Minireview

Tackling rare diseases: Clinical trials on chips

Sandra H Blumenrath[1], Bo Y Lee[2], Lucie Low[3], Ranjini Prithviraj[1] and Danilo Tagle[3]

[1]Drug Information Association, Washington, DC 20036, USA; [2]National Institutes of Health, Bethesda, MD 20892, USA; [3]National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD 20892, USA
Corresponding author: Sandra H Blumenrath. Email: Sandra.Blumenrath@DIAglobal.org

Impact statement

Designing and conducting clinical trials are extremely difficult in rare diseases. Adapting tissue chips for rare disease therapy development is pivotal in assuring that treatments are available, especially for severe diseases that are difficult to treat. Thus far, the NCATS-led National Institutes of Health (NIH) Tissue Chip program has focused on deploying the technology towards *in vitro* tools for safety and efficacy assessments of therapeutics. However, exploring the feasibility and best possible approach to expanding this focus towards the development phase of therapeutics is critical to moving the field of CToCs forward and increasing confidence with the use of tissue chips. The working group of stakeholders and experts convened by NCATS and the Drug Information Association (DIA) addresses important questions related to disease setting, test agents, study design, data collection, benefit/risk, and stakeholder engagement—exploring both current and future best use cases and important prerequisites for progress in this area.

Abstract

Technological advances with organs-on-chips and induced pluripotent stem cells promise to overcome hurdles associated with developing medical products, especially for rare diseases. Organs-on-chips—bioengineered "microphysiological systems" that mimic human tissue and organ functionality—may overcome clinical trial challenges with real-world patients by offering ways to conduct "clinical trials-on-chips" (CToCs) to inform the design and implementation of rare disease clinical studies in ways not possible with other culture systems. If applied properly, CToCs can substantially impact clinical trial design with regard to anticipated key outcomes, assessment of clinical benefit and risk, safety and tolerability profiles, population stratification, value and efficiency, and scalability. To discuss how tissue chips are best used to move the development of rare disease therapies forward, a working group of experts from industry, academia, and FDA as well as patient representatives addressed questions related to disease setting, test agents for microphysiological systems, study design and feasibility, data collection and use, the benefits and risks associated with this approach, and how to engage stakeholders. While rare diseases with no current therapies were considered the ultimate target, participants cautioned against stepping onto too many unknown territories when using rare disease as initial test beds. Among the disease categories considered ideal for initial CToC tests were well-defined diseases with known clinical outcomes; diseases where tissues on chips can serve as an alternative to risky first-in-human studies, such as in pediatric oncology; and diseases that lend itself to immuno-engineering or genome editing. Participants also considered important challenges, such as hosting the chip technology in-house, the high variability of cell batches and the resulting regulatory concerns, as well as the financial risk associated with the new technology. To make progress in this area and increase confidence with the use of tissue chips, the re-purposing of approved drugs ought to be the very first step.

Keywords: Tissue chips, clinical trials on chips, microphysiological systems, rare diseases, therapy development

***Experimental Biology and Medicine* 2020; 245: 1155–1162. DOI: 10.1177/1535370220924743**

Introduction

Recent technological advances with organs-on-chips and induced pluripotent stem cells (iPSCs) have created opportunities to create a paradigm shift in therapy development, promising to overcome various hurdles associated with developing medical products for many disorders, especially rare diseases. Although the field of 3D tissue engineering offers many opportunities, the technology also has limitations. Several experts in the field have reviewed the opportunities associated with tissue chips and organoids as well as the challenges that still need to be addressed.[1,2]

Designing and conducting clinical trials pose a particularly difficult challenge to the development of rare disease treatments: Trial participants often have to be recruited and retained from different geographic areas, and the clinical trial protocol must consider the rarity of the disease in its

methodology and statistical analysis plan, as well as the medical needs of the patient population; it also has to address ethical concerns, particularly with pediatric patients and using proper control groups. What's more, eligibility criteria often reduce the number of available subjects, hampering the ability to extrapolate clinical trial findings to a larger cohort of patients or to other relevant subpopulations. Many rare diseases also require therapies that involve multiple specialties, such as neurology, gastroenterology, psychiatry, endocrinology, cardiology, and physical therapy, especially if the disease is a genetic disorder with clinically significant comorbidities.

