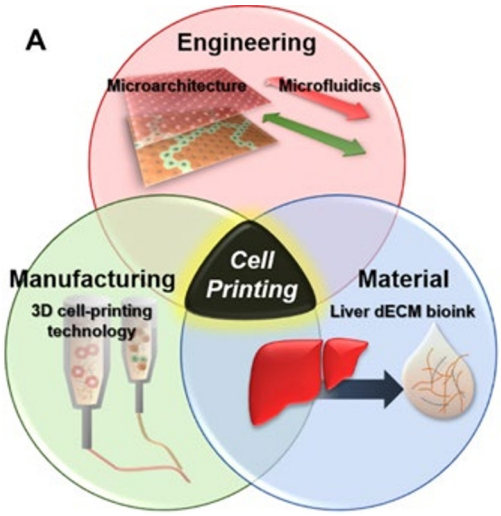

Fig. 2. Key component of liver-on-a-chip [14]

As shown of Fig 2 above is the schematic illustration of crucial elements of 3-Dimensional liver chips consists of Engineering, Manufacturing and Material. In Engineering part, there are Microarchitecture and Microfluidics. In Manufacturing part, it has 3D cell-printing and technology. The Material only has Liver dECM bioink [14].

For high-throughput drug screening, this liver organoid system can be improved for large-scale organoid formation by incorporating additional microfluidic components. Additionally, by exposing it to free fatty acids, this system was also utilized to simulate human non-alcoholic fatty liver disease (NAFLD). The usual clinical characteristics of steatohepatitis, such as aberrant triglyceride accumulation, improper lipid metabolism, and hepatic fibrosis, were evident in liver organoids. These characteristics may offer hints for potential processes and medication development in NAFLD. In the future, liver organoid microarray systems may provide a promising platform for studying diseases such as host immune inflammation and viral infections and individualized medicine.

3.3 Miniature Kidney Tissue Organ Chip

The kidneys play a crucial role, with their primary functions being urine production to aid in eliminating metabolic waste and toxins and regulating the body's electrolyte and acid-base balance. However, many drugs exhibit potential hepatorenal toxicity during the drug screening process, which could lead to irreversible damage to the kidney's filtration function. Therefore, the development of microscale kidney organ chips holds significant importance for drug toxicity screening [15]. To simulate the mouse renal filtration system, a multilayer microfluidic control mechanism for cultivating mouse renal collecting duct cells was originally created in 2010..As shown of the Fig 3 below, the system consists of two chambers, an upper chamber with channels to pass fluid to simulate the urinary lumen, which also generates shear stress as fluid passes through, and a lower chamber with a culture medium to cultivate cells, and the chambers

are divided by a porous membrane [16]. The device offers a bionic environment to maximize the simulation of the real working conditions of the kidney.

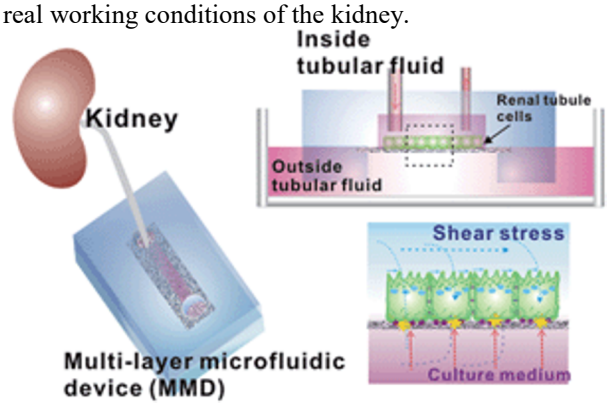

Fig. 3. Detailed structure of kidney-on-a-chip [16]

This figure precisely shows the general structure, side view and internal structure of multi-layer microfluidic device (MMD), also known as a kidney chip.

For the evaluation of the effectiveness and safety of medications and vaccines as well as for biomedical research, the development of renal microarray technology has produced a more accurate and affordable research model of the physiological and pathological conditions of the human body.

