ejpmr, 2018,5(11), 167-170

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ON ORGAN ON CHIP TECHNOLOGY

Swarupa Arvapalli*, P. Nandini, Md. Nabil Ahmed, Roshini Sharma and G. Jyosthna

Joginpally B. R. Pharmacy College.

***Corresponding Author: Swarupa Arvapalli**

Joginpally B. R. Pharmacy College.

Article Received on 23/08/2018 **Article Revised on 13/09/2018** **Article Accepted on 03/10/2018**

ABSTRACT

Invitro cultured cells are showing potential advantage in assay for evaluation of Safety, efficacy, toxicity of drug candidates. These Invitro cell based assays show two major applications in drug discovery process namely; Investigation of seed molecule and Assessment of safety. They are designed to evaluate safety and toxicity in single organs, but the in vivo pharmacokinetics and pharmacodynamics of the administered drug candidates have not been considered. So an evaluating system interconnecting cell cultures is required. Accordingly, the in vitro ADME-Tox culture system known as ADME-Tox culture system has been proposed. This current review article deals with advantages, disadvantages of organs on chip and their current availability and its applications.

KEYWORDS: Seed molecule, ADME-Tox culture system, organs on chip, Invitro cell based assay.

INTRODUCTION

The process of drug development begins with target screening for effective treatment of target disease. After undergoing clinical trials, the drug is considered for approval by regulatory agencies. The entire process takes very long period, e.g., more than 15 years, and may cost more than 100 billion rupees. Testing on cell cultures in petri dishes do not allow to prove the efficiency of a new therapy: cells do not react as they would in the human body when outside of their natural environment. In vitro cellular assays have emerged as a method for improving the efficiency of this process. They have two main applications in the drug discovery process: searching for a compound that is effective against the target disease (seed investigation) and confirmation of safety during use of the identified compounds (safety assessment). Organs on chip: cell cultures, often in 3D, that use microfluidics to reproduce the way a tissue or part of an organ work. Organ on chip research already allowed to create many microfluidic chips that can partially simulate organ function: liver, lungs, gut, etc… and even tumors on chip. Multi-organs on chip could also allow us to witness the side effects of certain drugs on different organs.

Advantages of Organ on Chip technology

- Low cost of manufacturing
- Allows testing a wide range of concentration in the dosage of medicine.
- Due to its three-dimensional aspect, compared to petri dishes, the micro-environment of human cells (oxygen levels, temperature, pH…) is better reproduced inside a chip.
- Use of microfluidics, makes these chips an interesting and innovative solution for research.
- They are easy to use, portable, small sized and can undergo mass production.

Disadvantages of Organ on Chip technology

- The quality of analysis can be affected by the adsorption of products on the inner linings.
- The Reynolds number will always remain small, the flow remain laminar not favouring mixing.

Different Organs on Chip

Liver on Chip

Liver cells are most difficult to keep alive in a petridish which makes its necessity to develop Liver on chip for research on new medicine. Many potential treatments fail before animal testing phase due to hepatotoxicity. Chen-Ta et al.[15] have recreated, on a microfluidic chip, a lover lobule which is the functional unit of the liver, by dielectrophoresis. This lobule consists in liver cells and endothelial cells. The main advantage of the liver on chip is its capacity to replicate microscopic details, for more reliable tests.[16] The liver on chip becomes most important as of all bigger multi organs on a chip. Poly Di Methyl Siloxane is mostly used, it can sometimes absorb small hydrophobic compounds as well as some medicine which can skew results, whereas newly discovered polymers based on polyurethane do not show this fault. The longevity of these livers on chip rarely exceeds two weeks, so it is difficult of measure liver responses for long term studies in new treatments.