Organs-on-chips, on the other hand, may hold the potential for overcoming such clinical trial challenges with real-world patients by offering ways to conduct "clinical trials-on-chips" (CToCs) that would help inform the design and implementation of clinical studies for rare diseases.

Organs-on-chips as gateway to rare disease therapies

Organs-on-chips (or "tissue chips") are bioengineered "microphysiological systems" (MPS) that mimic human tissue and organ functionality in ways not possible with conventional 2D or other 3D culture systems:

- MPS recapitulate the multicellular architectures, tissue–tissue interfaces, physicochemical microenvironments, vascular perfusion, and innervation of human organs.
- Innovative biosensing and readout approaches enable these devices to employ high-resolution, real-time imaging, and non-invasive analyses of biochemical, genetic, and metabolic activities of living cells in a functional tissue and organ context.

Because designing and conducting clinical trials can be difficult in rare diseases, improving and adapting MPS for rare disease therapy development are pivotal in assuring that treatments for rare diseases are available, especially for diseases with the lowest prevalence and greatest severity, as well as for those that are most difficult to treat. Two FDA guidances offer recommendations on how to conduct more successful drug development programs for rare diseases,[3,4] and published *in silico* approaches both for orphan drug developlement[5] and for clinical trial implementation for rare pediatric orphan diseases[6] highlight how *in vitro* models can inform drug and therapeutic development for rare diseases.

In the past, MPS have been used to successfully model a number of rare disorders, such as Barth syndrome,[7] progeria,[8,9] Timothy syndrome,[10] and hereditary hemorrhagic telangiectasia.[11] There have also been several important advances for more common diseases, for example modeling cancer metastasis with organs-on-chips for precision medicine applications[12] as well as Huntington's disease using mouse models.[13] With the use of tissue chip technology, it may be possible to conduct CToCs using differentiated iPSCs from rare disease patients that are useful not only for safety and tox studies, but also for efficacy testing of promising therapeutics.

Benefits of CToCs. CToCs have the advantage that a chip can be made from an individual or several persons and even from banked cell lines from deceased patients, thereby increasing the number of "subjects" in an initial safety trial. It is also possible to use treated and untreated chips from the same group of individuals and screen for drug effects at the tissue level without repeat biopsy. Moreover, CToCs allow for patient-centric trials where the trials are designed with affected patient groups and patient-related outcomes can be collected. These approaches would not only increase trial efficiency and enhance the sensitivity of study outcomes, they would also ensure an outcome that is as informative as possible for the patient. Furthermore, CToCs can provide empirical support of the intervention's safety and efficacy as well as the mechanism underlying clinical benefit, while simultaneously revealing possible toxicity issues. This includes evidence that the intervention engages its intended targets and leads to functional improvement. Table 1 provides a quick overview of the main benefits associated with CToCs.

Overall, compared to existing approaches, CToCs have the potential to substantially impact clinical trial design in terms of anticipated key outcomes, assessment of clinical benefit and risk, safety and tolerability profiles, identification of best responders through population stratification, value and efficiency, and scalability potential.

Clinical trials on chips – Modeling basics

CToCs can provide patient-relevant drug testing models if the design of these platforms, tissue architecture, and readouts replicates relevant clinical outcomes in the treated patient.

Critical to this modeling is to precisely replicate the organ-to-organ communication to fully capture the pharmacokinetics and pharmacodynamics (PK/PD) of a drug in a multi-organ system interaction, i.e. how the drug or substance is transported, metabolized, and excreted, and how it impacts targeted and non-targeted tissues. Drug metabolism by the liver, clearance via the kidneys, or absorption through the intestines, for example, plays critical roles in the PK/PD of many drugs. Another important element in drug development is for studies to reliably generate predictive values of induction and downregulation as

Table 1. Overview of some of the unique benefits the tissue chip technology and CToCs offer.

CToC benefits at a glance	
• Larger number of "subjects" in safety trial	• Increased trial efficiency, enhanced sensitivity of study outcomes
• Treated and untreated chips from the same patient group	• Empirical support of the intervention's safety, efficacy, and mechanism
• No repeat biopsy to screen for drug effects at tissue level	• Simultaneous revelation of possible toxicity issues
• Patient-centric trials with highly informative outcomes	

well as of any time-dependent or irreversible inhibition of enzymes (e.g. certain Cytochrome P450 (or CYP) proteins) that metabolize the drug. CToCs should therefore be able to hold studies over several weeks in order to produce those predictive values.

