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Designer Assays for Your Sick, Subdivided Heart

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Using induced pluripotent stem cells and microelectromechanical device technology Zhao et al. have developed 'organs on chips' representing the different chambers of the heart and used them to replicate healthy and diseased tissues *in vitro*. These systems offer investigators and the pharmaceutical industry a new tool in testing the safety and efficacy of new medicinal therapeutics.

It has been an all-too-frequent occurrence that cardiovascular drugs in well-intentioned clinical trials have proven harmful or fatal to patients, most famously in the cardiac arrhythmia suppression trial (CAST) (Echt et al., 1991). One of the prime motivations for the field of microphysiological systems, often called "organs on chips", is to develop *in vitro* models of the heart that can be used to assess potential safety of new treatment. Organs on chips combine advances in stem cell biology, tissue engineering, and microelectromechanical systems to create tools for high-fidelity pharmacological studies, where human tissues fashioned from stem cells replicate enough of an organ's physiology and pathophysiology to be used as an early warning system to test candidate molecules for toxicity and efficacy. Organs on chips offer an elegant means of gaining a granular understanding of how a drug affects cellular and tissue physiology, with the assumption that this understanding can be extrapolated to the whole organ. The challenge is that the whole organ, especially in the case of the heart, is actually several different tissues (Figure 1), each characterized by unique microenvironments and cell population demographics that potentiate unique structure-function relationships, which can be highly localized and lend themselves to the unique failure modes that distinguish the wide variety of fatal cardiomyopathies. Capturing all of this in a tissue smaller than a penny is no easy task.

In this issue of *Cell*, Zhao et al. (2019) present a designer mimic of the atria and ventricles of the heart using tissues derived from healthy and patient-harvested cells that have been driven down developmental pathways to assume the unique phenotypes of atrial and ventricular myocytes. These cells are then embedded in a hydrogel as part of a microelectromechanical device, a biowire, to allow studies of their self-organization into a papillary-like tissue for electrophysiological and contractility studies. When various drugs are administered to these chips, the physiological and pathophysiological effects of the molecules could be measured, and those measurements could be extrapolated to predict the drug effects on the whole of the organ.

The design of the system is like that of a piece of papillary muscle string between two parallel, wired lines in a small tissue culture well within polystyrene. The system is built by taking cardiac myocytes, either ventricular or atrial, with a sprinkling of cardiac fibroblasts included, and mixing them with a hydrogel within the small well. Over the course of a week, the authors report the spontaneous organization of the cells as "compaction," forming small cylindrical, trabeculated strips, (termed "Biowires II" by the authors) that are suspended in the well between the two wires. After a week of acclimating to their culture environment and forming the muscle strips, the cells are then electrically paced by electrodes inserted into

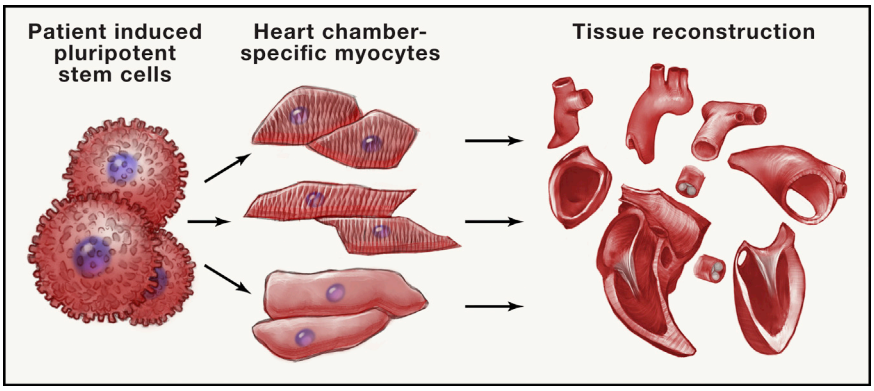

Figure 1. A Cardiac Organ on a Chip
Using induced pluripotent stem cells from patients, Zhao et al. (2019) derive heart chamber-specific myocytes and reconstruct tissues whose gene expression, structure, function, and in some cases dysfunction mapped to the clinical condition of the patients they were derived from.

the well. The induced excitation-contraction coupling within the myocytes potentiates further alignment of the myofibrils within the cells over six weeks in culture.