Brain on Chip

A small part of brain, blood brain barrier has been reproduced on chip with research. Blood brain barrier protects brain from all the pathogens in the blood flow and only lets through the nutrients the brain needs, this barrier can be a problem for some drug treatments because it bars some active sites from accessing the brain. The advantage of brain on chip over other in vivo and in vitro models comes from more realistic dimensions and geometry. Those microfluidic chips allow to test the flow of a physiological fluid on the epithelium.[29] This flow mimics the blood flow and allows the brain cells proper differentiation and maturation. Brains on chips have proved more accurate than static cultures to predict permeability of the blood-brain barrier.[30,31]

Lungs on Chip

It is unable to mimic an entire lung on a microfluidic chip. However, Huh et al.[11] have reproduced the smallest functional unit in the lung i.e function of an alveolo-capillary membrane. That organ is vital to test new medicine as it acts as the physical barrier. In order to reproduce this membrane, Polydiméthylsiloxane (PDMS) was used, covered in collagen for a better cell adherence, separating epithelial cells in contact with the air on one side, and endothelial cells in contact with a fluid made of nutrients in lieu of blood, on the other. The experiment was also conducted by Jain et al.[12] by using blood instead of a nutrient fluid, in order to get as close as possible to a real lung. Along this microfluidic channel run two empty micro-channels, in order to reproduce the compression cycle that the alveolo-capillary membrane undergoes during breathing.

Gut on Chip

Kim et al.[33] developed a two-layers gut on chip system, it allowed to re-create the mechanical tension, simulating peristaltic movement. She collected stem cells from a patient with digestive issues, and developed a gut on chip to study its response to certain types of food and new treatments. The gut is a key organ for the absorption of medicine, and these breakthroughs would help us better understand these issues and fast forward research.

Applications

- Organs on chips could prove extremely useful in a future where they are more than a research subject to become a research tool.
- These cell cultures allow, with the help of microfluidic technology, to mimic the micro-environment of cells in the human body.
- These chips could become incredible research accelerators, and they could become the default pre-clinical testing solution which would replace animal testing.
- It is possible to recreate each patient on a cell with their induced pluripotent stem cells and directly test the treatment on the cells, in order to adapt the dosage paving for personalized medicine.
- Organs on chips will allow to fight against cancer by helping to develop new treatments.

CONCLUSION

Evaluation of safety of medicines in humans, it is necessary to conduct preclinical trails. However, species difference is one of the problems that cannot be overcome by animal experiments; thus, systems that reflect human pharmacokinetics and pharmacodynamics are anticipated for a long time. In recent years, with the progress of cell culture technology, various culture systems including the organs-on-a-chip system, have been proposed.[39] In order to widely and effectively utilize the organs-on-a-chip systems in drug development process, establishing cell quality standards guaranteeing their reproducibility and robustness is needed. Further studies of the quality control of cells mounted in the organ unit of organs-on-a-chip systems are needed for the enhancement of organs-on-a-chip system application to the drug development process.

REFERENCES

1. Van der Meer, A. D., van den Berg, A. (2012). Organs-on-chips: breaking the in vitro impasse. Integrative Biology, 4(5): 461-470.
2. Moraes, C., Mehta, G., Lesher-Perez, S. C., Takayama, S. (2012). Organs-on-a-chip: a focus on compartmentalized microdevices. Annals of biomedical engineering, 40(6): 1211-1227.
3. Huh, D., Hamilton, G. A., Ingber, D. E. (2011). From 3D cell culture to organs-on-chips. Trends in cell biology, 21(12): 745-754.
4. Polini, A., Prodanov, L., Bhise, N. S., Manoharan, V., Dokmeci, M. R., Khademhosseini, A. (2014). Organs-on-a-chip: a new tool for drug discovery. Expert opinion on drug discovery, 9(4): 335-352.
5. Chabert, M. (2007). Microfluidique de gouttes pour les analyses biologiques. Biophysique [physics.bio-ph]. Université Pierre et Marie Curie – Paris VI.
6. Lipsi, R., Rogliani, P., Calzetta, L., Segreti, A., Cazzola, M. (2014). The clinical use of regenerative therapy in COPD. International journal of chronic obstructive pulmonary disease, 9: 1389.
7. Mannino, D. M., Homa, D. M., Akinbami, L. J., Ford, E. S., Redd, S. C. (2002). Chronic obstructive pulmonary disease surveillance—United States, 1971–2000. Respiratory care, 76(10).
8. Huh, D., Matthews, B. D., Mammoto, A., Montoya-Zavala, M., Hsin, H. Y., Ingber, D. E. (2010). Reconstituting organ-level lung functions on a chip. Science, 328(5986): 1662-1668.
9. Baker, M. (2011). Tissue models: a living system on a chip. Nature, 471(7340): 661-665.
10. Huh, D., Leslie, D. C., Matthews, B. D., Fraser, J. P., Jurek, S., Hamilton, G. A., … Ingber, D. E. (2012). A human disease model of drug toxicity–induced pulmonary edema in a lung-on-a-chip microdevice. Science translational medicine, 4(159): 159ra147-159ra147. ISO 690