The question of what platform designs are most relevant and how to achieve the proper tissue architecture has been addressed extensively elsewhere.[1,14–16] In summary, relevant platform designs should precisely recapitulate the microenvironments of various organs, such as the extracellular matrix, the biochemical environment, the biotic and abiotic interfaces, and the incorporation of the dynamic mechanical signaling for any particular organ system. Proper tissue architecture would comprise multicellular architecture that represents characteristics of the tissues or organs (including all relevant cell types found in a tissue in the correct ratios) ensuring the signaling and metabolic interactions of the various cell types; the presence of vascularized endothelial cells known to influence the development and functions of certain tissues (e.g. barrier function); and, in some cases, tissue innervation. Importantly, for patient-derived iPSC lines, the genotype, phenotype, and developmental maturity of these lines must be well-characterized.

Generating adult tissue from iPSCs for tissue-specific *in vitro* modeling remains a well-acknowledged challenge. There are, however, ongoing efforts within the field to develop methods that enable proper maturation of iPSC-derived cells for more accurate disease modeling.[1,17,18]

Functional readouts. Functional readouts should entail:

- functional representation of normal and diseased human biology;
- appropriate biomarkers that provide insights into the mechanisms of disease progression and drug effects;
- the ability to provide static structural information using traditional methods, such as biochemical and histological assays;
- "-omics"-based readouts, and non-destructive, real-time imaging techniques that provide a dynamic and comprehensive systems biology understanding of physiological responses;
- combined efficacy and safety assessments; and
- surrogate endpoints that are indicative of clinical outcomes.

Problem statement and approach

Thus far, the NCATS-led and -supported National Institutes of Health (NIH) Tissue Chip program (https://ncats.nih.gov/tissuechip) has focused primarily on deploying the tissue-chip technology towards more predictive *in vitro* tools for safety and efficacy assessments of candidate therapeutics. However, as mentioned earlier, a few case studies have demonstrated the beneficial use of tissue chips in understanding disease pathology and testing the efficacy of certain treatments by modeling rare diseases such as Barth syndrome, and progeria.[7,8] Another study published in 2016 investigated the efficacy of chemotherapeutics in vascularized microtumors, such as breast and colorectal cancer.[19]

In a collaborative effort, the Drug Information Association (DIA) and NIH-NCATS expanded this initial focus towards the development phase of therapeutics, convening two working groups of experts from industry (including the IQ Consortium MPS Affiliate members), academia (NIH staff), and FDA as well as patient representatives to consider how tissue chips could best be used to move the development of rare disease therapies a significant step forward. The working groups considered questions related to disease setting, test agents for MPS, study design and feasibility, data collection and use, the benefits

Table 2. Questions to consider for utilization of MPS technology in therapy development.

Considerations	Questions
Disease setting	• Which disease **categories** (e.g. rare diseases, cancer, neurodegenerative diseases) would be most amenable for use as a testbed for CToCs, and why? • Are there specific **criteria** that a rare disease would need to meet to warrant use of MPS in early phase trials?
Test-agent for MPS	• What type of test agent would be best suited? Small molecules, macromolecules, biologics, or genome editing/gene therapy?
Study design	• How would tissue chips impact the clinical development plan? • Should there be **parallel or sequential testing**? • What type of **patient representation and associated clinical data** should the chips have to be most informative? • What **outcome measures** can be determined from CToCs? ○ What type of **data** needs to be collected from tissue chips to provide substantial evidence of efficacy? ○ What **surrogate endpoints** are reasonably likely to predict clinical benefit (such as for an accelerated approval)?
Data collection and use	• What **protocols** need to be put into place to ensure high-quality data? • How can this data be used to inform the clinical development plan? • What kind of data, evidence, and regulatory validation are needed to support tissue chips as a clinical trial model?
Feasibility	• Given the above, is the study feasible? ○ What are the **resources (time, training)** needed to complete this study? ○ How much time will it take to complete an early phase clinical trial on a tissue chip?
Benefit and risk	• What are the **benefits of this approach** compared to other approaches? • How can the **risks for the sponsors** be mitigated? • How could these approaches impact **regulatory decision-making**?
Engagement	• What are the recommended **approaches to engage** patient advocacy groups and pharma partners?

and risks associated with this approach, and how to engage different stakeholders (see Table 2).

