



Image courtesy of
Emulate, Inc

Table 1. A Dozen Reasons Why Micro-Physiological Systems (MPS) Like Organ-Chips are Better at Modeling Human Diseases

When it comes to modeling human diseases, MPS are exciting new frontiers. These advanced research models are made possible by the convergence of many disciplines such as biophysics, regenerative medicine, electrical engineering and materials science. Using these systems, the scientific discovery process - from the development of new medicines to environmental health and safety testing - can be approached in more sophisticated, ambitious and human-relevant ways.

Center for Contemporary Sciences

- | | |
|--|--|
| <p><input type="checkbox"/> 1. Can incorporate AI platforms and biosensors providing actionable health data in real-time throughout discovery as well as during and after treatment.</p> <p>This is critical for (i) the modern design of effective drugs, (ii) the refinement of therapeutic responses, and (iii) the tracking of molecular outcomes at the granular level. Ideal too for 'digital twin' frontier in medicine. [1, 2]</p> | <p><input type="checkbox"/> 5. Can replicate with marked fidelity the unique features of the human gut flora, microbiomes, and characteristics of immunological nature in people.</p> <p>A striking difference between humans and animals is the function of the microbiome and other species- and gender-specific digestive and immune responses that can be modeled elegantly using MPS. [2, 3]</p> |
| <p><input type="checkbox"/> 2. Can predict the safety of drugs with 87% sensitivity as compared to less than 50% using existing models.</p> <p>This is vital for producing safer, cheaper, and more effective drugs all-around. It will reduce the high failure rate in clinical trials (currently at 95%), and lower post-market withdrawal and termination of drugs. [2, 4]</p> | <p><input type="checkbox"/> 6. Can facilitate the rapid repurposing of 100s of existing drugs with approved and established safety profiles.</p> <p>This is a key advantage when testing the efficacy of repurposed drugs or exploring new indications. A recent example is the FDA acceptance of efficacy data for rare neuropathies using a repurposed antibody, TNT005. [2, 5]</p> |
| <p><input type="checkbox"/> 3. Can prevent the ill-advised jettison of scores of potentially life-saving drugs as often dictated by animal data.</p> <p>Scores of drugs are being discarded prematurely due to misleading safety and efficacy data in animals. The use of MPS has proven its advantage of not falsely labeling safe drugs as toxic with 100% specificity. [2, 4]</p> | <p><input type="checkbox"/> 7. Can enable modeling of high-complexity anatomies, pathologies, and conditions traditionally deemed risky, inoperable, and inmedicable.</p> <p>The entanglement of immunity, metabolism, and tissue homeostasis underlies many human complex diseases and phenomena (IBD, BM injury, Angiogenesis). Here, MPS are potentially gamechangers. [2, 6, 7]</p> |
| <p><input type="checkbox"/> 4. Can provide repeated, serial, or sequential testing, including same site re-interrogation in ways that are impossible using any other model.</p> <p>Technological advantages intrinsic to microfluidics and MPS platforms have practical implications for designing accurate physiological simulations and generating high-content experimental and therapeutics data. With more progress in improving throughput, MPS can soon deliver unique high-content/high-throughput outcomes. [2, 8]</p> | <p><input type="checkbox"/> 8. Can spark investments in neglected and rare conditions that receive little to no attention due to financial return on investment considerations.</p> <p>Hundreds of rare diseases with small patient populations are deemed risky. On average, it takes \$2.6 billion to bring a new drug to market. In this regard, MPS can reduce the barriers of entry for many startups given the MPS manageable infrastructure needs and the no reliance on costly and unreliable animal models. [2, 5]</p> |

9. Can save critical time during pandemics and other emergencies, including rapid deployment to eliminate poor candidates in vaccine target screening.

Critical for future pandemic prevention and public health emergencies. As an example, MPS platforms were able to predict the poor response of SARS-CoV-2 to Hydroxychloroquine effectively and rapidly. [9, 10]

10. Can generate productivity gains, in part, by reducing the cost and time R&D requires to develop new drugs.

Overall, the failure rate in developing drugs safe and effective in humans is a stupefying 95%, caused in part by the poor predictive value of animal models. MPS can reduce this and lead to productivity gains of \$24 billion annually according to some industry estimates. \$3 billion could be gained annually if Liver-Chips were used to predict liver toxicity across the discovery pipeline. [4]

11. Can capture the physio-mechanical properties of tissues and organs which are critical for the precise modeling of proper biological functions in humans.