11. Khetani, S. R., Bhatia, S. N. (2008). Microscale culture of human liver cells for drug development. Nature biotechnology, 26(1): 120-126.
12. Yip, D., Cho, C. H. (2013). A multicellular 3D heterospheroid model of liver tumor and stromal cells in collagen gel for anti-cancer drug testing. Biochemical and biophysical research communications, 433(3): 327-332.
13. Prot, J. M., Bunescu, A., Elena-Herrmann, B., Aninat, C., Snouber, L. C., Griscom, L., … Corlu, A. (2012). Predictive toxicology using systemic biology and liver microfluidic "on chip" approaches: application to acetaminophen injury. Toxicology and applied pharmacology, 259(3): 270-280.
14. Yang, Y., Li, J., Pan, X., Zhou, P., Yu, X., Cao, H., … Li, L. (2013) Co-culture with mesenchymal stem cells enhances metabolic functions of liver cells in bioartificial liver system. Biotechnology and bioengineering, 110(3): 958-968.
15. Ho, C. T., Lin, R. Z., Chang, W. Y., Chang, H. Y., Liu, C. H. (2006). Rapid heterogeneous liver-cell on-chip patterning via the enhanced field-induced dielectrophoresis trap. Lab on a Chip, 6(6): 724-734.
16. Lee, K. H., Lee, J., Lee, S. H. (2015). 3D liver models on a microplatform: well-defined culture, engineering of liver tissue and liver-on-a-chip. Lab on a Chip, 15(19): 3822-3837.
17. Domansky, K., Leslie, D. C., McKinney, J., Fraser, J. P., Sliz, J. D., Hamkins-Indik, T., … Ingber, D. E. (2013). Clear castable polyurethane elastomer for fabrication of microfluidic devices. Lab on a Chip, 13(19): 3956-3964.
18. Parker, K. K., Tan, J., Chen, C. S., Tung, L. (2008). Myofibrillar architecture in engineered cardiac myocytes. Circulation research, 103(4): 340-342.
19. Grosberg, A., Kuo, P. L., Guo, C. L., Geisse, N. A., Bray, M. A., Adams, W. J., … Parker, K. K. (2011). Self-organization of muscle cell structure and function. PLoS Comput Biol, 7(2): e1001088.
20. Klauke, N., Smith, G., Cooper, J. M. (2007). Microfluidic systems to examine intercellular coupling of pairs of cardiac myocytes. Lab on a Chip, 7(6): 731-739.
21. Saint, D. A. (2008). The cardiac persistent sodium current: an appealing therapeutic target?. British journal of pharmacology, 153(6): 1133-1142.
22. Depre, C., Vatner, S. F. (2007). Cardioprotection in stunned and hibernating myocardium. Heart failure reviews, 12(3-4): 307-317.
23. Martewicz, S., Michielin, F., Serena, E., Zambon, A., Mongillo, M., Elvassore, N. (2012). Reversible alteration of calcium dynamics in cardiomyocytes during acute hypoxia transient in a microfluidic platform. Integrative Biology, 4(2): 153-164.
24. Agarwal, A., Goss, J. A., Cho, A., McCain, M. L., Parker, K. K. (2013). Microfluidic heart on a chip for higher throughput pharmacological studies. Lab on a Chip, 13(18): 3599-3608.
25. Palchesko, R. N., Zhang, L., Sun, Y., Feinberg, A. W. (2012). Development of polydimethylsiloxane substrates with tunable elastic modulus to study cell mechanobiology in muscle and nerve. PloS one, 7(12): e51499.