Working group findings

Disease setting

Disease categories. Rare diseases offer a useful testing ground for disease modeling, drug testing, and patient stratification. Using tissues of patients on chips allows us to answer questions of safety and early efficacy without putting patients at risk. In very severe cases, tissues-on-chips even allow for efficacy tests in deceased patients when CTs would pose a far too high risk.

Working group participants pointed out several disease categories that could serve as starting points for initial tests of CToCs, but cautioned against stepping onto too many unknown territories when using rare disease as initial test beds. Instead, well-defined diseases with known clinical outcomes were considered as ideal first test settings. Some examples include single-gene Mendelian disorders as well as common disease complexes such as cancer, cardiovascular disease (CVD), diabetes, and autoimmune disorders that may better inform studies on rare diseases for which clinical outcomes are not known.

While rare diseases with no current therapies were considered the ultimate target, CToCs were also deemed ideal for various other, yet more common diseases. For example, CToCs could find application in neurology and oncology, and in combination therapies. The National Cancer Institute, for example, showed particular interest in pediatric oncology where CToCs could be used to test pediatric and young adult tissues on chips as an alternative to risky first-in-human studies with pediatric populations. This would provide some valuable first insights into rare disease cases where patients are often children and where there is a requirement to demonstrate efficacy in preclinical tests before testing humans. Here, MPS in early phase trials might have the potential to resolve remaining uncertainties.

Although many neurological mechanisms are still not understood, using such devices to investigate neurological and neurodevelopmental disorders would offer many opportunities as there are currently no fully reliable neurological *in vivo* models. Participants raised Duchenne Muscular Dystrophy, a monogenic movement disorder, as one example of a specific neurological application. Here, the failure rate of finding effective treatments is very high. Therefore, early attempts to investigate potential translational markers or other metrics with MPS on chips would have to address simple key questions first to make any progress in this area.

In gene therapy, CToCs could help evaluate safety parameters and the effects of certain biomarkers. In fact, MPS could play an important quantification and qualification role in the biomarker surrogate space by determining the minimum difference in biomarkers needed to be accepted as surrogate. It is also conceivable that MPS could be used to support or even validate current gene editing techniques where the proof of concept has been tested *in vitro* but no clear animal models exist.

Table 3. Major disease categories identified by participants as most suitable for initial tests.

Rare disease categories
• Well-defined diseases with known clinical outcomes
• Oncology, particularly pediatric oncology
• Neurological and neurodevelopmental disorders
Other applications
• Evaluation of safety parameters in gene therapy
• Modeling of physiological processes

Note: More rare diseases potentially suitable for modeling on chips are listed at www.rarediseasesnetwork.org.

Participants also recognized that multi-organ systems on chips have a great potential for modeling physiological processes using PK/PD models and *in vitro* to *in vivo* extrapolation (IVIVE) combined with physiologically based pharmacokinetic (PBPK) modeling to predict the absorption, distribution, metabolism, and excretion (ADME) of certain synthetic and natural substances. Table 3 provides an overview of major disease categories that are particularly well-suited as initial test beds.

Disease criteria. In more general terms, participants agreed that, at least for now, MPS and CToCs are most relevant in cases where CToCs could be used alone or as validation of findings alongside CTs. Here is a selection of suggested criteria:

- Small sample size: only a small patient population is available for testing.
- Heterogeneous patient populations: patients have multiple disease phenotypes.
- Lack or paucity of available clinical trial data.
- Attenuated phenotypes: reliance on biomarkers or single efficacy trials.
- Dosing regimens: efficacious doses are difficult to predict (this is especially important in gene therapy where only single doses are administered).
- Absence of a concordant animal model of the disease.

Type of test agent for MPS

The working group discussions quickly revealed that the best test agents for MPS would be those that are fast-acting, have short lifespans, and whose reversibility is already known. Certain small molecules and biologics, for example, could be used in the evaluation of biomarkers and safety parameters in gene therapy trials. It was argued though that the choice of test agent will ultimately be dependent on disease state, drug disposition, and drug distribution, among others. And to become a "gold standard," systems using specific test agents should be reproducible without fail. It remains unclear, however, how much data regulatory agencies would require to effectively demonstrate that a specific test agent is appropriate for any given disease.

