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Facilitating the commercialization and use of organ platforms generated by the microphysiological systems (Tissue Chip) program through public–private partnerships

Christine A. Livingston [1], Kristin M. Fabre [1], Danilo A. Tagle *

National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD 20892, United States

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ABSTRACT

Microphysiological systems (organs-on-chips, tissue chips) are devices designed to recapitulate human physiology that could be used to better understand drug responses not easily addressed using other in vivo systems or in vitro animal models. Although still in development, initial results seem promising as tissue chips exhibit in vivo systems-like functional responses. The National Center for Advancing Translation Science (NCATS) identifies this technology as a potential tool that could improve the process of getting safer, more effective treatments to patients, and has led to the Tissue Chip Program, which aims to develop, integrate and validate major organ systems for testing. In addition to organ chip development, NCATS emphasizes disseminating the technology to researchers. Commercialization has become an important issue, reflecting the difficulty of translation from discovery to adoption and wide availability. Therefore, NCATS issued a Request for Information (RFI) targeted to existing partnerships for commercializing tissue chips. The goal was to identify successes, failures and the best practices that could provide useful guidance for future partnerships aiming to make tissue chip technology widely available.

Primary obstacles to the development of new therapeutic drugs are the significant time and resources required to identify and refine new compounds, the lack of better in vitro and in vivo models that are able to accurately predict the safety and efficacy of candidate therapeutics in humans, and submission of the data needed for Food and Drug Administration (FDA) regulatory approval [1–3]. The needed capital investment, coupled with high failure rates in clinical trials, makes pharmaceutical development high risk [3–5]. Many compounds ultimately fail in clinical trials due to toxicity or lack of efficacy in humans that is not evident in preclinical data from in vitro or animal testing [6]. To increase the rate at which promising compounds are identified and to reduce the number of compounds that fail in costly and time-consuming clinical trials, the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) in collaboration with the Defense Advanced Research Projects Agency (DARPA) and the FDA, initiated the NIH Tissue Chip for Drug Screening Program to develop human microphysiological organ systems (MPS) for toxicity and efficacy testing.

The Tissue Chip (TC) Program is to develop human tissue or organ systems (e.g., heart, liver, kidney, nervous system) on bioengineered platforms (i.e., "chips") [7]. The platforms support the key functional elements (such as 3D tissue architecture, multi-cellularity, biomechanical transduction properties, etc.) of organs under conditions that mimic the physiological and mechanical environment found in vivo, and are designed to facilitate functional readouts (e.g., cardiac contractility, gene expression) [4,8–14]. A long term objective is to integrate multiple organ system platforms into a "human on a chip" for a more comprehensive evaluation of drug toxicity and efficacy (Tissue Chip-Integration) [14–17]. The development and integration of "organs on chips" requires multidisciplinary collaboration of basic scientists, clinicians and bioengineers [10,11,13,14,18]. These collaborations have been facilitated greatly by productive public–private partnerships that advance the interests of both sectors. To foster additional partnerships and to identify factors contributing to their success, NCATS issued a Request for Information (NOT-TR-14-008, *Public–Private Partnerships for Organ Systems and Platforms Developed by Microphysiological Systems (MPS) Investigators*). In this report we summarize the responses, which reveal not only factors contributing to success, but also highlight broad interest in the further development, adoption and availability of the tissue chip technology for pharmaceutical development and research purposes.

* Corresponding author.
[1] Equal authorship contribution.

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1. Characteristics of successful public–private partnerships

Many partnerships within the TC Program include academic and private sector scientists with mutual interests in the development of the organ systems and in advancing the design of the bioengineered platforms. In some cases, NIH and DARPA-funded academic scientists have contributed biological expertise and provided feed-back related to design requirements, while private sector participants contributed engineering expertise, production efficiency and marketing experience. The collaborative aims of the public and private sectors are further refinement and marketing of the microphysiological organ systems and platforms as relevant research and testing tools. Participants in productive partnerships that achieve these aims consistently cite certain factors that contribute to their success: 1) opportunities for balanced contributions and mutual benefits for both the private and public participants; 2) an organized leadership team with well-defined roles; 3) effective communication between basic scientists, engineers and senior members of the leadership team; 4) productive exchange with potential stakeholders; 5) early identification of a target market; and 6) early consideration of collaborative agreements that address intellectual property issues.

The most productive TC public-private partnerships are based on balanced contributions and subsequent benefits for all. Most importantly, public and private partners first need to identify and align their goals. Additional approaches to balanced contributions are discussed below. The benefits for public and private partners are more rapid scientific development and adoption of the organ system platforms, with the potential for scientific advances and financial profit. The most successful partnerships may lead to widespread use of tissue chips by the pharmaceutical industry, adoption for toxicology testing, and translation for clinical applications (e.g., personalized or precision medicine).

