CONCEPT CLEARANCE RECORD

FY 2016 RESEARCH INITIATIVE – NCATS

TITLE: Tissues-on-Chips: Part II

INITIATIVE TYPE: Request for Application using cooperative agreements

OBJECTIVE(S): The goal of Part I of the Tissue Chip for Drug Screening program was to develop bio-engineered microdevices that represent functional units of the 10 major human organ systems: circulatory, respiratory, integumentary, reproductive, endocrine, gastrointestinal, nervous, urinary, musculoskeletal and immune. In the first part of this program, several unique and novel *in vitro* platforms have demonstrated human organotypic physiological functions and response to drug exposure, ensuring that safe and effective therapeutics are identified sooner and that ineffective or toxic ones are rejected early in the drug development process. These microfabricated devices also have proven to be useful for modeling human diseases and may prove to be sufficient alternatives to animal testing. Despite these successes, there is a clear need to evolve the technology in order to fully exploit the use of the tissues-on-chips at the preclinical stage but also as a clinical tool. The following initiatives are proposed for Part II of the Tissue Chip for Drug Screening program.

DESCRIPTION: A Funding Opportunity Announcement(s) will be issued focused on furthering the development and use of tissues-on-chips.

1. **Clinical trials-on-chips:** The drug development community is keenly interested in new models for improving the efficiency of our current three-phase process for clinical trials leading to drug approvals. In many cases, the U.S. Food and Drug Administration (FDA) is extending its oversight (and incorporating some ideas from its European counterpart) by requiring that approvals remain current via adding post-marketing approval studies in which the new drug is examined in the real-world setting in a broader patient population. Such complex efforts can be much less costly and time consuming by incorporating model systems that are predictors of human responses across multiple tissues and patient phenotypes. Specifically, tissue chips could inform the composition of a treatment cohort or (given sufficient statistical power) even reduce the number of patients needed to show the desired effect. Multiple, linked tissue mimics can act as test beds to stratify populations into drug responders and nonresponders, examine multi-organ toxicities, study susceptibilities to environmental toxins and explore the effect of the microbiome in human health and disease at a scale not possible in studying the whole human in such large numbers.

2. **You-on-a-chip as part of the Precision Medicine Initiative:** With the use of induced pluripotent stem cells (iPSCs) from thousands of individuals who are fully sequenced as part of the cohort for the Precision Medicine Initiative, it is possible to have human bodies-on-chips for these individuals (you-on-a-chip). The “low-hanging fruit” here easily could be a greater understanding of metastatic spread in cancer and interventions to prevent this deadly outcome, or the ability to see longer-term effects of therapies for such “lifestyle” diseases as hypertension and diabetes from the use of personalized human bodies-on-chips.

3. **Disease modeling:** The majority of drugs fail due to lack of effectiveness or efficacy in human trials. Tissue chips will be used to represent familial mutations derived from iPSCs of patients with rare diseases for studies on pathophysiology, customized therapy development and representation of the full spectrum of mutations for a rare disease, even after the patient has passed. In addition, with the use of gene editing technologies, it is possible to introduce genetic polymorphisms on an isogenic iPSC line to dissect the contribution of genetics versus environment in human disorders. This approach also could potentially dissect the contribution of genetic polymorphisms as risk factors in polygenic diseases. Perhaps the greatest use may be in uncovering the mechanisms of complex disease processes in these physiologically relevant and metabolically faithful systems.

4. **Homunculus:** Organ representation in the current tissue chips is weak for endocrine, lymphatic and immune systems. These need further development to further improve upon the current organ systems.

IMPORTANCE: At the end of the proposed five-year extension of the Tissue Chip for Drug Screening program, it is anticipated that the availability of these systems to the broader scientific community will foster a multitude of new research applications, including but not limited to studies in personalized medicine, environment exposures, reproduction and development, autoimmune disorders, infectious diseases, cancer, countermeasures for chemical warfare, immune responses and neuro-inflammation.

HISTORY: Advances in basic and preclinical science continue to fuel the drug discovery pipeline; however, only a small fraction of compounds meet criteria for approval by the FDA. More than 30 percent of promising medications have failed in human clinical trials because they are determined to be toxic despite promising preclinical studies in animal models, and another 60 percent fail due to lack of efficacy. The challenge of accurately predicting drug toxicities and efficacies is due in part to inherent species differences in drug metabolizing enzyme activities and cell type-specific sensitivities to toxicants. To address this challenge in drug development and regulatory science, NIH, in partnership with DARPA, the FDA, and more recently the pharmaceutical industry, has invested in the Tissue Chip for Drug Screening program to develop alternative approaches that would enable early indications and potentially more reliable readouts of toxicity and efficacy. Part II of the Tissue Chips for Drug Screening program will involve partnerships with multiple Institutes and Centers at NIH, pharmaceutical companies, regulatory agencies (FDA, EMA, PDMA), patient groups and other stakeholders.

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