



International Journal of Biomedical Science and Research

Journal homepage: <https://trpub.org/journal.php?id=DBwGBwGwyu>

TRPub

IJBSR

International Journal of
Biomedical Science and
Research

Vol. 1 Issue 1 2026

Review Article

Open Access

Organ-on-Chip Platforms for Drug Toxicity Screening: Progress and Translational Bottlenecks

Minh Cho^{1*}, Haruka Gauthier², Elin Dominguez³

¹Department of Medical Sciences, Niger University Centre for Medical Sciences, Senegal

²Department of Medical Sciences, Tamiraparani Academy of Medical Sciences, Kenya

³Department of Medical Sciences, Douro Institute for Advanced Medical Sciences, Serbia

Article Info

Volume 1, Issue 1, 2026

doi: [10.62715/ijbsr.2026.v1.i1.pp8-14](https://doi.org/10.62715/ijbsr.2026.v1.i1.pp8-14)

Received: 19 February 2026

Accepted: 09 April 2026

Published: 14 June 2026

Abstract

Unexpected toxicity remains a leading reason why drug candidates fail, and the cell cultures and animal studies used to anticipate it have well-known blind spots, the liver prominent among them. Organ-on-chip devices, or microphysiological systems, culture human cells in perfused microchannels with engineered tissue interfaces and mechanical cues, and have been advanced as a more human-relevant way of testing safety. This narrative review considers how far that claim is supported. It describes what perfusion and tissue architecture add to conventional culture, surveys the liver, kidney, heart, intestine and linked multi-organ models applied to toxicity questions, and examines the published evidence for predictive value, including a blinded evaluation of a human liver chip against drugs of known clinical hepatotoxicity. It then sets out the obstacles to routine use: absorption of drugs by device materials, the supply and maturity of human cells, limited throughput, the absence of shared standards, and the need for qualification for a stated context of use, which legislation permitting alternatives to animal tests does not itself supply. The review concludes that chips are at present a mechanistic complement to established assays, and that replacing specific animal studies depends on multi-site validation not yet done.

Keywords: *Organ-on-chip, Microphysiological systems, Drug-induced liver injury, Predictive toxicology, Alternatives to animal testing, Regulatory qualification*

© 2026 Minh Cho et al. This is an open access article under the CC BY license (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

1. Introduction

Most drug candidates that enter development never reach patients, and unexpected toxicity is among the commonest reasons. An analysis of the pipelines of four large pharmaceutical companies found safety problems, non-clinical toxicology above all, to be the leading cause of project termination (Waring *et al.*, 2015). The tests meant to catch such liabilities, cultured cell lines and studies in rodents and a second species, are imperfect guides. In the survey by Olson *et al.* (2000), animal studies anticipated most human toxicities overall but did less well for some organs, the liver among them, and hepatic injury is a frequent cause of late failure and of withdrawal after marketing.

* Corresponding author: Minh Cho, Department of Medical Sciences, Niger University Centre for Medical Sciences, Senegal. E-mail: minh.cho@niger.edu

© 2026 Minh Cho et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Organ-on-chip devices, also called microphysiological systems, were conceived partly as an answer. They culture human cells in microfabricated channels under continuous perfusion, often with two tissue types separated by a porous membrane and subjected to forces that mimic breathing, peristalsis or blood flow (Bhatia and Ingber, 2014). The promise is a human-relevant test that sits between the simplicity of a culture dish and the complexity of an animal, in keeping with the long-standing aim of replacing, reducing and refining animal use (Russell and Burch, 1959).

The field has now existed long enough for sober assessment. Several chips are sold commercially, pharmaceutical companies have evaluated them in-house, and legislation in the United States has removed the statutory insistence on animal tests before first-in-human trials. Yet chips have not displaced conventional assays in routine safety screening. This review describes what the platforms can do for toxicity testing, what evidence supports their predictive value, and which obstacles, technical and institutional, stand between a persuasive demonstration and a qualified regulatory tool.

