Published in final edited form as:

Trends Pharmacol Sci. 2017 January ; 38(1): 4–7. doi:10.1016/j.tips.2016.10.009.

Clinical Trials in a Dish

David G. Strauss^{1,*} and Ksenia Blinova²

¹Division of Applied Regulatory Science, Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD 20993, USA

²Division of Biomedical Physics, Office of Science of Engineering Laboratories, Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, MD 20993, USA

Abstract

Clinical trials ‘in a dish’ involve testing medical therapies for safety or effectiveness in the laboratory with human tissue. This has become possible owing to recent biotechnology advances including induced pluripotent stem cells, organs-on-a-chip, and whole-genome sequencing. We provide here an overview of the landscape and highlight steps the FDA is taking to advance the science of clinical trials in a dish and to support the development and validation of new regulatory paradigms to assess drug safety using these new technologies.

What are Clinical Trials in a Dish?

Clinical trials in a dish (Figure 1), or *in vitro* clinical trials, have received increased attention recently because emerging technologies can allow drug developers to test novel compounds on patient cells before moving into actual clinical trials. The FDA has highlighted that ‘*In vitro* clinical trials use specimens collected from patients to test how a particular cancer or disease will react to a specific therapy or combination of therapies’ [1]. This can be used for the development of drugs for specific populations, and also potentially for precision medicine purposes to predict responses in individual patients – for example to predict, in advance of therapy, which patients will benefit and which will be harmed.

The potential for clinical trials in a dish increased significantly with the discovery and advancement of induced pluripotent stem cells (iPSCs) [2]. As opposed to embryonic stem cells, iPSCs are generated by reprogramming peripheral blood or skin cells into a stem cell state, and then differentiating iPSCs into large numbers of any cell type, such as cardiomyocytes, neurons, or hepatocytes [2]. The noninvasive nature and unlimited supply of this patient-derived tissue makes the advancement of clinical trials in a dish possible as opposed to the highly impractical task of large-scale harvesting of primary human tissue.

*Correspondence: David.Strauss@fda.hhs.gov (D.G. Strauss).

Disclaimer Statement

The opinions presented here are those of the authors. No official support or endorsement by the FDA is intended, nor should it be inferred.

Clinical trials in a dish have potential application across multiple areas of drug development - from early drug discovery, to later lead optimization for safety and efficacy testing, to regulatory safety assessment. If properly validated, there is the potential for clinical trials in a dish to replace animal testing, some types of clinical trials, or to be used to select patient populations or even individual patients most likely to benefit or least likely to be harmed by therapies. Some of these potential applications are farther from reality, while others are relatively close to implementation.

FDA Efforts around Clinical Trials in a Dish

FDA has multiple regulatory science research initiatives to advance clinical trials in a dish involving the use of iPSC-derived tissues. iPSCs retain the DNA of the donor, and thus can be used for testing personalized response to drugs. The farthest along involves the use of iPSC-derived cardiomyocytes for cardiac safety testing.

In August 2015 we published the results of an FDA-sponsored clinical trial that evaluated the ability of novel clinical electrocardiographic (ECG) biomarkers to predict the risk of drug-induced abnormal heart rhythms [3]. In addition to studying the effect of five different drugs on the ECG, we are generating iPSC-cardiomyocytes from each of 20 clinical trial participants at two different commercial laboratories, and a clinical trial in a dish is being performed at the FDA to determine if the personalized iPSC-cardiomyocytes can predict each individual drug response. This study will also assess whether patient-specific iPSC-cardiomyocytes generated from different commercial laboratories using different techniques produce similar results, which is important for establishing standards for this new technology. The FDA intends to biobank the iPSCs from the 20 subjects in the clinical trial to enable additional research.

In addition to the above effort, the FDA is engaged in a public-private partnership involving the Health and Environmental Sciences Institute, the Safety Pharmacology Society, and the Cardiac Safety Research Consortium, as well as multiple global regulators, pharmaceutical companies, and academic laboratories, to develop a comprehensive *in vitro* proarrhythmia assay (CiPA) [4]. The goal of the CiPA initiative is to use a combined *in vitro* and *in silico* (computational) testing strategy to predict the risk of drug-induced arrhythmias. This would be performed for all new drugs in place of a current clinical trial (The Thorough QT Study) in drug development. There are four components of CiPA: (i) assessing the effects of a drug on multiple human cardiac ventricular ion channel cell lines, (ii) integrating the individual ion channel effects in a computer model of the human ventricular cardiomyocyte and outputting a proarrhythmic risk score, (iii) checking that no major drug-induced effects were missed with *in vitro* iPSC-cardiomyocyte assays, and (iv) confirming there are no unanticipated clinical electrophysiology effects in early Phase I clinical trials [4]. The CiPA initiative is well on its way because the four working groups have already presented the qualification/validation study plans to the International Conference on Harmonization (ICH) Discussion Group that focuses on proarrhythmic safety (S7B/E14), and qualification/validation studies are expected to be completed by December 2017. The steps the global drug development and regulatory communities are going through to study and qualify this new *in vitro* paradigm for regulatory review can serve as an example for clinical trials in a

dish in other areas. A key point is that qualification/validation studies are based on assessing a set of marketed drugs that have a known low, intermediate, or high risk of arrhythmias based on clinical experience. In addition, the studies are being performed at many labs around the world, with multiple commercially available cell types and device assays, to be able to establish data standards and understand assay variability to establish confidence in this approach that is anticipated to be used for regulatory purposes and for predicting clinical risk of arrhythmias.