A key feature of advanced MPS is mimicking the movement of cells, liquids and materials for unique insights into the relationship between kinetics, hemodynamics, signaling, and flow. All essentials in physiological measurements/treatment response. [9, 11]

12. Can lead to new frontiers in personalized medicine by producing health assessments based on the very individual's natural history, gender, genetic predispositions, and/or specific response to therapy.

Disparate elements of this are now being tested. Future application of MPS in personalized diagnosis and treatment using one's own biological materials will be a disruptive innovation in healthcare delivery & services.

Informative literature and reviews: [12-17]

Abbreviations -- AI: Artificial Intelligence; IBD: Inflammatory Bowel Disease; BM Injury: Bone Marrow Injury

1. Bavli, D., et al., *Real-time monitoring of metabolic function in liver-on-chip microdevices tracks the dynamics of mitochondrial dysfunction*. Proc Natl Acad Sci U S A, 2016. 113(16): p. E2231-40.
2. Nahle, Z., *A proof-of-concept study poised to remodel the drug development process*. Frontiers in Medical Technology, 2022. 4.
3. Jalili-Firoozinezhad, S., et al., *Establishment of a Modular Anaerobic Human Intestine Chip*. Methods Mol Biol, 2022. 2373: p. 69-85.
4. Ewart, L., et al., *Performance assessment and economic analysis of a human Liver-Chip for predictive toxicology*. Commun Med (Lond), 2022. 2(1): p. 154.
5. Rumsey, J.W., et al., *Classical Complement Pathway Inhibition in a "Human-On-A-Chip" Model of Autoimmune Demyelinating Neuropathies*. Adv Ther (Weinh), 2022. 5(6).
6. Trapecar, M., et al., *Gut-Liver Physiomechanics Reveal Paradoxical Modulation of IBD-Related Inflammation by Short-Chain Fatty Acids*. Cell Syst, 2020. 10(3): p. 223-239 e9.
7. Chou, D.B., et al., *On-chip recapitulation of clinical bone marrow toxicities and patient-specific pathophysiology*. Nat Biomed Eng, 2020. 4(4): p. 394-406.
8. Benam, K.H., et al., *Small airway-on-a-chip enables analysis of human lung inflammation and drug responses in vitro*. Nat Methods, 2016. 13(2): p. 151-7.
9. Si, L., et al., *A human-airway-on-a-chip for the rapid identification of candidate antiviral therapeutics and prophylactics*. Nat Biomed Eng, 2021. 5(8): p. 815-829.
10. Thacker, V.V., et al., *Rapid endotheliitis and vascular damage characterize SARS-CoV-2 infection in a human lung-on-chip model*. EMBO Rep, 2021. 22(6): p. e52744.
11. Huh, D., et al., *Reconstituting organ-level lung functions on a chip*. Science, 2010. 328(5986): p. 1662-8.
12. Vulto, P. and J. Joore, *Adoption of organ-on-chip platforms by the pharmaceutical industry*. Nat Rev Drug Discov, 2021. 20(12): p. 961-962.
13. Tagle, D.A., *The NIH microphysiological systems program: developing in vitro tools for safety and efficacy in drug development*. Curr Opin Pharmacol, 2019. 48: p. 146-154.
14. Nahle, Z., *COVID Boosters Are Critical, But Using Only Animal Data Is a Needless Gamble*, in Truthout. 2022.
15. Low, L.A., et al., *Organs-on-chips: into the next decade*. Nat Rev Drug Discov, 2021. 20(5): p. 345-361.
16. Ingber, D.E., *Human organs-on-chips for disease modelling, drug development and personalized medicine*. Nat Rev Genet, 2022. 23(8): p. 467-491.

17. Ewart, L. and A. Roth, *Opportunities and challenges with microphysiological systems: a pharma end-user perspective*. Nat Rev Drug Discov, 2021. 20(5): p. 327-328.