

Of human-on-a-chip and humans: Considerations for creating and using microphysiological systems

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Recent advances in biomedical research have offered a broad range of approaches and tools that enhance our capability to practice evidence-based medicine and evidence-based regulation and thereby to improve human health. From innovation to practice has never been a straight line or an easy path, however; innovation is of the essence of science, but it does not automatically result in real-world applications. Many factors, such as “fit for purpose” and reproducibility, must be closely and repeatedly investigated to assure the translation of innovation to the benefit of public health. To this end, regulatory science, the fundamental and applied science that is used to make regulatory decisions by governing bodies and agencies such as the FDA, has played a critical role in the engagement of stakeholders and research communities to assure the appropriate translation of new findings and approaches by standardizing the analysis protocols and emphasizing that innovative and emerging technologies must reflect the underlying biology and be reproducible.

The temptation is always to see our own innovation as the pinnacle of science that solves all the challenges, which can lead to overpromising its applicability and thus setting a bar too high for success. In the near term this limits the usefulness of new discoveries, although knowledgeable individuals might have predicted their true value versus what was promised. It is clear, no matter how a technology will be applied, that its fate is largely decided by how it is developed or constructed and whether the results of testing it can be reproduced.

If the goal is to simulate a human, at least in terms of chemical effects, safety evaluation, and the practice of regulatory science, what are the critical considerations that are required to provide a high degree of prediction? The criteria will depend on the intention of the assays; that is, is the microphysiological system a tool for screening or a step toward building an actual replacement of an existing organ system? The latter may require much more research and universal acceptance than the former. Regardless of the intent, for maximum benefit one needs the system of cells or tissue to reflect the human condition. The cells may need to simulate a particular organ system, and within that organ, there is the consideration of the type of cells, their differentiation state, and the cell–cell interactions needed to provide normal function, as well as susceptibility to a disease or

toxicant exposure. For example, are the appropriate cell types and interactions present to exhibit the desired phenotype, such as the normal beating of the heart, and can perturbation of such a system reproduce responses to disease or exposure to drugs or toxicants?

“Human-on-a-chip” and “human organ construct” microphysiological systems are a new, emerging technology that has the potential to correlate *in vivo* with *in vitro* and simulate human organ systems. The human-on-a-chip technology basically uses *in vitro* human organ constructs in which the various cells communicate. These chips and constructs are designed to reflect biological activity similar to the *in vivo* situation. The organ-on-a-chip can then be used to determine if drugs and chemicals can elicit *in vitro* the physiological activity of a human organ observed *in vivo*. These microphysiological systems have the potential to be used to assess basic biology and physiology, as well as the pharmacology and toxicology of drugs and chemicals, to study organ–organ interactions, and/or to be used as a human disease model.

The use of human cells is an enormous advantage because there is no need to extrapolate across species, but even so, there may be the requirement that different cell types interact in a three-dimensional relationship in order to provide prediction of the intact human. The immediate environment of the cells in culture, including cell types (single or multiple origins), the need for specialized media to keep them in a differentiated state (e.g., presence of growth factors, cytokines, and other hormones), and the three-dimensional configuration can all affect outcome measures. The inclusion of multiple cell types and cell layers or scaffolding has proved an important variable in cellular function.

The question of what human these selected cells represent is another issue. If embryonic stem cells or other cell types are the cells of choice, they may represent a rather limited genomic diversity. One could argue that this shortcoming may be overcome by increasing the N so that many genomes are included, but this raises the issues of increased cost, availability of cells from a wide enough range of individuals to represent the population, and ethics. The growing interest in induced pluripotent stem cells raises the possibility of personalized organs-on-chips that could eventually guide an individual’s therapy.

Quantitative outcome measures are essential to the overall success of the microphysiological approach, and they should reflect the human condition and be relevant to improving the practice of evidence-based medicine and regulation. Most of these quantitative measures should reproduce the normal functioning of the tissue *in situ* and be consistent with a mechanistic understanding.

The model systems will need to reflect an appropriate disease state or developmental stage in order to provide a valid prediction. Additional features to be considered include dose-response characterization and the influence of varying the developmental stage of selected cells. And to reproduce the desired outcome, standard procedures will need to be developed and widely accepted. A series of mutually agreed upon positive and negative test agents will be useful to ascertain functional status and reproducibility. Multi-center trials will be necessary to confirm reproducibility and the ability to perform the assays in many different environments.

Another important consideration of simulating human outcome is the quantification of chemical exposure. Absorption, distribution, metabolism and elimination are features that need to be taken into account. The linking

together of several organs-on-a-chip to simulate an intact human-on-a-chip is a possibility with well-constructed and well-tuned fluid dynamic systems. Microfluidic control of multiple organ systems is possible, and models envisioned by bioengineers have been developed. The challenges include the requirement for each organ type to have its own specialized media yet be connected so that the human circulatory system can be replicated.

The goal that has been put forth by the National Institutes of Health, the Food and Drug Administration, the Defense Advanced Research Projects Agency, the Defense Threat Reduction Agency and agencies in Europe and Asia is to accomplish this human-on-a-chip capability in a decade – a feat somewhat equivalent to the moon shot of the 1960s – and, like landing man on the moon, simulating a human being from a physiological/toxicological perspective may indeed be possible. But even if ultimately it is not, a great deal of fundamental biology and physiology will be elucidated along the way, much to the benefit of our understanding of human health and disease processes.

The views presented are those of the author and do not necessarily reflect those of the U.S. Food and Drug Administration.