2. Scope and Approach

The article is a narrative review of the published literature, organised around the organs most relevant to drug attrition and the stages through which a new test method passes on its way to regulatory use. It relies on primary reports of influential devices, on evaluation studies conducted with or by industry, on consensus papers from stakeholder workshops, and on earlier reviews (Esch *et al.*, 2015; Low *et al.*, 2021; Ingber, 2022). It does not attempt a systematic search and gives no pooled performance figures, since the studies differ too much in design to be combined. Disease modelling and efficacy testing, large subjects in their own right, are left aside except where they bear on safety.

3. What a Chip Adds to Cell Culture

Hepatocytes in a conventional dish lose their characteristic functions within days. Cytochrome P450 activity falls and polarity is lost, and with them goes the capacity to form the reactive metabolites responsible for much drug-induced injury. One early remedy was architectural. Khetani and Bhatia (2008) patterned islands of primary human hepatocytes among supportive fibroblasts and obtained cultures whose metabolic competence lasted for weeks, which made repeated dosing possible. Three-dimensional spheroids pursue the same aim by self-assembly and have been tested against sizeable sets of hepatotoxic and safe drugs (Proctor *et al.*, 2017).

Chips add two features that static formats lack. The first is flow. Perfusion supplies nutrients and oxygen, removes waste, exposes endothelium and epithelium to physiological shear, and allows drug concentrations to rise and fall as they do in plasma instead of sitting at a fixed level. The second is the engineered tissue interface. The lung device of Huh *et al.* (2010) placed alveolar epithelium and capillary endothelium on opposite faces of a flexible membrane and stretched it rhythmically; cyclic strain changed the tissue's inflammatory response to nanoparticles in a way that static culture had not shown. That experiment supplied the argument on which the field rests: mechanical and multicellular context alters toxicological responses, so leaving it out risks missing them.

4. Organ Models Used in Safety Testing

Table 1 lists the organ models most often applied to toxicity questions, the readouts they offer and the principal weakness of each.

4.1. Liver

The liver has received the most attention, for obvious reasons. A widely used design places primary hepatocytes in one channel and sinusoidal endothelial cells, with or without Kupffer and stellate cells, in the other. Jang *et al.* (2019) built matching chips from rat, dog and human cells and showed that they reproduced species-specific hepatotoxicities, including patterns of injury such as steatosis, cholestasis and fibrosis that depend on the non-parenchymal cells. Species-matched chips have a use beyond prediction: they allow an animal finding of uncertain human relevance to be examined in the corresponding human

tissue.

Table 1: Organ-on-chip models applied to drug toxicity testing, with typical cells, readouts and limitations			
Organ model	Typical cells	Toxicity readouts	Principal limitation
Liver	Primary hepatocytes with endothelial, Kupffer and stellate cells	Albumin output, enzyme release, steatosis, bile transport	Donor variability; scarce primary cells
Kidney proximal tubule	Primary tubular epithelium under luminal flow	Injury markers, transporter-dependent uptake	Other nephron segments seldom modelled
Heart	Stem cell-derived cardiomyocytes	Beat rate, contractility, electrical activity	Immature, fetal-like phenotype
Intestine	Caco-2 or organoid-derived epithelium	Barrier integrity, absorption	Cell line origin; microbiota hard to sustain
Lung	Alveolar or airway epithelium with endothelium	Barrier leak, cytokine release	Mainly relevant to inhaled compounds
Linked multi-organ	Two or more of the tissues above	Metabolite-driven and systemic effects	Scaling, shared medium, complexity

4.2. Kidney, heart and intestine

For the kidney, proximal tubule cells cultured under luminal flow form a polarised epithelium with primary cilia and transporter activity closer to the native tubule, and respond to cisplatin in a manner that depends on those transporters (Jang et al., 2013). Cardiac chips mostly use cardiomyocytes derived from induced pluripotent stem cells, aligned into tissue that beats and responds to drugs affecting rate and rhythm (Mathur et al., 2015). Intestinal chips subject an epithelial layer to flow and cyclic deformation, which promotes villus-like differentiation and permits co-culture with bacteria (Kim et al., 2012). Each has shown responses to reference toxicants. Fewer have been evaluated against large blinded sets of compounds.

