## Organ-on-a-Chip: New Tool for Personalized Medicine

Nureddin A. Ashammakhi, MD,  $PhD^{*\dagger}$  and Adam Elzagheid, MD,  $PhD^{\dagger}$ 

**N** ewly developed drugs need to be tested by using cell culture and in vivo using animals. Following these experiments, medicines can then enter into clinical trials to first assess their safety and then efficacy. After appropriate acceptable results obtained, producers apply for approvals from concerned bodies, such as the FDA in the United States. In many cases even with medicines that are approved, complications may occur.<sup>1,2</sup> Because of the failure of two-dimensional (2D) cell culture system to recapitulate in vivo events and failure of animal models to be representative of a different species, that is, human,<sup>3</sup> it remains necessary to search for new possibilities and be able to overcome limitations related to current drug testing methods.<sup>4</sup>

Given also the fact of demanding that all medicines and chemicals undergo animal testing, the cost of development will be tremendously huge, and will be reflected in the prices of developed drugs and time they take before they become available. With new EU regulation (REACH Policy for Registration, Evaluation, and Authorization of Chemicals) requesting the testing for toxicity of c. 30,000 chemicals, we will need about 2.5 to 54 million animals<sup>5</sup> to use for testing (costing about 1.3–9.3 trillion Euros).<sup>6,7</sup> The development of a single drug formulation can take up to 13.5 years<sup>8</sup> and cost 2.5 billion USD.<sup>9</sup>

With the advent of organ-on-a-chip technology which evolved from lab-on-a-chip<sup>10</sup> by culturing cells into microchannels, it seems that an alterative to 2D culture and animals is emerging with promises to be more biomimetic to human physiology. So far, various tissue models were developed to represent lung,<sup>11</sup> gut,<sup>12,13</sup> kidney,<sup>14</sup> heart,<sup>15</sup> liver,<sup>16,17</sup> and bone marrow.<sup>18</sup> Multiorgan-on-a-chip devices were also connected to develop a more biomimetic system to test for studying systemic<sup>19</sup> and secondary<sup>20</sup> toxicity where kidney, liver gut, and so on can interact and provide more reliable results regarding drug absorption, metabolism, clearance, and toxicity. With a more complex level, where about 10 organ-on-a-chip organ types are connected, human-on-a chip is developed to study systemic toxicity.<sup>21</sup>

In addition to drug testing and development, organ-on-a-chip technology represents also a good platform to study physiology and pathology of certain disease processes. Using cells taken from patients, it will be possible to develop personalized medicine in future where specimens taken from patients are tested to define appropriate drug and dose for individual patients in a way similar to what we have today with antibiotic sensitivity testing.

Accepted for publication March 15, 2018.

Copyright © 2018 by Mutaz B. Habal, MD

ISŜN: 1049-2275

Organ-on-a-chip technology is well welcome and funding agencies are putting calls forward for applications to carry our projects in this important niche area. Organ-on-a-chip technology is projected to have a global market of \$6.13 billion by 2025.<sup>22</sup> It is important to prove that the organ-on-a-chip platform can effectively address the core criteria of drug absorption, distribution, metabolism, and excretion. Nevertheless, it will be necessary to validate this technology against well-established standard tests and outcomes in the current practice that are obtained with known compounds.<sup>23</sup> Once established, we will certainly be able to avoid a lot of limitations, problems, and unnecessary loading of patients with ineffective drugs, toxic medicines, or over- or underdosing. We will certainly have more effective medicines and efficient practice of medicine in the next decade, with the use of this new tool, organ-on-a-chip.