iPSCs for Disease Modeling and Precision Medicine

In addition to testing drug response in a general or healthy human population, case examples are emerging of iPSCs being used to predict personalized clinical responses in patients. As highlighted in a recent study of doxorubicin cardiotoxicity in breast cancer patients using patient-specific iPSCs [5], it may be possible for cancer patients to have their iPSC-cardiomyocytes generated to determine which patients are at increased risk of cardiotoxicity in advance of treatment. However, there may be practical limitations to this approach (e.g., waiting for iPSC-cardiomyocytes to be generated), and such strategies will require careful validation as *in vitro* diagnostic tests. iPSCs allow investigators to model diverse populations, including males and females, different races, and both healthy subjects and patients with disease. There are now multiple iPSC libraries established from patients with various genetic mutations. In addition, the diversity of genetic diseases available has increased by applying gene-editing techniques to iPSCs. Using zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and clustered regularly interspaced short palindromic repeats (CRISPR) techniques, two isogenic iPSC lines can be generated that have identical cells except for a specific gene mutation in one of the lines [6]. These new biotechnologies can speed the study of rare genetic diseases because individual or multiple combinations of mutations can be rapidly created and studied in iPSCs instead of needing to recruit individual patients with each permutation. For example, Wang *et al.* [7] show that genome editing of iPSCs from a healthy subject yielded cells with a phenotype of an actual congenital long-QT patient, allowing drug testing for a rare patient population.

In addition to safety assessment, iPSC-based platforms are already being used for drug efficacy screening. Patients with viral cardiomyopathy were used to generate iPSC-cardiomyocytes for use in an antiviral drug screening platform to predict novel drug effectiveness in a high-throughput fashion [8]. iPSC-hepatocytes have been used to study antiviral drugs for hepatitis B, and antimalarial drugs following liver-stage malaria infection [9,10]. Another recent example is a report on using iPSC-neurons to screen for existing antiviral drugs that can be repurposed to fight Zika virus infection [11].

Organs-on-Chips

Patient-derived iPSCs may provide the patient-relevant foundation for clinical trials in a dish with diverse populations. However, the platforms in which iPSCs are used should ideally mimic the dynamic, 3D structures of the tissues being targeted. To accomplish this, organs-on-chips are being designed to model tissue complexity and capture the effect of vasculature. [12] Organs-on-chips are devices for culturing living cells in continuously

perfused microchambers designed to mimic the physiological microenvironment. These systems can potentially combine multiple cell types, allowing modeling of intra- and inter-organ interactions. There is a large effort from the National Center for Advancing Translational Sciences, together with the Defense Advanced Research Projects Agency (DARPA) and the FDA, to advance the technology (<https://ncats.nih.gov/tissuechip>). An integrated human-body-on-a-chip is the ultimate goal, enabling scientists to test the varied potential effects of a drug across the entire body before any testing in humans.

While some aspects of clinical trials in a dish are farther on the horizon, others (such as the CiPA initiative) are close to implementation. iPSCs and clinical trials in a dish are the future of precision medicine, and may greatly improve patient outcomes by aiding in drug discovery and safety testing in specific populations, and even in predicting response in individual patients. Realizing this future requires continued collaboration among academic, industry, and regulatory colleagues to develop, validate, and implement new approaches.

References

1. Department of Health and Human Services. Fiscal Year 2017 Food and Drug Administration. Justification of Estimates for Appropriations Committees, US Department of Health and Human Services; 2016.
2. Grskovic M, et al. Induced pluripotent stem cells – opportunities for disease modelling and drug discovery. *Nat Rev Drug Discov.* 2011; 10:915–929. [PubMed: 22076509]
3. Johannesen L, et al. Late sodium current block for drug-induced long QT syndrome: results from a prospective clinical trial. *Clin Pharmacol Ther.* 2016; 99:214–223. [PubMed: 26259627]
4. Colatsky T, et al. The comprehensive in vitro proarrhythmia assay (CiPA) initiative – update on progress. *J Pharmacol Toxicol Methods.* 2016; 81:15–20. [PubMed: 27282641]
5. BurrIDGE PW, et al. Human induced pluripotent stem cell-derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. *Nat Med.* 2016; 22:547–556. [PubMed: 27089514]
6. Merkert S, Martin U. Site-specific genome engineering in human pluripotent stem cells. *Int J Mol Sci.* 2016; 17:1000.
7. Wang Y, et al. Genome editing of isogenic human induced pluripotent stem cells recapitulates long QT phenotype for drug testing. *J Am Coll Cardiol.* 2014; 64:451–459.
8. Sharma A, et al. Human induced pluripotent stem cell-derived cardiomyocytes as an in vitro model for coxsackievirus B3-induced myocarditis and antiviral drug screening platform. *Circ Res.* 2014; 115:556–566. [PubMed: 25015077]
9. Ng S, et al. Human iPSC-derived hepatocyte-like cells support *Plasmodium* liver-stage infection in vitro. *Stem Cell Rep.* 2015; 4:348–359.
10. Shlomai A, et al. Modeling host interactions with hepatitis B virus using primary and induced pluripotent stem cell-derived hepatocellular systems. *Proc Natl Acad Sci USA.* 2014; 111:12193–12198. [PubMed: 25092305]
11. Xu M, et al. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. *Nat Med.* 2016; 22:1101–1107. [PubMed: 27571349]
12. Capulli AK, et al. Approaching the in vitro clinical trial: engineering organs on chips. *Lab Chip.* 2014; 14:3181–3186. [PubMed: 24828385]

Trends in Pharmacological Sciences

Figure 1. Clinical Trials in a Dish Are Applicable to Precision Medicine, Disease Modeling, and Drug Testing

Abbreviations: CiPA, comprehensive *in vitro* proarrhythmia assessment; CRISPR, clustered regularly interspaced short palindromic repeats; iPS, induced pluripotent stem (cells).