4.3. Linked organs

Much toxicity involves more than one organ: a metabolite formed in the liver injures the kidney, or intestinal absorption determines hepatic exposure. Multi-organ platforms connect tissue compartments through a shared circulating medium. Maschmeyer et al. (2015) maintained intestine, liver, skin and kidney equivalents on one chip for four weeks, robotic systems have since coupled as many as eight vascularised chips (Novak et al., 2020), and pharmacokinetic parameters for test drugs have been estimated from such linked systems by computational scaling (Herland et al., 2020). The intellectual appeal is plain. So are the difficulties: organs must be sized relative to one another, a single medium must sustain all of them, and each added tissue multiplies the opportunities for failure (Wikswow et al., 2013).

5. Evidence of Predictive Value

The strongest published test of a chip for safety prediction is the study by Ewart et al. (2022). Several hundred human liver chips were dosed in blinded fashion with 27 drugs of known clinical hepatotoxicity status, following evaluation guidelines proposed by an industry consortium (Baudy et al., 2020). The chips detected the large majority of the hepatotoxic drugs, which had passed animal testing before causing injury in patients, and did not flag any of the non-toxic comparators. The authors went on to estimate the economic value of avoiding late failures if such a model were used routinely.

The result is encouraging and needs careful reading. The compound set is small and made up of drugs with unambiguous clinical histories, whereas a screening tool meets mostly compounds whose liabilities

are subtle or absent. The study was conducted by the manufacturer of the chip. Performance depended on correcting nominal doses for drug lost to the device material. And one study with one platform in one organisation says little about transferability. These points are not peculiar to this work. They describe the distance between a demonstration and a qualification, which is where most of the field now sits (Low et al., 2021).

6. Translational Bottlenecks

The obstacles to wider use can be arranged as a stack, shown in Figure 1, in which each layer must hold before the one above it can be trusted. Problems at the base, in materials and cells, propagate upwards into irreproducible biology and finally into regulatory hesitation.