3.4 Micro Skin Chip and its Progress

Since skin grafts are relatively straightforward and can be easily performed due to the flat nature of the skin, the incorporation of microtissue cores into skin slices adds complexity to the micro-organ engineering process. The focus of nowadays study is to investigate methods that promote vascularization, aiming to develop micro-organs that function more akin to natural skin. This exploration also involves the possibility of creating micro-organs with functions closely resembling those of normal skin. A four-channel microfluidic device for human epidermal keratinized cells (HEK) was invented in 2008, the bottom layer of the device is a 50*75mm slide, and then a patterning collagen channel is placed on the surface to expand human epidermal keratinized cells in the channel, and then PDMS cell culture channels are placed on the collagen strip, and the four channels are perfused with cells at different flow rates [17].

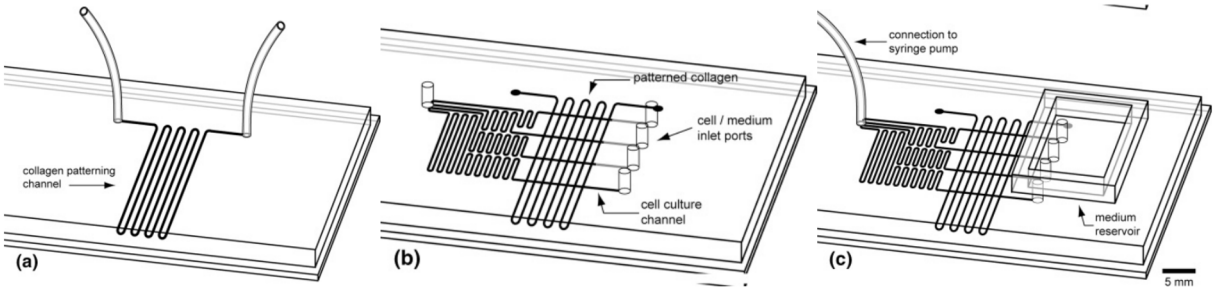

Fig. 4. microfluidic device assembly [17]

As shown of Figure 4 above, the microfluidic device must be put together in the following order: (a) vertically patterning collagen on a glass slide measuring 50 mm by 75 mm, (b) aligning a four-channel PDMS structure over the collagen, and (c) attaching a medium reservoir and tubing [17].

Whether it is common cell model or organoid technology, there are still many limitations about skin chips, the relevant research still cannot meet the requirements of practical applications, the future also needs to be able to massively stabilize the production of technology and methods. It is believed that shortly, skin organoid chips will cover an increasingly rich variety of cells and tissues, with immune response, metabolism, blood circulation and other in vivo functions, and can be realized in the in vitro environment closer to the real state of the skin physiological ecosystem.

3.5 The four-organ-chip interconnected system

The Systems known as "Organ-on-a-Chip" use microengineering, microfluidics, and analogous concepts to accurately reproduce important features of live organs, such as vital microarchitecture, spatiotemporal cell-cell connections, and extrinsic small-scale environments. This cutting-edge platform enables the exploration of fundamental disease etiology and organogenesis mechanisms. Furthermore, it is vital in advancing drug development through effective toxicity screening and precise target identification [18]. Notably, this technology has the potential to revolutionize research practices by offering an ethical alternative to animal testing, ensuring more humane and sustainable scientific progress. With its wide-ranging applications, it promises to reshape the future of biomedical research and therapeutic development. IIka's team successfully developed a microfluidic MOC (Multi-Organ-on-a-Chip) device featuring two distinct micro physiological fluid flow circuits. These circuits intersect within the kidney proximal tubule culture compartment, and the beauty lies in their independent control facilitated by separate peristaltic on-chip micropumps [19]. This groundbreaking innovation opens exciting possibilities for advanced studies in organ interaction and dynamic cellular responses, bringing us one step closer to accurately modeling complex physiological systems and drug testing in a controlled and scalable laboratory setting. Integrating these sophisticated microfluidic technologies signifies a significant advancement in biomedical

research and holds great promise for enhancing our understanding of organ function and disease mechanisms.

