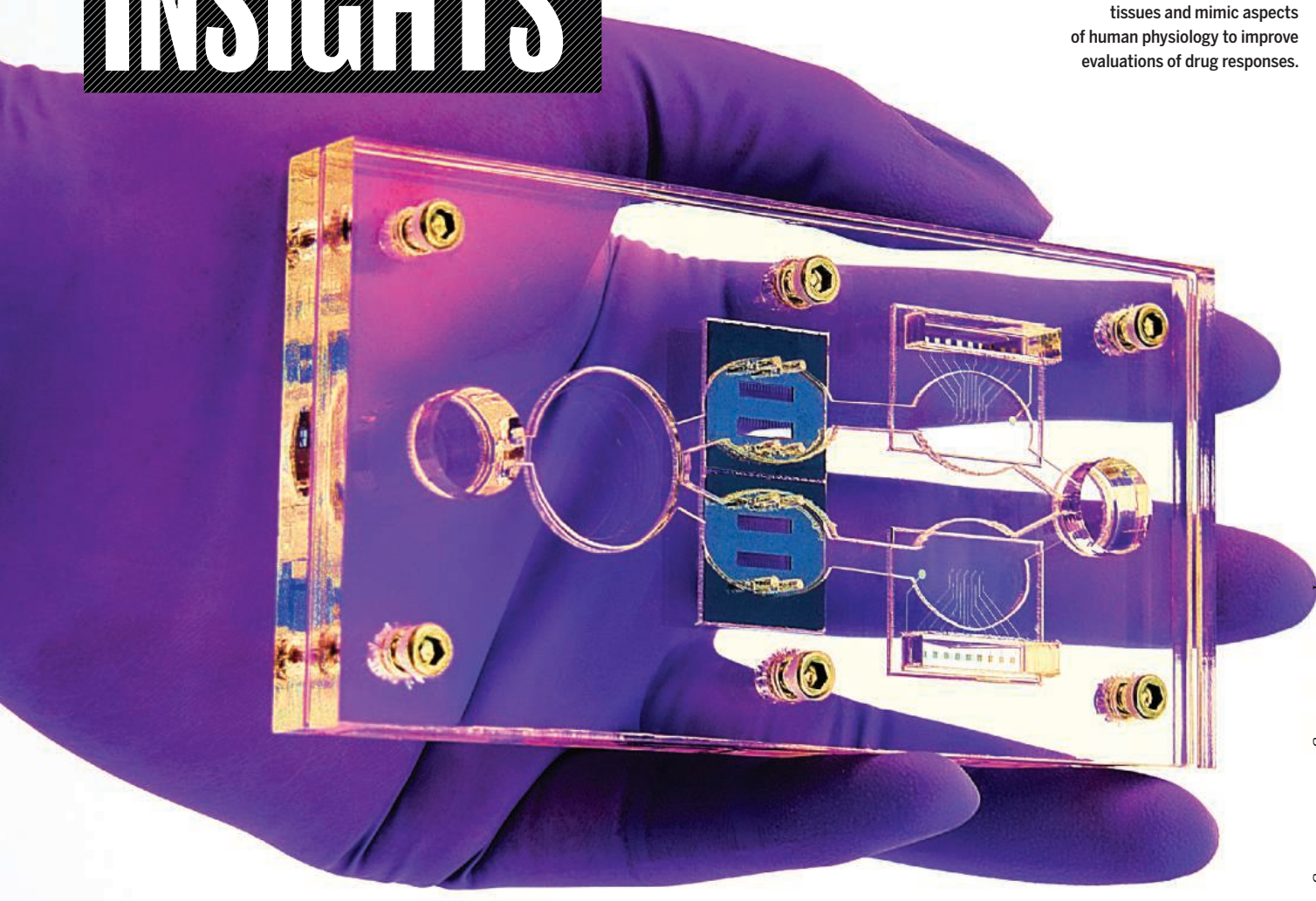

Microfluidic systems can connect multiple types of human tissues and mimic aspects of human physiology to improve evaluations of drug responses.