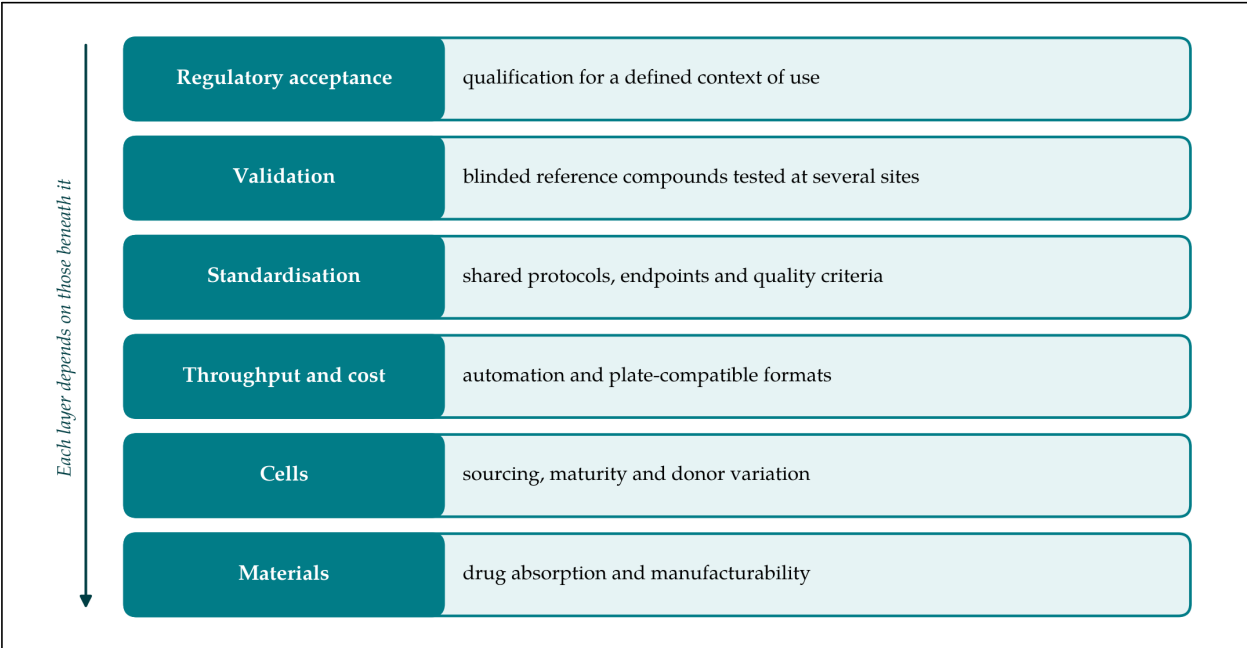


Figure 1: Layers of the translational path for organ-on-chip toxicity models, from device materials to regulatory acceptance

6.1. Materials and drug loss

Most research chips are cast in polydimethylsiloxane, a silicone that is transparent, permeable to gases and easy to mould. It also absorbs small hydrophobic molecules, as Toepke and Beebe (2006) pointed out early on, and many drugs are small and hydrophobic. The concentration reaching the cells may then be a fraction of the concentration applied, and the fraction differs from compound to compound (van Meer et al., 2017). Workarounds exist: measuring concentrations in the effluent, modelling the loss, coating the channels, or switching to thermoplastics. Each adds work, and the alternative materials give up the gas permeability or elasticity that made silicone attractive in the first place.

6.2. Cells

A chip is only as human as the cells in it. Primary hepatocytes and tubular cells are scarce, costly and variable between donors, and a lot that performs well cannot be reordered indefinitely. Cell lines are consistent but often lack the metabolic enzymes that matter. Induced pluripotent stem cells promise an unlimited, genetically defined supply, yet their derivatives tend to resemble fetal tissue more than adult tissue, a recognised weakness of cardiomyocytes and hepatocyte-like cells alike (Ingber, 2022). Donor variation is itself informative, given that idiosyncratic toxicity affects a minority of patients, but capturing it requires many donors, and that collides with throughput.

6.3. Throughput, cost and standardisation

Early safety screening handles compounds by the thousand in multi-well plates. A chip experiment handles tens, takes weeks and requires trained staff. Chips are therefore better placed later in the pipeline, for mechanistic follow-up of a few candidates, than as a first filter. Even there, comparison between laboratories is hampered by the variety of designs, media, flow rates and endpoints. Stakeholder workshops have repeatedly called for agreed performance criteria and lists of reference compounds (Marx *et al.*, 2016; Marx *et al.*, 2020), and the industry guidelines for liver models were a concrete step in that direction (Baudy *et al.*, 2020).

6.4. Qualification and regulatory acceptance

Regulators do not approve a technology in the abstract. They accept data from a method for a stated context of use: a particular question, in a particular class of compound, at a particular stage. The FDA Modernization Act 2.0 removed the legal requirement that animal studies precede human trials and named microphysiological systems among the admissible alternatives (United States Congress, 2022). The law permits; it does not qualify. A sponsor who submits chip data in place of an animal study must still persuade reviewers that the model is fit for that purpose, and the evidence for doing so, reproducibility across sites above all, is thin. In practice chips are currently used alongside animal studies, to explain or to prioritise, and not instead of them.

7. Gaps and Future Work

The most useful next step is probably the least glamorous: independent evaluation of existing liver and kidney chips in several laboratories, against larger blinded compound sets that include many negatives, with full reporting of failed runs. Such studies would establish reproducibility and realistic predictive values, and would show whether chips outperform simpler three-dimensional cultures by enough to justify their cost. Comparative work of this kind is rare, since developers have little incentive to fund trials against cheaper competitors.

On the technical side, non-absorbing materials compatible with mass manufacture, integrated sensors that replace end-point assays with continuous readouts, and better protocols for maturing stem cell derivatives would each remove a known weakness. Immune components are largely missing from current models, although immune mechanisms underlie much idiosyncratic injury. Linked multi-organ systems remain research instruments. Their path to regulatory use is longer, and it may prove more productive to combine single-organ data through physiologically based modelling than to build ever larger physical assemblies (Herland *et al.*, 2020).