26. Vidéo de Hamilton G. (2016) Want to test new drugs? Put a fake lung on a chip. https://www.youtube.com/watch?v=UICBOcnN4Y4
27. Abbott, N. J., Dolman, D. E., Yusof, S. R., Reichel, A. (2014). In vitro models of CNS barriers. In Drug Delivery to the brain (pp. 163-197). Springer New York.
28. Booth, R., Kim, H. (2014). Permeability analysis of neuroactive drugs through a dynamic microfluidic in vitro blood–brain barrier model. Annals of biomedical engineering, 42(12): 2379-2391.
29. Deosarkar, S. P., Prabhakarpandian, B., Wang, B., Sheffield, J. B., Krynska, B., Kiani, M. F. (2015). A Novel Dynamic Neonatal Blood-Brain Barrier on a Chip. PloS one, 10(11): e0142725.
30. Booth, R., Kim, H. (2012). Characterization of a microfluidic in vitro model of the blood-brain barrier (BBB). Lab on a chip, 12(10): 1784-1792.
31. Prabhakarpandian, B., Shen, M. C., Nichols, J. B., Mills, I. R., Sidoryk-Wegrzynowicz, M., Aschner, M., Pant, K. (2013). SyM-BBB: a microfluidic blood brain barrier model. Lab on a chip, 13(6): 1093-1101.
32. Van der Helm, M. W., van der Meer, A. D., Eijkel, J. C., van den Berg, A., Segerink, L. I. (2016). Microfluidic organ-on-chip technology for blood-brain barrier research. Tissue barriers, 4(1): e1142493.
33. Kim, H. J., Huh, D., Hamilton, G., Ingber, D. E. (2012). Human gut-on-a-chip inhabited by microbial flora that experiences intestinal peristalsis-like motions and flow. Lab on a chip, 12(12): 2165-2174.
34. Kirby, B. J., Jodari, M., Loftus, M. S., Gakhar, G., Pratt, E. D., Chanel-Vos, C., … Navarro, V. N. (2012). Functional characterization of circulating tumor cells with a prostate-cancer-specific microfluidic device. PloS one, 7(4): e35976.
35. Wlodkowic, D., Cooper, J. M. (2010). Tumors on chips: oncology meets microfluidics. Current opinion in chemical biology, 14(5): 556-567.
36. Mauk, M. G., Ziober, B. L., Chen, Z., Thompson, J. A., Bau, H. H. (2007). Lab-on-a-Chip Technologies for Oral-Based Cancer Screening and Diagnostics. Annals of the New York Academy of Sciences, 1098(1): 467-475.
37. Kim, C., Bang, J. H., Kim, Y. E., Lee, S. H., Kang, J. Y. (2012). On-chip anticancer drug test of regular tumor spheroids formed in microwells by a distributive microchannel network. Lab on a chip, 12(20): 4135-4142.
38. Van Midwoud, P. M., Merema, M. T., Verpoorte, E., Groothuis, G. M. (2010). A microfluidic approach for in vitro assessment of interorgan interactions in drug metabolism using intestinal and liver slices. Lab on a Chip, 10(20): 2778-2786.

39. Imura, Y., Sato, K., Yoshimura, E. (2010). Micro total bioassay system for ingested substances: assessment of intestinal absorption, hepatic metabolism, and bioactivity. Analytical chemistry, 82(24): 9983-9988.
40. Imura, Y., Yoshimura, E., Sato, K. (2012). Micro total bioassay system for oral drugs: evaluation of gastrointestinal degradation, intestinal absorption, hepatic metabolism, and bioactivity. Analytical Sciences, 28(3): 197-197.