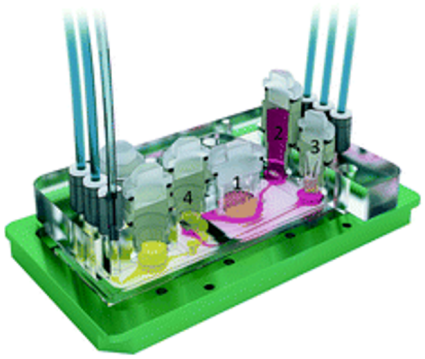

Fig. 5. The microfluidic organ chip system [19]

It consists of two polycarbonate cover-plates and a PDMS-glass chip with dimensions of 76 mm × 25 mm and a height of 3 mm. As shown of Fig 5 above, the gadget contains an excretory flow circuit (yellow) and a substitute blood flow circuit (pink). A 3D representation of four tissue culture compartments for (1) intestine, (2) liver, (3) skin, and (4) kidney tissue is shown. Each tissue culture compartment is aligned along the interconnected microchannels, can providing a comprehensive and interconnected setup to study organ interactions and responses in a controlled and dynamic environment [19]. However, to simulate the whole human body system, connecting different organ chips in series is necessary. Existing organ chips are mainly single chips, and each organ chip still needs to be assembled independently for the tandem cultivation of multiple organ chips, which is cumbersome to operate and occupies a large space after assembling, which is not conducive to high-throughput testing. In addition, when multiple individual organoids are connected in series, there are many pipelines, and the connection is complicated, so it is easy to have connection error or liquid leakage phenomenon.

Table.2. Micro Organ Chip Research Overview

Organ name	Structure of imitation	Cultivate method	Function parameters	Reference
Lung	pulmonary alveoli	Co-cultivation of membrane segregation	inflammation response	[8]
	pulmonary alveoli	Co-cultivation of membrane segregation	cellular metabolism	[20]
	respiratory tract	Co-cultivation of membrane segregation	inflammation response	[21]
Liver	hepatotoxicity	Adherence	Albumin, urea synthesis	[13]
	Liver structure	Suspension and Adherence	toxic metabolism	[22]
	Liver structure	Suspension and Adherence	P450 enzyme activity, Albumin, urea synthesis	[23]
	Liver structure	Adherence	Albumin, urea synthesis	[24]
Kidney	Uremia and edema	porous membrane lamination	molecular transporter capacity	[16]
	Renal drug transport	porous membrane lamination	molecular transporter capacity	[25]
	hypertensive nephropathy	porous membrane lamination	filtration function	[26]
	nephrotoxicity	Terephthalic Acid Membrane Adhesion	metabolic activity	[27]
Skin	dermal toxicity	Adherence	Cellular activity	[17]
	dermal toxicity	Isolated co-culture	Cellular proliferation, permeability	[28]
	follicles	Isolated co-culture	Histology	[29]
	Inflammation and edema	porous membrane lamination	Permeability, inflammation reaction	[30]

The Table 2. furnishes a comprehensive insight into the research pertaining to the four distinct types of microarrays. This overview delves into subdivided aspects, offering an in-depth understanding of each microarray type. The aspects covered include the intricate mimicry of organ structure, the specialized culture methodologies employed, the indicators utilized to assess action and functionality, and the precise citations referencing the sources of information.

4 Conclusion

To summarize, this article begins by describing the selection and application of materials for organ chips, with five materials - PDMS, glass, silicon, Hydrogel and PMMA - all offering different advantages, yet also disadvantages that should not be neglected. Therefore, various chip materials should be customized according to the different research or clinical treatment needs. In addition, different types of organ chips are known

including lungs, liver, kidney, skin and so on. They all have different structures and operating principles, and the combined organ-on-chip system has a more complex internal construction and theories. These novel and intriguing technologies are developing progressively all the time. As this multidimensional exploration unfolds, it underscores the advancements within the Organ-on-a-Chip field and accentuates the potential for transformative breakthroughs in biomedical research and therapeutic development. Secondly, organ-on-a-chip technology also contributes to the realization of personalized medicine. Since everyone's physiological characteristics and disease response may be different, there are limitations to traditional generalized treatments. By using organ-on-a-chip, doctors can customize a more precise treatment plan based on the patient's individual characteristics, thus improving the treatment effect and the patient's quality of life. The intricate tapestry of materials, organoids, and integrated systems weaves a story of innovation that holds promise for shaping the future of healthcare and scientific discovery.