8. Conclusion

Organ-on-chip platforms have shown that human cells kept under flow and mechanical load reproduce toxic responses that static cultures and, in some instances, animals miss. For the liver in particular there is now a blinded evaluation suggesting real predictive value. The distance between that evidence and routine regulatory use is set by drug absorption into device materials, the supply and maturity of human cells, low throughput, a lack of shared standards, and the absence of multi-site validation for defined contexts of use. These are problems of engineering, logistics and evidence, and none appears insuperable. For the present the realistic role of the technology is as a mechanistic complement to established tests, with replacement of specific animal studies a prospect that depends on validation work still to be done.

Conflict of interest

To be declared by the author(s) before publication.

Funding

To be declared by the author(s) before publication.

References

- Baudy, A.R., Otieno, M.A., Hewitt, P., Gan, J., Roth, A., Keller, D., et al. (2020). [Liver microphysiological systems development guidelines for safety risk assessment in the pharmaceutical industry](#). *Lab on a Chip*, 20(2): 215-225.
- Bhatia, S.N. and Ingber, D.E. (2014). [Microfluidic organs-on-chips](#). *Nature Biotechnology*, 32(8): 760-772. <https://doi.org/10.1038/nbt.2989>
- Esch, E.W., Bahinski, A. and Huh, D. (2015). [Organs-on-chips at the frontiers of drug discovery](#). *Nature Reviews Drug Discovery*, 14(4): 248-260. <https://doi.org/10.1038/nrd4539>
- Ewart, L., Apostolou, A., Briggs, S.A., Carman, C.V., Chaff, J.T., Heng, A.R., et al. (2022). [Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology](#). *Communications Medicine*, 2: 154. <https://doi.org/10.1038/s43856-022-00209-1>
- Herland, A., Maoz, B.M., Das, D., Somayaji, M.R., Prantil-Baun, R., Novak, R., et al. (2020). [Quantitative prediction of human pharmacokinetic responses to drugs via fluidically coupled vascularized organ chips](#). *Nature Biomedical Engineering*, 4(4): 421-436. <https://doi.org/10.1038/s41551-019-0498-9>
- Huh, D., Matthews, B.D., Mammoto, A., Montoya-Zavala, M., Hsin, H.Y. and Ingber, D.E. (2010). [Reconstituting organ-level lung functions on a chip](#). *Science*, 328(5986): 1662-1668. <https://doi.org/10.1126/science.1188302>
- Ingber, D.E. (2022). [Human organs-on-chips for disease modelling, drug development and personalized medicine](#). *Nature Reviews Genetics*, 23(8): 467-491. <https://doi.org/10.1038/s41576-022-00466-9>
- Jang, K.-J., Mehr, A.P., Hamilton, G.A., McPartlin, L.A., Chung, S., Suh, K.-Y. and Ingber, D.E. (2013). [Human kidney proximal tubule-on-a-chip for drug transport and nephrotoxicity assessment](#). *Integrative Biology*, 5(9): 1119-1129. <https://doi.org/10.1039/c3ib40049b>
- Jang, K.-J., Otieno, M.A., Ronxhi, J., Lim, H.-K., Ewart, L., Kodella, K.R., et al. (2019). [Reproducing human and cross-species drug toxicities using a Liver-Chip](#). *Science Translational Medicine*, 11(517): eaax5516. <https://doi.org/10.1126/scitranslmed.aax5516>
- Khetani, S.R. and Bhatia, S.N. (2008). [Microscale culture of human liver cells for drug development](#). *Nature Biotechnology*, 26(1): 120-126. <https://doi.org/10.1038/nbt1361>
- Kim, H.J., Huh, D., Hamilton, G. and 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. <https://doi.org/10.1039/c2lc40074j>
- Low, L.A., Mummery, C., Berridge, B.R., Austin, C.P. and Tagle, D.A. (2021). [Organs-on-chips: Into the next decade](#). *Nature Reviews Drug Discovery*, 20(5): 345-361. <https://doi.org/10.1038/s41573-020-0079-3>
- Marx, U., Akabane, T., Andersson, T.B., Baker, E., Beilmann, M., Beken, S., et al. (2020). [Biology-inspired microphysiological systems to advance patient benefit and animal welfare in drug development](#). *ALTEX*, 37(3): 365-394. <https://doi.org/10.14573/altex.2001241>
- Marx, U., Andersson, T.B., Bahinski, A., Beilmann, M., Beken, S., Cassee, F.R., et al. (2016). [Biology-inspired microphysiological system approaches to solve the prediction dilemma of substance testing](#). *ALTEX*, 33(3): 272-321. <https://doi.org/10.14573/altex.1603161>
- Maschmeyer, I., Lorenz, A.K., Schimek, K., Hasenberg, T., Ramme, A.P., Hübner, J., et al. (2015). [A four-organ-chip for interconnected long-term co-culture of human intestine, liver, skin and kidney equivalents](#). *Lab on a Chip*, 15(12): 2688-2699. <https://doi.org/10.1039/c5lc00392j>
- Mathur, A., Loskill, P., Shao, K., Huebsch, N., Hong, S., Marcus, S.G., et al. (2015). [Human iPSC-based cardiac microphysiological system for drug screening applications](#). *Scientific Reports*, 5: 8883. <https://doi.org/10.1038/srep08883>
- Novak, R., Ingram, M., Marquez, S., Das, D., Delahanty, A., Herland, A., et al. (2020). [Robotic fluidic coupling and interrogation of multiple vascularized organ chips](#). *Nature Biomedical Engineering*, 4(4): 407-420. <https://doi.org/10.1038/s41551-019-0497-x>

