

InvivoSciences Inc.

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# Predicting cardiotoxicity with engineered 3D human cardiac tissue models

InvivoSciences harnesses human induced pluripotent stem cells to generate patient-specific disease models for drug and diagnostics development.

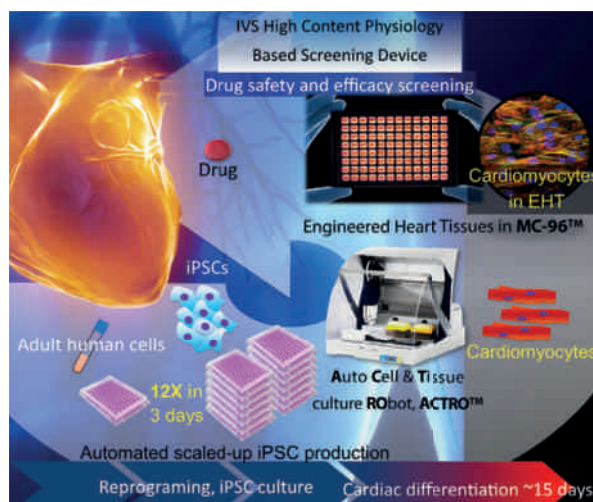
**C**ardiovascular safety liabilities caused 52.3% of 44 marketed drug withdrawals according to data from 1980 to 2011, and cardiovascular disease remains the leading cause of death globally, yet only 8.7% of cardiovascular drugs successfully pass clinical trials. These statistics demonstrate the need to address a patient's specific genetic make-up and phenotype by adopting a personalized treatment methodology for cardiovascular diseases.

Established in 2001 in St Louis, Missouri, InvivoSciences Inc. (IVS) provides innovative solutions to address the unmet technological needs in drug discovery and development for cardiovascular diseases and to predict adverse cardiotoxicity effects at the preclinical stage. Today operating in Madison, Wisconsin, the founders work with scientific advisers and collaborate with leading academic and government institutions.

## Drug discovery platform

IVS has become a leading developer of human 3D cell and tissue culture models by providing a high-throughput, functional system for testing cardio safety and efficacy to screen and identify compounds or pathways that may alter cardiac physiology and pathology. The high-content analysis of human engineered tissues is instrumental in drug discovery at their screening and lead optimization stage. The IVS proprietary technology allows the growth of engineered tissues in 3D to mimic healthy and disease-naïve human tissues, which enables the gap to be bridged between cell-based assays and studies using isolated organs, tissues or animal models. The engineered tissue, developed without a synthetic supporting layer, allows physiological measurements (e.g., contraction) and analysis. IVS technology improves clinical approval success rates by predicting patients' responses to drug candidates which is achieved by using the tissue-based discovery platform to predict patient-specific responses to treatments in engineered human tissues derived from patient-specific samples.

Abnormalities in muscle function are observed in many inherited or acquired diseases, such as muscular dystrophy, chronic obstructive pulmonary disease, and congestive heart failure. The Palpator is a high-throughput mechanical tissue analyzer that measures the mechanical properties of engineered tissues growing in



96- or 384-well plates and allows chemical library screening. IVS has carried out proof-of-concept studies to analyze the molecular mechanisms of action of different compounds on the contractile activities of different muscle cell types.

IVS provides services to develop heart failure models driven by genetic mutations. Current projects include phenotyping of patient-specific engineered heart tissues (EHTs) for Duchenne muscular dystrophy and congenital heart disease.

## Precision medicine focus

Human induced pluripotent stem cell (iPSC) technology is critical within precision medicine because it generates a disease model in a dish. The iPSC's capacity to yield large numbers of pluripotent cells able to differentiate into almost any somatic cell type is attractive. However, performing this feat industrially is daunting as well-defined, uniform and reproducible patient derived iPSCs are essential for cells to differentiate into somatic cells and to develop tissues and organs for faithful disease modeling. Automation of iPSC culture can normalize and standardize cell proliferation, enabling researchers to handle large numbers of human cell lines. Moreover, the personalized 3D human cardiac tissue models empower researchers to conduct drug safety and efficacy analysis using enriched study population at preclinical stages.

IVS has developed an *in vitro* disease model that recapitulates an individual patient's cardiomyopathy in 3D EHTs using patient-derived cells. Automated cell culture and cardiomyocyte-differentiation protocols demonstrate both improved productivity and reproducibility for generating

patient-specific disease models for drug and diagnostics development (see figure).

## Products and services

IVS's products and services will reduce the cost and use of animal studies. The company's assay platforms assess the therapeutic efficacy of pharmaceutical candidates by analyzing key physiological functions of engineered tissues *in vivo*. The Palpator is used for analyzing the structural and mechanical integrity of heart heart muscle equivalent. The live-in-tissue analysis (LITA), a high-content phenotypic analyzer, quantifies treatment-induced changes in a tissue construct's physiological function and the biomolecular activities that underlie those changes. IVS offers services

using the LITA for testing the efficacy and safety of drug candidates. The LITA will soon be available for in-house operations at customers' sites and is also available in other applications including regenerative medicine, cancer, autoimmune disorders and many rare diseases. IVS also provides a device, ACTRO that automates cell and tissue culture of iPSCs and can handle an increasing number of patient-specific iPSC lines.

## Future perspectives

US National Institutes of Health (NIH) Small Business Innovation Research (SBIR) grants have supported IVS's drug discovery applications of its innovative technologies, allowing the company to build a strong foundation. The strategic collaborations with key industry and academic partners have helped IVS to create a unique product/assay and service portfolio that provides solutions to unmet needs in drug discovery and patient populations with debilitating cardiac diseases. IVS has developed global commercial growth plans by boosting its scaled-up and fully automated manufacturing of human engineered tissues and their personalized derivatives. IVS seeks potential private funding partners to share the business opportunity. IVS also wants to expand its strategic partnerships with pharmaceutical and biotech companies.

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