Study design

As with any experiment involving tissue chips, the appropriate study design depends on the disease system and the

model used. Participants across stakeholder groups agreed that study designs in the clinical trials context should emphasize tissue chips as a means to identify and validate target mechanisms to build confidence in the modeled mechanism and the chip technology itself. [removed sentence here] It was suggested that validation could occur with already approved drugs, or drugs that have failed or were withdrawn. Alternatively, already concluded trials could be replicated.

Tissue chips and CToCs also offer opportunities for patient stratification that regular clinical trials do not. Thus, with a study design that stratifies patient representation, CToCs could yield data that would be much more informative than data obtained from traditional clinical trial studies.

An important challenge, however, is the chip design itself. The pharmaceutical industry is looking at MPS companies that can bring the technology in-house. However, some pharmaceutical companies are unable to partner with chip developers, because (a) the technology is not a guaranteed novel tool yet, or because (b) the company won't have the capacity to run chips in-house later. Big pharmaceutical companies have been outsourcing innovation and research services to other companies for years, and although pharmaceutical companies differ in the type of business model they prefer, there is a general preference for outsourcing the chip technology to CROs.[20] However, there are examples of pharmaceutical companies bringing the technology in-house; a few of them are listed here in chronological order:

- In 2015, GSK, BASF, Sanofi, Abbvie, NC3Rs, and others funded Mimetas for a 3D culture system intended for neurotoxicity screening.
- In 2017, Johnson & Johnson and Merck partnered with Emulate to test and develop applications for its human organs-on-chips technology.
- In 2018, Emulate, Inc. and AstraZeneca's Innovative Medicines and Early Development (IMED) Biotech Unit agreed to work side by side on the organs-on-chips technology to improve predictions of drug safety and efficacy.

The clinical development plan: How would tissue chips impact the clinical development plan?

- Tissue chips provide empirical support of the intervention's safety and efficacy, and the mechanism that underlies clinical benefit. For example, tissue chips could show that the intervention engages its intended targets and leads to functional improvement while informing of possible toxicity issues.
- Tissue chips can help identify and test appropriate surrogate endpoints that provide valid and reliable measures of change that correlate with clinical benefit.
- By recreating patient tissues on multiple MPS platforms, tissue chips also allow for the expansion of small patient population sizes, thereby increasing statistical power of small/underpowered clinical trials.

Clinical tests: Parallel vs. sequential testing with tissue chips

- *In vitro* surrogates preserve treatment-naïve patient populations for clinical trials. Allowing patients to remain eligible for multiple clinical trials increases the possibility of identifying matching therapeutics for the respective disease.
- Utilizing MPS platforms with repurposed drugs or drugs from failed clinical trials can provide important information on potential dugs and may help identify alternative drug candidates.
- With MPS platforms, it is possible to demonstrate and compare clinical trial outcomes of approved drugs and confirm that the MPS technology produces similar outcomes. This in turn increases confidence that the MPS technology faithfully represents disease pathophysiology and responses.

Outcome measures: What outcomes should be measured and how? For data collected from tissue chips to provide substantial evidence of efficacy, the chips have to produce functional readouts that are able to:

- provide static structural information using traditional methods, such as biochemical and histological assays;
- produce omics-based readouts and allow for non-destructive, real-time imaging that will help us understand the dynamic and comprehensive systems biology of physiological responses; and
- provide combined efficacy and safety assessments and surrogate endpoints indicative of clinical outcomes.

The demonstration and comparison of clinical trial outcomes of approved drugs on MPS platforms would constitute a reasonable surrogate endpoint that is likely to predict clinical benefit. It would confirm that the MPS technology derives similar outcomes, thereby increasing confidence that it faithfully represents disease pathophysiology and responses.

Data collection and use

Protocols and quality data. All participants agreed that we need high quality data in order for the tissue chip technology to be useful and successful. Following rigorous protocols and standard operating procedures (SOPs) that conform to international standards set by, e.g. the OECD and FDA (such as Good Laboratory Practices (GLPs) and Good Manufacturing Practices (GMPs)) would ensure that the data derived from CToCs are reliable and of high quality. Governmentally funded bioengineering and biomanufacturing efforts including the Advanced Regenerative Manufacturing Institute (ARMI)/BioFab USA and the Multi-Agency Tissue Engineering Science

Group (MATES), for example, have already pushed for more rigorous protocols and SOPs for both cellular and device bioengineering.