References

1. F. Yokoi, S. Deguchi, K. Takayama, BBA, **1870**, 6 (2023).
2. J. Li, HQ. Bai, ZH. Wang, BB. Xu, N. Kristen, P. Olson, CY. Liu, YL. Su, JW. Hao, JY. Shen, XT. Xi, J. Zhen, R. Yu, YC. Sun, X. Xie, WX. Tian, F. Yu, XH. Liu, LH. Zhang, DM. Zhou, LL. Si, OOC, **5**,1 (2023).
3. M, Radisic and P. Loskill, ACS Biomater. Sci. Eng., **7**,7 (2021).
4. D. Kefallinou, M. Grigoriou, V. Constantoudis, I. Raptis, E. Xenogiannopoulou, A. Dimoulas, T. Boumpas, A. Tserepi, Surf. Coat. Technol., **466**,1 (2023).
5. P. Haan, K. Mathwig, L. Yuan, Brandon W. Peterson, E. Verpoorte, OOC, **5**,1 (2023).
6. Y. Wang, R. Kumar Kankala, CW. Ou, A. Chen, Z. Yang, Bioact. Mater., **9**,198 (2022).
7. A. Thakur, OpenNano, **13**,1 (2023).
8. D. Huh, BD. Matthews, A, Mammoto, Sci., **328**,1662 (2010).
9. S. Yang, TY. Zhang, YL. Ge, YP. Cheng, LH. Yin, YP. Pu, ZZ. Chen, GY. Liang., J. Hazard. Mater. **458**,1 (2023).
10. D. Konar, M. Devarasetty, DV. Yildiz, Biomed Eng Comput Biol, **7**,17 (2016).
11. J. Shrestha, S. Razavi Bazaz , Es H Aboulkheyr, Crit Rev Biotech, **40**,2 (2020).
12. S. Hassan, S. Sebastian, S. Maharjan, A. Lesha, AM. Carpenter, X. Liu, X. Xie, C. Livermore, YS. Zhang, A. Zarrinpar., Hepatology. **71**,733 (2020).
13. BJ. Kane, MJ. Zinner, ML. Yarmush, Anal Chem. **78**,4291 (2006).
14. H. Lee, S. Chae, JY. Kim, W. Han, JM. Kim, YJ. Choi and DW. Cho, Biofabrication, **11**,2 (2019).
15. DR. Finco. Kidney function, AP,**1**, 441 (1997).
16. KJ. Jang, KY. Suh., Lab Chip. **10**, 36 (2010).
17. AT. O'Neill, NA. Monteiro-Riviere, GM. Walker, Cytotechnology.**56**, 3 (2008).
18. FY. Zheng, FF. Fu, Y. Cheng, CY. Wang, YJ. Zhao, ZZ. Gu, Small**, 12,** 2253 (2016)**.**
19. I. Maschmeyer, AK. Lorenz, K. Schimek, T. Hasenberg, AP. Ramme, J. Hübner, M. Lindner, C. Drewell, S. Bauer, A. Thomas, NS. Sambo, F. Sonntag, R. Lauster and U. Marx, Lab Chip,**15**, 2688 (2015).
20. AO. Stucki, JD. Stucki, SR. Hall, Lab Chip. **15**, 1302 (2015).
21. C. Blume, R. Reale, M. Held, PLoS One. **10**,10 (2015).
22. PJ. Lee, PJ. Hung, LP. Lee, Biotech. Bioeng. **97**,5 (2007).
23. SA. Lee, Y. No da, E. Kang, Lab Chip. **13**, 3529 (2013).
24. AA. Banaeiyan, J. Theobald, J. Paukštyte, Biofabrication. **9**,1 (2017).
25. KJ. Jang, AP. Mehr, GA. Hamilton, Integr Biol (Camb). **5**,9 (2013).
26. M. Zhou, X. Zhang, X. Wen, Sci Rep. **6**, 1 (2016).
27. I. Maschmeyer, AK. Lorenz, K. Schimek, Lab Chip. **15**, 2688 (2015).
28. I. Wagner, B. Atac, G. Lindner, BMC Proc. **7**,93 (2013).
29. B. Ataç, I. Wagner, R. Horland, Lab Chip. **13**,3555 (2013).
30. HE. Abaci, K. Gledhill, AM. Guo, Lab Chip. **15**,882 (2015).