Optimally, partnerships are built on an organized leadership team with each member having a well-defined role. Experienced individuals serving in leadership roles can articulate objectives clearly and focus team efforts. The most efficient partnerships include a small group of select individuals serving as team leaders who can identify primary objectives, integrate them, and direct development. Proximity of leadership and private sector partners to basic and clinical scientists is advantageous in the early stages of development, as this facilitates discussion, testing, access to clinical resources, and can eliminate "middlemen." Ongoing feedback from private sector partners based on their knowledge of manufacturing and marketing is critical for later stages of development. The integration of this feedback and that from publically funded biomedical scientists is essential to achieving long-term objectives.

Effective communication between publically supported TC scientists and private sector partners is necessary to assure both scientific validity and that organ system platforms will meet market needs. Early identification of the key features required and goals for use of the platforms is essential for efficiency and aggregate solutions, leading to well integrated design. The functional read-outs that are needed should be identified ahead of time, ideally with input from public, private and regulatory sectors. Platform design is driven in part by requirements for validation, but also by the organ systems' and/or platforms' intended use(s). They may be designed for a narrowly targeted market, or allow for modifications to meet the needs of a broader market. For example large pharmaceutical companies may have a wide variety of applications for ex vivo organ systems, dictating that a range of platform options be available: they may need 2- or 3-dimensional systems, single or paired organ system platforms, or multi-organ integrated platforms. Design priorities that consider the scientific validity of the organ systems while balancing market demand should be determined early in development.

In addition to communication between scientists and engineers partnering to develop and/or market the tissue chips, valuable input may come also from stakeholders and early consumers. Therefore, during early translation of the organ systems and platforms to consumers, it is advantageous to anticipate an extended period of technical support and discussion. This facilitates closer collaboration between engineers and biologists, and between developers and consumers, leading to more rapid improvements in design and assurance that the devices meet requirements. Importantly, private sector partners should be prepared to provide a high level of technical support, particularly in the early marketing phase.

As a target market is identified, demonstrating the profit potential may be necessary to attract investors. These markets may include the pharmaceutical/biotechnology, research or clinical sectors. The pharmaceutical or biotechnology sectors, acting as service providers, are likely to use the organ systems and/or platforms for preclinical assays. This may be the most profitable market initially and therefore likely to attract the largest capital investment. Alternatively, the research sector may implement the organ systems and/or platforms as tools. This sector may represent numerous users, but is likely to provide a lower profit margin and may be more attractive to smaller investors. The clinical sector, using the organ system platforms for diagnostics and individualized medicine applications, may be limited initially, but has much potential for growth. Until an organ system platform is validated and progresses towards regulatory qualification, this market may attract limited financial support. Larger investments in products targeting the clinical sector may not occur until development by smaller biotechnology firms has progressed far enough to establish a viable clinical market. Notably, the features of the organ system platforms required by each of these sectors will be different and may dictate shifts in design and development as each market comes to the forefront. Parallel development of platforms for different uses and multiple markets should be feasible.

In parallel with the scientific development and engineering of the organ system platforms, it is imperative that both academic and private sector partners give early consideration to legal issues and to a business plan. These should be addressed early to avoid later complications that would delay scientific progress or the broader distribution of this novel technology. For example, provisions for confidentiality and intellectual property must be agreed upon in the early stages of development, in consultation with institutional and corporate legal representatives. Agreements should address issues such as patenting, licensing arrangements, revenue sharing, and when appropriate, NIH resource sharing requirements. Once a good legal plan is established, it can serve as a general model for future partnership agreements.

2. Regulatory considerations

A key incentive for private sector participation and investor interest is regulatory qualification and validation of the organ system platforms. Validation processes will depend on the intended use of the TCs, either as a stand-alone approach (e.g., precision medicine) or as one element in an integrated set of approaches (e.g., dose–response, toxicity and efficacy testing) [4,14–16]. The TCs may be used as a tool for mechanistic studies with a reduced number of variables [12]; they may be developed for preliminary or efficient dose–response testing for efficacy and off-target effects, thus reducing the cost of drug development [19]; or TCs developed from human cells can serve as a preclinical approach to identify compounds whose efficacy or toxicity is different in animal vs. human tissue [4,8,9,20]. As an example of the latter, TCs can illustrate significant differences in hepatotoxicity in animals vs. humans [21,22].

Validation of human organ chips for any use will be a complex process, requiring a long term commitment to the goal of the FDA qualifying the MPS as a valid research tool. Ultimately, validation will require a comparison of the toxicity and efficacy data for compounds tested in preclinical animal studies, using the human tissue chip platforms, and in clinical trials. Demonstration that the results of testing using human microphysiological organ systems parallel those from clinical trials is critical for regulatory approval. Demonstration that the TC platforms can be used to identify toxic or ineffective compounds that have failed in human clinical trials despite promising preclinical data from animals would incentivize the market and investors.