PHOTO: HESPEROS INC.

PERSPECTIVES

MEDICINE

# Human microphysiological systems for drug development

## Organs-on-chips could be used to assess drug efficacy and support personalized medicine

*By* **Adrian Roth**[1] *and* **MPS-WS Berlin 2019**[2]

Microphysiological systems (MPS), such as microfluidic organs-on-chips, have rapidly evolved as promising in vitro tools to recapitulate human physiology by recreating key biological processes and disease states. However, their value for drug development is only now becoming clear. MPS combine microsystems engineering with cell biology, yielding cell-culture models that can display three-dimensional architecture, multicellular interactions, tissue-tissue interfaces, fluid flow, and organ-level mechanical cues. For example, they can incorporate breathing mechanics of human lungs (*1*), circulating immune cells trafficking through perfused microvasculature (*2*), living microbiotas (*3*), and interconnections with other organs (*4*, *5*). They add to the toolbox of assays to identify potential therapeutics for diseases, including COVID-19 (*6*). These features enable human multi–cell-type systems that can better replicate complex tissue and organ functions than conventional cell culture. Consequently, MPS have gained broader attention as a tool to improve the prediction of human efficacy and potential undesired effects of drugs before patients are exposed to them (*7*).

MPS technologies may provide a way to better understand and address the main failures of clinical programs: lack of efficacy or unacceptable side effects that are not predicted in animals or simpler cell systems during early preclinical stages. The key advantage that MPS offer is the creation of more physiologically relevant human organ–like models that can potentially yield data on drug action that will better trans-

late to humans than that from in vivo animal models or conventional cell systems. Whereas research data from animals do not always translate to humans because of differences in the physiology of the different species, traditional human in vitro models lack three-dimensionality, tissue-tissue interfaces, and mechanical cues, which leads to dedifferentiation of cultured cells and, consequently, reduced human relevance. Despite the mostly exploratory nature of current MPS, there is an appetite for the uptake of the technology by pharmaceutical and biotechnology industries to improve on human predictivity, with the long-term goal of eventually replacing animal models wherever possible. Simultaneously, both academic groups and multiple biotech companies are developing increasingly refined MPS models to meet the needs and quality standards required for drug development such as scalability and robustness.

Up to now, adoption of MPS was primarily for preclinical safety (drug toxicology and metabolism), and some test systems have already reached the requirements in the pharmaceutical industry for internal decision-making, often for application in a defined context of use that requires only limited validation efforts (*7*). MPS have also been used to address disparities between different preclinical animal models, as well as between animals and humans. For example, rat, dog, and human liver organs-on-chips were shown to reproduce species-specific toxicities previously observed in testing by pharmaceutical companies while also providing new insights into potential toxicity mechanisms (*8*). Because effects observed in preclinical animal species sometimes have an unclear potential to translate to humans, toxicity signals may lead to selection of suboptimal drug-candidate molecules for further development. Thus, systems to test for toxicities relevant to humans could greatly help advance the most promising candidates into the clinic.

MPS have also been used to model many other toxicities, including cases where no suitable animal models are available or where animal models are unable to predict human responses. For instance, a human blood vessel-on-a-chip recreated thrombotic toxicities that led to failure of a therapeutic monoclonal antibody in human clinical trials, toxicities that were never detected during preclinical testing of this drug in animals (*9*). A vascularized human bone marrow–on-a-chip that supports differentiation and maturation of multiple blood cell lineages also recapitulates myelo-erythroid toxicities after clinically relevant exposures to chemotherapeutic drugs and ionizing radiation, as well as bone marrow recovery after drug-induced myelosuppression (*10*). Moreover, an MPS model composed of bone tissue was exposed to hip implant–associated dissolved cobalt and chromium at clinically relevant concentrations, which led to the identification of direct cytotoxic effects and successfully verified the integration of chromium into cancellous bone and binding to intertrabecular matrix previously found in patients (*11*).