Participants also saw an opportunity for the National Institute of Standards and Technology (NIST) to help tissue chip developers and users establish best practices by partnering with small and medium-sized enterprises (SMEs).

In the end, to inform the clinical development plan, the collected data should enable clinicians to cross-validate disease model endpoints with clinical measures in humans, and characterize parameters of treatment, intervention, or response to exposure. With these data, it should also be feasible to develop translatable pharmacodynamics, i.e. target engagement and biomarkers for validated therapeutic targets.

Tissue chips as a clinical trial model. To support tissue chips as a clinical trial model and their use in therapy development, it is pivotal to develop strategies for rapidly and openly disseminating methodology, data, and disease models.

Furthermore, the FDA provides qualification programs for regulatory-grade biomarkers, clinical outcome assessments, and animal models that help sponsors with the use of such tools in drug development. Similarly, for tissue chips, an important first step will be for the FDA to validate and evaluate the chip platform's ability to accurately predict PK/PD. Therefore, an FDA-issued guidance for implementing this technology will bring the tissue chips closer to clinical trial. Part of the validation process is to ensure, for example, that the phenotype of the disease is captured appropriately by the tissues and cells used on the chips. The represented cell types are dictated by, among other things, which cell types are affected by a specific disease as well as any neighboring cells in the tissue that could affect outcome. As for the size of the patient population, FDA representatives in the working group pointed out that the FDA would likely recommend the use of one patient per chip in the case of supplemental trails, because a limited set of patients on chips would suffice if the trial on chip merely provides supplemental information (e.g. in the form of complementary data) to an ongoing clinical trial. However, if the trial on chip is designed to be a standalone trial replacing a traditional clinical trial to predict the outcome of a study, the chips will have to represent the demographics and diversity of the patient population and hence require more patients on chips per trial.

Feasibility

The feasibility of the study will largely depend on the final study design. Participants expected to see both a large variability in the feasibility of studies as well as a great potential for achieving a successful outcome. It was pointed out that most MPS companies are open to feedback as long as they are engaged early in the process.

From a regulatory perspective, one challenge with CToCs is that cell batches can be highly variable and that results may vary much more in cellular performance than in platform performance.

Benefits, risks, and regulatory buy-in

The precise benefits of this approach will not become clear until the results of the first few use cases or proof-of-concept studies are released. Some of the major benefits known at this stage, however, include the ability to:

- perform *in vitro* tests,
- protect small and vulnerable patient populations,
- stratify patient populations, and
- de-risk First in Human studies, such as dosage escalation tox studies.

The novel technology of CToCs is a risk for end-users. Pharma companies are generally reluctant to invest in new technologies for drug discovery whose outcomes are uncertain, and instead outsource to CRO services or the small companies who developed the technology. However, the financial risks could be mitigated if initial test runs demonstrate that overall R&D costs decrease significantly and that there is potential for novel biomarker discovery.

From a regulatory perspective, the long-term goal is to gain the confidence and buy-in from FDA and other regulatory authorities. However, this will require a considerable paradigm shift in how regulatory bodies and the healthcare community approach benefit/risk assessment of potential therapies.

Engagement

The working group recommended several approaches to engage patient advocacy groups and pharma partners:

- Encourage the involvement of rare disease-focused initiatives at, for example, NCATS and the Office of Rare Diseases Research, along with their associated programs, such as the Rare Diseases Clinical Research Network (RDCRN and Rare Disease Network websites).
- Entities such as the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)—a permanent committee of the National Toxicology Program at NIEHS—could bring together developers and end users, aiding the walkthroughs of risk assessment for each platform with the toxicology community.
- The North American 3Rs Collaborative, which works to refine, reduce, and replace animal use in research, could help reach a broader audience and engage the public with these research efforts to ultimately increase patient engagement.
- Patient and clinician communities should be involved from the start to increase patient engagement from both recruitment and end user perspectives.

- It is also important for researchers to engage with the biomedical and pharmaceutical industries that will require data from well-characterized patient cohorts and iPSC lines. Advances are being made to obtain mature phenotypes from iPSC-derived cells,[1,17] and researchers in this sphere should place high importance on cell sourcing when considering using tissue chips in the clinical trials decision-making process.
- There are also possibilities for supplemental funding from the above-mentioned organizations, which may be topics for future discussion between funding agencies, researchers, and end users.