- Olson, H., Betton, G., Robinson, D., Thomas, K., Monroe, A., Kolaja, G., et al. (2000). [Concordance of the toxicity of pharmaceuticals in humans and in animals](#). *Regulatory Toxicology and Pharmacology*, 32(1): 56-67. <https://doi.org/10.1006/rtph.2000.1399>
- Proctor, W.R., Foster, A.J., Vogt, J., Summers, C., Middleton, B., Pilling, M.A., et al. (2017). [Utility of spherical human liver microtissues for prediction of clinical drug-induced liver injury](#). *Archives of Toxicology*, 91(8): 2849-2863. <https://doi.org/10.1007/s00204-017-2002-1>
- Russell, W.M.S. and Burch, R.L. (1959). *The Principles of Humane Experimental Technique*. Methuen, London.
- Toepke, M.W. and Beebe, D.J. (2006). [PDMS absorption of small molecules and consequences in microfluidic applications](#). *Lab on a Chip*, 6(12): 1484-1486. <https://doi.org/10.1039/b612140c>
- United States Congress (2022). [FDA Modernization Act 2.0, enacted as part of the Consolidated Appropriations Act, 2023](#). Public Law 117-328, Washington, DC.
- van Meer, B.J., de Vries, H., Firth, K.S.A., van Weerd, J., Tertoolen, L.G.J., Karperien, H.B.J., et al. (2017). [Small molecule absorption by PDMS in the context of drug response bioassays](#). *Biochemical and Biophysical Research Communications*, 482(2): 323-328. <https://doi.org/10.1016/j.bbrc.2016.11.062>
- Waring, M.J., Arrowsmith, J., Leach, A.R., Leeson, P.D., Mandrell, S., Owen, R.M., et al. (2015). [An analysis of the attrition of drug candidates from four major pharmaceutical companies](#). *Nature Reviews Drug Discovery*, 14(7): 475-486. <https://doi.org/10.1038/nrd4609>
- Wikswa, J.P., Curtis, E.L., Eagleton, Z.E., Evans, B.C., Kole, A., Hofmeister, L.H. and Matloff, W.J. (2013). [Scaling and systems biology for integrating multiple organs-on-a-chip](#). *Lab on a Chip*, 13(18): 3496-3511. <https://doi.org/10.1039/c3lc50243k>