Often, determination of the schedule and dosing of combination therapy in oncology is done by trial and error in clinical trials. Cytotoxic therapies, which target the bone marrow, remain a mainstay of therapy, and for these drugs in combination with targeted therapy, bone marrow MPS could eventually improve clinical scheduling and dosing regimens as well as possibly provide inroads for personalized medicine by defining individual treatment regimens based on patient-specific MPS testing before dosing the patient.

Although addressing well-known shortcomings of preclinical safety testing was an early focus of MPS research, newer models now aim at efficacy testing. For example, a human lung airway–on-a-chip with an interfaced endothelium was used to measure responses to anti-inflammatory compounds that inhibit cytokine-induced recruitment of circulating neutrophils under flow and, more recently, to evaluate the effects of existing and potential antiviral therapeutics on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and host inflammatory responses (*6*). A bone marrow–on-a-chip was also used to model a rare genetic disorder (Shwachman-Diamond syndrome) using cells isolated from patients, which reproduced key hematopoietic defects of this disease (*10*). These studies demonstrate the potential value of using MPS for developing personalized approaches that make use of patient cells for therapy optimization and potentially assist in clinical trial design, which will be particularly useful for patients with disorders that are so rare that it would otherwise be difficult to carry out preclinical drug testing in a systematic manner.

Complex physiological processes in the human body typically involve more than one organ, and thus MPS researchers have started to model multiorgan interactions to better investigate disease biology or drug action. For example, multiorgan MPS have been established to study how neuroactive drugs, such as methamphetamine, cross the blood-brain barrier and exert effects on neurons of the brain (*12*). First-pass pharmacokinetic models composed of linked human liver, kidney, and intestine organs-on-chips have also been used in combination with computational modeling to quantitatively predict human drug pharmacokinetics and pharmacodynamics (*4*). Linked intestine, liver, brain, and kidney MPS models have been differentiated using induced pluripotent stem cells from a single donor (*13*), which might enable personalized donor-specific, multiorgan research and drug testing in the future. If combined with patient-derived stem cell or organoid approaches (*14*), such models could provide tailored precision medicine tools at the individual patient level, supporting ambitions for personalized treatments. However, introducing patient-derived cells can only be realized with broad acceptance through informed consent and ethics approvals that these cells can be obtained and used for research and precision medicine.

Unlike commonly used immune-deficient or semihumanized animal models, human MPS lend themselves to grafting with tumors (*15*) and to infection with microbial pathogens (*6*), with particular advantages for human-specific viruses. However, none of the MPS assays have so far been used as part of the regulatory documentation in the drug approval process (*7*) owing to lack of adequate validation and experience with this newly emerging technology. Thus, an important challenge is to make the leap from research-grade MPS assays into validated drug development tools that will produce results that meet the requirements of regulatory review. As drug development increasingly focuses on developing highly engineered therapeutic molecules that do not cross-react with targets in any animal model, there is often simply no other choice than to use human in vitro models. The use of nonhuman primates for drug and vaccine testing is also becoming more difficult because of shortages in supply (e.g., owing to COVID-19 vaccine testing), in addition to the attendant ethical concerns. Thus, there is now a greater need than ever before for in vitro alternatives to preclinical models with human cells.

MPS can also enable rapid development of new therapies to confront urgent medical needs [e.g., messenger RNA (mRNA) vaccines for pandemic viruses or chimeric antigen receptor (CAR) T cell cancer immunotherapies]. Although these therapies have been approved using traditional methods, postapproval follow-up studies will often be required for such innovative drug modalities to enlarge the safety and

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efficacy databases. MPS models could be of great value, for example, for bridging personalized "patient-on-chip" data with matched data from postapproval studies in a head-to-head manner, thus enabling a "prediction–reverse translation" loop where real world data help establish a model that can then be used for prediction. This approach could be greatly enhanced if either sponsors (including, for example, patient organizations for rare diseases) or clinical research organizations involved in pursuing such therapies would liaise with developers of MPS assays to ensure that disease features are emulated in a patient-specific manner. The success of this approach would be further strengthened by incorporating advice from the relevant regulatory authority into the on-chip trial design. For example, the US Food and Drug Administration Drug Development Tool qualification process could be used, much like it is used for the validation of biomarkers as part of the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program that supports the development of new approaches to drug development that may be acceptable for regulatory use in the future. Together with advanced data analytics, in silico modeling, and simulation, exploring this approach in an iterative manner for one particular context of use (e.g., a particular disease and treatment modality) at a time could eventually result in acceptable datasets for regulators that are of higher predictive power than those previously generated with animal models. Once proof of concept is demonstrated successfully for one indication, others would follow. ■