Concluding remarks

To make progress in the area of CToCs and increase confidence with the use of tissue chips, the repurposing of approved drugs is an obvious first step. When it comes to addressing actual treatment needs, current low-hanging fruit is in the area of pediatric or rare diseases, such as Duchenne's, sickle cell disease, coronary heart disease, cancer, neurological disorders, and diseases that lend itself to immuno-engineering or genome editing.

Eventually, MPS models may play a pivotal role in streamlining the clinical trial process. Advances in stem cell engineering could be integrated into organ-on-chip technology to develop personalized models ("you on chip"[10]) to predict patient-specific toxicity and efficacy. This could then lead to more efficient human trials with significantly reduced preclinical testing requirements. Such personalized models may also be useful in exploring patient-specific biomarkers and individualized dosing regimens based on patient-specific pharmacokinetics.

The next 5–10 years in particular will be crucial for the MPS platform to overcome challenges with standardization and regulatory endorsement. To realize the full potential of this emerging technology, collaboration across various stakeholders is essential.

Regulatory and pharma considerations. The use of CToCs for rare diseases can be responsive to the FDA's Safety and Innovation Act (FDASIA) in 2012, updating the pathway for new drug development. The purpose of FDASIA was to "expedite the development and access to novel treatments for patients with serious and life-threatening diseases and conditions." Moreover, in the "Enrichment Strategies for Clinical Trials" published by the FDA,[21] the prospective use of tools (such as MPS) to identify specific patient characteristics to further select subpopulations that are more likely to show desired drug responses could lead to more cost efficient and less risky clinical trials. Clearly, MPS preclinical and clinical models that enable these types of predictive studies earlier in the drug development pipeline could help refine patient pools for clinical trials.

Authors' contributions: All authors participated in the working group discussions, contributed to the review of key discussion takeaways, and drafted, revised, and approved the final manuscript.

ACKNOWLEDGMENTS

Attendees of the two working groups convened for these discussions included representatives from DIA, FDA, the IQ Consortium MPS Affiliate group (consisting of representation from AbbVie, Amgen, Astellas, AstraZeneca, Biogen, Bristol Myers Squib, Celgene, Eisai, Eli Lilly, Genentech, GlaxoSmithKline, Jansen, Merck, Merck KgA, Mitsubishi Tanabe, Novartis, Pfizer, Sanofi, Seattle Genetics, Takeda, Theravance, and Vertex), and the NIH MPS Working Group (consisting of representation from NCATS, NCI, NEI, NHLBI, NIA, NIAID, NIAMS, NICHD, NIDA, NIDCD, NIDCR, NIDDK, NIEHS, NIMH, and NINDS). We would like to thank all working group participants for their invaluable input during the discussions. We are also thankful to Raleigh Malik for helping initiate the project.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: NCATS support of the tissue chips program is made available through the Cures Acceleration Network. The authors received no other financial support for convening, participating in, and reviewing the working group discussions, nor for the authorship and publication of this article.

ORCID IDS

Sandra H Blumenrath https://orcid.org/0000-0003-1273-1348
Lucie Low https://orcid.org/0000-0001-6082-8625

REFERENCES

1. Ronaldson-Bouchard K, Vunjak-Novakovic G. Organs-on-a-chip: a fast track for engineered human tissues in drug development. *Cell Stem Cell* 2018;**22**:310–24
2. Park SE, Georgescu A, Huh D. Organoids-on-a-chip. *Science* 2019;**364**:960–5
3. US Food and Drug Administration. Rare diseases: common issues in drug development. Guidance for industry, www.fda.gov/media/120091/download (2019, accessed 15 January 2020)
4. US Food and Drug Administration. Human gene therapy for rare diseases. Draft guidance for industry, www.fda.gov/media/113807/download (2018, accessed 15 January 2020)
5. Nony P, Kurbatova P, Bajard A, Malik S, Castellan C, Chabaud S, Volpert V, Eymard N, Kassai B, Cornu C, CRESim, Epi-CRESim. A methodological framework for drug development in rare diseases. *Orphanet J Rare Dis* 2014;**9**:164
6. Carlier A, Vasilevich A, Marechal M, de Boer J, Geris L. In silico clinical trials for pediatric orphan diseases. *Sci Rep* 2018;**8**:2465
7. Wang G, McCain ML, Yang L, He A, Pasqualini FS, Agarwal A, Yuan H, Jiang D, Zhang D, Zangi L, Geva J, Roberts AE, Ma Q, Ding J, Chen J, Wang DZ, Li K, Wang J, Wanders RJ, Kulik W, Vaz FM, Laflamme MA, Murry CE, Chien KR, Kelley RI, Church GM, Parker KK, Pu WT.