The authors test the system with several compounds with known cardiac effects. Using isoproterenol, a β-adrenoceptor agonist, the ventricular biowires contracted harder. Blocking L-type calcium channels with diltiazem reduced the beating frequency of the heart tissues. Blocking sodium channels with lidocaine made the tissues less excitable. Inhibiting cAMP phosphodiesterase 3 with the drug milrinone, increased the contractile strength of the tissues. So manipulation of some of the various signaling pathways regulating excitation-contraction coupling suggested that the ventricular biowires were, indeed, ventricular.

But the real test of a microphysiological system's utility for the safety pharmacologist is to test its ability to replicate the proarrhythmic effects of drugs binding to the human Ether-a-go-go (hERG) potassium channel. These channels are responsible for potassium currents bleeding out of the myocyte, repolarizing the cell and ending the cardiac action potential. When these channels are blocked, the action potential is prolonged, inducing a change to the shape of the electrocardiogram (EKG) signal referred to as long QT. The hope with organs on chips is that human-derived tissue might be studied to see who is sensitive to long QT because long QT can potentiate a particularly nasty cardiac arrhythmia, polymorphic ventricular tachycardia of the torsade de pointes. It turns out that the majority of drugs that are proven to have some cardiotoxicity bind the hERG channel, prolonging the QT interval (long QT) of the EKG and mimicking the genetic disease associated with the channel, Long QT Syndrome. Zhao et al. (2019) test their ventricular biowires by administering the hERG channel blocker E-4031. The resulting irregular beating patterns, or extrasystoles, are interesting because they are commonly associated with long QT in patients. The authors conclude that these irregular beating patterns are consistent with arrhythmogenesis.

The atrial and ventricular biowires were further distinguished by their response to exogenous electrical pacing. Gene expression of the atrial and ventricular samples diverged during pacing, with the ventricular cells, the more contractile of the two cardiac myocytes, showing the greatest changes. While both cell types show architectural changes during pacing, they each exhibit changes and behaviors reminiscent of adult cells in the atria and ventricles of the heart. Action potentials, force frequency relationships are unique and the response to drugs affecting calcium metabolism differ between the two biowires.

Moving beyond safety pharmacology, the authors also show the effectiveness of the biowires in modeling disease. Using induced pluripotent stem cell (iPS) derived cardiac myocytes from hypertensive patients, they can distinguish, in their *in vitro* preparation, the differences between the two patient groups they studied, namely, those with, and without, ventricular hypertrophy. Both gene expression and contractility studies, after eight months in culture, show differences between the tissue. This is notable, because the challenge with any *in vitro* system is to replicate the subtleties of the cell and tissue microenvironment in such a way that the cell expresses itself as if *in vivo*. In so far as the metrics reported indicate, the authors were successful in this regard.

While organs on chips are rapidly developing as a boutique assay, their introduction to the automated, drug discovery protocols of industry will be slower. Whereas the pharma industry tends to rely on large quantities of low quality data in their earliest preclinical studies, organs on chips offers high quality, albeit lower quantities of data. The advantages of the systems to the safety pharmacologist are clear: high fidelity human data without endangering a patient. For rare diseases, organs on chips offer a unique opportunity for gathering human data in patient bases that are too small to make normal clinical trials possible. Finally, the most interesting opportunity for organs on chips may be in screening clinical trial enrollees for toxicity and efficacy before enrollment. This model will require streamlined efforts to derive organ cells uniquely by iPS methods, integration into easily maintained, instrumented chip models, and readouts that can be mapped clearly to clinical diagnostics. The report by Zhao et al. is a step in this direction.

DECLARATION OF INTERESTS

Declaration of Interests K.K.P. is a principal at KK Parker & Associates, with consulting responsibilities to several biotech and pharam companies.

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