## REFERENCES

- Redfern WS, Ewart L, Hammond TG, et al. Impact and frequency of different toxicities throughout the pharmaceutical life cycle. *Toxicologist* 2010;114:1081
- Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician 2008;78:743–750
- Wang B, Gray G. Concordance of noncarcinogenic endpoints in rodent chemical bioassays. *Risk Anal* 2015;35:1154–1166
- Jang KJ, Mehr AP, Hamilton GA, et al. Human kidney proximal tubuleon-a-chip for drug transport and nephrotoxicity assessment. *Integr Biol* (*Camb*) 2013;5:1119–1129
- Hartung T, Rovida C. Chemical regulators have overreached: the costs—both in animal lives and euros—of the European REACH legislation on chemical testing are escalating. Thomas Hartung and Costanza Rovida argue for a suspension of certain toxicity tests. *Nature* 2009;460:1080
- Blaauboer B, Andersen M. The need for a new toxicity testing and risk analysis paradigm to implement REACH or any other large scale testing initiative. *Arch Toxicol* 2007;81:385–387
- Greim H, Arand M, Autrup H, et al. Toxicological comments to the discussion about REACH. Arch Toxicol 2006;80:121–124
- Schacht AL, Dunwiddie CT, Lindborg SR, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov* 2010;9:203–214
- DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. J Health Econ 2016;47:20–33
- Ugolini GS, Visone, R, Redaelli A, et al. Generating multicompartmental 3D biological constructs interfaced through sequential injections in microfluidic devices. *Adv Healthc Mater* [published online ahead of print March 7, 2017] doi: 10.1002/ adhm.201601170
- Huh D, Matthews BD, Montoya-Zavala M, et al. Reconstituting organlevel lung functions on a chip. *Science* 2010;328:1662–1668
- Kim HJ, Ingber DE. Gut-on-a-chip microenvironment induces human intestinal cells to undergo villus differentiation. *Integr Biol (Camb)* 2013;5:1130–1140
- Kim SH, Lee JW, Choi I, et al. A microfluidic device with 3-d hydrogel villi scaffold to simulate intestinal absorption. J Nanosci Nanotechnol 2013;13:7220–7228
- Jang K, Suh K. A multi-layer microfluidic device for efficient culture and analysis of renal tubular cells. *Lab Chip* 2010;10:36–42

The Journal of Craniofacial Surgery • Volume 00, Number 00, Month 2018

Copyright © 2018 Mutaz B. Habal, MD. Unauthorized reproduction of this article is prohibited.

From the \*Division of Plastic Surgery, Department of Surgery, Oulu University Hospital, Oulu, Finland; and <sup>†</sup>Biotechnology Research Center, Authority for Natural Sciences Research and Technology, Tripoli, Libya. Received March 13, 2018.

Address correspondence and reprint requests to Nureddin A. Ashammakhi, MD, PhD, Institute of Science and Technology in Medicine, Helsinki, Finland; E-mail: n.ashammakhi@gmail.com, nureddin.ashammakhi@oulu.fi The authors report no conflicts of interest.

DOI: 10.1097/SCS.00000000004604

- Grosberg A, Alford PW, McCain ML, et al. Ensembles of engineered cardiac tissues for physiological and pharmacological study: heart on a chip. *Lab Chip* 2011;11:4165
- Hong S, Lee LP. Patient-specific iPSCs-based liver-on-a-chip. *Biophys J* 2014;106:245a
- Kang YBA, Sodunke TR, Lamontagne J, et al. Liver sinusoid on a chip: long-term layered co-culture of primary rat hepatocytes and endothelial cells in microfluidic platforms. *Biotechnol Bioeng* 2015;112:2571–2582
- Torisawa YS, Spina CS, Mammoto T, et al. Bone marrow-on-a-chip replicates hematopoietic niche physiology in vitro. *Nat Methods* 2014;11:663–669
- Oleaga C, Bernabini C, Smith AS, et al. Multi-organ toxicity demonstration in a functional human in vitro system composed of four organs. *Sci Rep* 2016;6:20030

- 20. Webb S. Cells in the third dimension. *Biotechniques* 2017;62: 93–98
- Abaci HE, Shuler ML. Human-on-a-chip design strategies and principles for physiologically based pharmacokinetics/ pharmacodynamics modeling. *Integr Biol (Camb)* 2015;7: 383–391
- Organ-on-chip market analysis & trends organ (heart-on-chip, human-on-chip, intestine-on-chip, kidney-on-chip, liver-on-chip, lung-on-chip), application - forecast to 2025. PR Newswire. January 18, 2017. Available from: https://search.proquest.com/ docview/1859588994.
- Wilmer MJ, Ng CP, Lanz HL, et al. Kidney-on-a-chip technology for drug-induced nephrotoxicity screening. *Trends Biotechnol* 2016;34:156–170

© 2018 Mutaz B. Habal, MD