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### SUPPLEMENTARY MATERIALS

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CANCER

# Opposing roles of the immune system in tumors

## Inflammation promotes early tumorigenesis but must be evaded as tumors progress

*By* **Won Jin Ho**[1] *and* **Laura D. Wood**[1,2]

The immune system can both promote and constrain cancer development. Chronic inflammatory conditions predispose to cancer formation in multiple organs, highlighting the role of the immune system in promoting tumorigenesis (*1*). Conversely, the immune system can target and kill neoplastic cells, owing to their molecular differences from normal cells (*2*). Therefore, tumor development is aided by processes intrinsic to cancer cells that either exploit protumorigenic inflammation or evade antitumor immune responses. On pages 1326 and 1327 of this issue, Del Poggetto *et al.* (*3*) and Martin *et al.* (*4*), respectively, demonstrate how cancer cells may co-opt these opposing effects of the immune system during tumor development. Together, these studies highlight how the immune system influences the genetic and epigenetic alterations in cancer cells, which may lead to improved strategies for cancer prevention and therapy.

Del Poggetto *et al.* interrogate the role of inflammation in promoting early pancreatic tumorigenesis, describing the molecular and phenotypic impacts of transient inflammation on non-neoplastic pancreatic epithelial cells. Using a mouse model combining caerulein-mediated chemical induction of pancreatic inflammation with inducible expression of the oncogenic *Kras* G12D ($Gly^{12}$→Asp) mutation, the authors show increased tumor formation even after remote and transient pancreatitis (inflammation of the pancreas). This increase is driven by postinflammation cell-autonomous alterations in the pancreatic epithelial cells, which show epigenetic reprogramming—i.e., particularly increased chromatin accessibility at thousands of genomic regulatory elements—persisting long after resolution of the inflammatory insult. These sustained alterations in chromatin accessibility led to alterations in transcription factor activity and resultant changes in gene expression, which remained even after histological resolution of the inflammatory changes.

The authors identify and functionally validate a key transcription factor, early growth response protein 1 (EGR1), in this response, the expression of which is dependent on the secretion of interleukin-6 (IL-6) from macrophages involved in the inflammatory response. However, more work remains to elucidate the mechanistic details of these far-reaching alterations. Del Poggetto *et al.* also show that the pancreatic damage after a second inflammatory insult is attenuated compared to the first, suggesting that epigenomic reprogramming facilitates rapid transdifferentiation of acinar cells during subsequent bouts of pancreatic inflammation. These changes in acinar cell differentiation include decreased production of pancreatic enzymes (zymogens), which limits injury-induced zymogen release and thus prevents further tissue damage. Similarly, induction of oncogenic *Kras* G12D also triggered acinar cell changes to abrogate surrounding tissue injury during a subsequent inflammatory insult, raising an intriguing mechanism by which a tumor-initiating oncogenic mutation may be selected in the setting of pancreatitis.

Although the link between inflammation and cancer has long been appreciated more broadly, the study of Del Poggetto *et al.* illustrates an epigenetic mechanism by which inflammation leads to lasting molecular consequences in pancreatic epithelial cells, shaping early pancreatic tumorigenesis. This complements the findings from another recent study that demonstrated epigenetic reprogramming of mouse pancreatic cells with a combination of inflammation and *Kras* G12D mutation (*5*). An important caveat to these findings is that they rely on elegant genetic manipulations and time course experiments that are only possible in mouse models, and thus the relevance of these findings to human pancreatic tumorigenesis remains unclear. Although chronic pancreatitis is an

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# Human microphysiological systems for drug development

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