Modeling the mitochondrial cardiomyopathy of Barth syndrome with induced pluripotent stem cell and heart-on-chip technologies. *Nat Med* 2014;**20**:616–23
8. Atchison L, Zhang H, Cao K, Truskey GA. A tissue engineered blood vessel model of Hutchinson-Gilford progeria syndrome using human iPSC-derived smooth muscle cells. *Sci Rep* 2017;**7**:8168
9. Ribas J, Zhang YS, Pitrez PR, Leijten J, Miscuglio M, Rouwkema J, Dokmeci MR, Nissan X, Ferreira L, Khademhosseini A. Biomechanical strain exacerbates inflammation on a progeria-on-a-chip model. *Small* 2017;**13**:1603737
10. Hinson JT, Chopra A, Nafissi N, Polacheck WJ, Benson CC, Swist S, Gorham J, Yang L, Schafer S, Sheng CC, Haghighi A, Homsy J, Hubner N, Church G, Cook SA, Linke WA, Chen CS, Seidman JG, Seidman CE. HEART DISEASE. Titin mutations in iPS cells define sarcomere insufficiency as a cause of dilated cardiomyopathy. *Science* 2015;**349**:982–6
11. van der Meer AD, Orlova VV, ten Dijke P, van den Berg A, Mummery CL. Three-dimensional co-cultures of human endothelial cells and embryonic stem cell-derived pericytes inside a microfluidic device. *Lab Chip* 2013;**13**:3562–8
12. Caballero D, Kaushik S, Correlo VM, Oliveira JM, Reis RL, Kundu SC. Organ-on-chip models of cancer metastasis for future personalized medicine: from chip to the patient. *Biomaterials* 2017;**149**:98–115
13. Virlogeux A, Moutaux E, Christaller W, Genoux A, Bruyère J, Fino E, Charlot B, Cazorla M, Saudou F. Reconstituting corticostriatal network on-a-chip reveals the contribution of the presynaptic compartment to Huntington's disease. *Cell Rep* 2018;**22**:110–22
14. Tagle DA. The NIH microphysiological systems program: developing in vitro tools for safety and efficacy in drug development. *Curr Opin Pharmacol* 2019;**48**:146–54
15. Watson DE, Hunziker R, Wikswo JP. Fitting tissue chips and microphysiological systems into the grand scheme of medicine, biology, pharmacology, and toxicology. *Exp Biol Med* 2017;**242**:1559–72
16. Esch EW, Bahinski A, Huh D. Organs-on-chips at the frontiers of drug discovery. *Nat Rev Drug Discov* 2015;**14**:248–60
17. Sances S, Ho R, Vatine G, West D, Laperle A, Meyer A, Godoy M, Kay PS, Mandefro B, Hatata S, Hinojosa C, Wen N, Sareen D, Hamilton GA, Svendsen CN. Human iPSC-derived endothelial cells and microengineered organ-chip enhance neuronal development. *Stem Cell Reports* 2018;**10**:1222–36
18. Machiraju P, Greenway SC. Current methods for the maturation of induced pluripotent stem cell-derived cardiomyocytes. *World J Stem Cells* 2019;**11**:33–43
19. Sobrino A, Phan DT, Datta R, Wang X, Hachey SJ, Romero-López M, Gratton E, Lee AP, George SC, Hughes CC. 3D microtumors in vitro supported by perfused vascular networks. *Sci Rep* 2016;**6**:31589
20. Middelkamp HHT, van der Meer AD, Hummel JM, Stamatialis DF, Mummery CL, Passier R, IJzerman MJ. Organs-on-chips in drug development: the importance of involving stakeholders in early health technology assessment. *Appl Vitro Toxicol* 2016;**2**:74–81
21. US Food and Drug Administration. Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products. Guidance for Industry, www.fda.gov/media/121320/download (accessed 24 October 2019)