CONCEPT CLEARANCE RECORD
FY 2016 RESEARCH INITIATIVE – NCATS

TITLE: Tissues-on-Chips: Part II

OBJECTIVE(S): The goal of Part I of the Tissue Chip for Drug Screening program was to develop bioengineered micro-devices 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 responses to drug exposure, ensuring that safe and effective therapeutics are identified sooner and ineffective or toxic ones are rejected early in the drug development process. These micro-fabricated devices also have proven to be useful for modeling human diseases, and they may prove to be sufficient alternatives to animal testing. Despite these successes, there is a clear need to advance the technology to fully exploit the use of the tissues-on-chips not only at the pre-clinical 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 will be issued to continue the development and use of tissues-on-chips.

1. Humonculus: Organ representation in the current tissue chip program is weak for the endocrine, lymphatic and immune systems needed to fully represent the major organ systems in the human body-on-a-chip. Moreover, there is a great need to independently validate these systems using reference sets of compounds and assays through partnerships with the Food and Drug Administration (FDA) and the pharmaceutical industry.

2. 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 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 chips (human body-on-a-chip) can act as test beds to stratify populations into drug responders and non-responders, examine multi-organ toxicities, study susceptibilities to environmental toxins, and study the contribution of the microbiome in influencing human health and disease, at a scale not possible in studying the whole human in such large numbers.

3. "You-on-a-chip": With the use of induced pluripotent stem cells (iPSCs) from thousands of individuals who will be fully sequenced as part of the million-person cohort for the Precision Medicine Initiative, it is possible to have human body-on-a-chip representations for these individuals. Personalized chips could lead to more precise diagnosis, prevention and treatment, and possibly customized intervention strategies. You-on-a-chip could lead to a greater understanding of various conditions, such as metastatic spread in cancer and individualized

interventions to prevent deadly outcomes or the ability to anticipate longer-term effects of therapies for such "lifestyle" diseases as hypertension and diabetes.

4. Disease modeling: The majority of drugs fail due to lack of effectiveness or efficacy in human trials. Tissue chips can be used to represent familial mutations derived from iPSCs of patients with rare diseases for studies on pathophysiology and customized therapy development. It also is possible to represent the full spectrum of mutations for a given rare disease, even after the patient has died, thus allowing for increased power in evaluating candidate therapies. 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 distinguish the contribution of various polymorphisms in a uniform genetic background as risk factors in polygenic diseases, thus aiding in uncovering the mechanisms of complex disease.

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 pre-clinical 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 pre-clinical studies in animal models, and another 60 percent fail due to lack of efficacy. The challenge of accurately predicting drug toxicities and efficacies is in part due 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 the Defense Advanced Research Projects Agency, 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 read-outs of toxicity and efficacy. Part II of the Tissue Chip for Drug Screening program will involve partnerships with multiple NIH Institutes and Centers, pharmaceutical companies, regulatory agencies (FDA, European Medicines Agency, Pharmaceuticals and Medical Devices Agency), patient groups and other stakeholders.

PROJECT/PROGRAM OFFICER:

Danilo A. Tagle, Ph.D., M.S.
Associate Director for Special Initiatives
Office of the Director
Phone: 301-594-8064
E-mail: tagled@mail.nih.gov