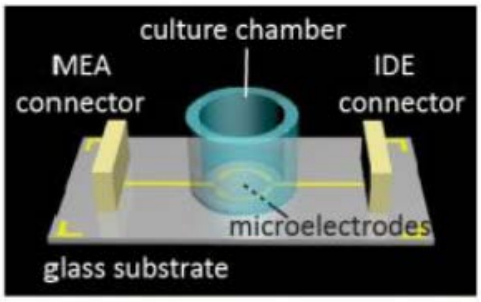
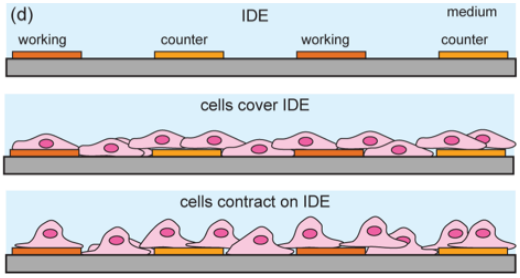
iCHIP & TISSUE RESEARCH

IL13165: SENSOR ARRAY AND APPARATUS FOR SIMULTANEOUS OBSERVATION OF TISSUE ELECTROPHYSIOLOGY, CONTRACTILITY, AND GROWTH (Pending US patent application)

Cardiac toxicity is one of the major causes of drug candidate failure in clinical studies and is responsible for the failure in regulatory approval of drugs as well as the retraction of numerous drugs from the market. Critical to the success of early stage drug discovery is the ability to obtain high-quality and high-throughput data in a cost-effective manner. Predicting cardiotoxicity requires the ability to create cardiac tissues that mimic in vivo physiology at multiple scales, as well as the ability to record two key cardiac functions: tissue electrophysiology and contractility**.**

Described is an iCHIP (in-vitro Chip-based Human Investigational Platform) that includes interdigitated electrodes (IDE) in a microelectrode array (MEA) that measures cardiac tissue growth, electrophysiology and contraction simultaneously in real time. The MEA is used to detect and map the propagation of action potentials, the IDE is used for monitoring tissue growth and contraction. Human iPS-CMs (induced pluripotent stem cell-derived cardiomyocytes) were initially cultured on the chip to investigate effect of norepinephrine, and validated computationally.





Applications

- Simultaneous mapping of cardiac electrophysiology and recording of contraction for safety pharmacology and toxicology screening in drug development process
- A great tool for basic research to understand physiology of cardiac cells
- Real-time non-invasive measurement
- High throughput analysis

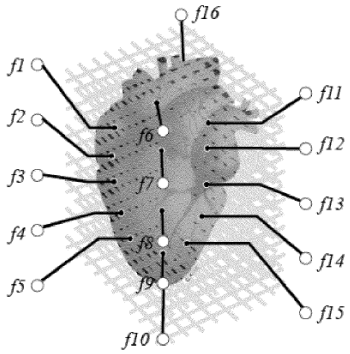
Reference: http://pubs.rsc.org/en/content/articlelanding/2017/lc/c7lc00210f#!divAbstract

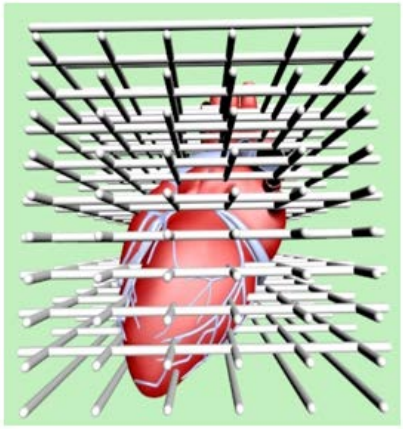
IL13005: THREE-DIMENSIONAL ELECTRONIC SCAFFOLD FOR CARDIAC APPLICATIONS (US Patent 10,018,615)

Cardiac toxicity is one of the major causes of drug candidate failure in clinical studies and is responsible for the failure in regulatory approval of drugs as well as the retraction of numerous drugs from the market. Incorporating effective *in vitro* assays early in preclinical development offers the potential to

improve clinical predictability, decreases R&D costs, and avoids adverse patient effects, late-stage clinical termination, and product recall from the market.

Three-dimensional cultures can better recapitulate *in vivo* cellular responses to drug treatment and has potential to be a superior platform for drug development. Therefore, there is a great need for *in vitro* 3D cell culture assays, which would bridge the 2D monolayer cell culture systems and the animal models. This invention describes a novel 3D electronic scaffold that facilitates the generation of *in vivo*-like tissues and records physiological functions in real time.





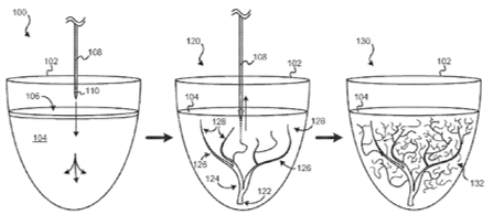
It provides a novel platform that enables new capabilities such as generating better tissue models within short time, supporting long-term tissue culture, high spatiotemporal resolution enabled by electrical detection, and capability to record intra-tissue functions.

Applications:

- Generating 3D cardiac tissues to assist in cardiac research
- Safety pharmacology and toxicology screening in drug development process
- Regenerative medicine
- Measurement of cardiac cell contractions using micro-strain gauges.

IL12754: OMNIDIRECTIONAL, MULTIAXIAL BIOPRINTED TISSUE SYSTEM TECHNIQUES AND APPLICATIONS (US Patent Application US2015/0050686)

Animal testing is used as a proxy to assess organic- and systemic-level response to drugs in advance of human clinical trials. However, human safety and drug performance is not always accurately predicted through animal testing. Therefore, there is a need to develop engineered human tissue to mimic human physiological systems. Standard scientific approaches that have been used to integrate vascular networks into engineered tissue include: 1) biodegradable scaffolds that release angiogenic growth factors and 2) microfluidic channels seeded with vascular cells and stacked to form 3D networks. The rationale for these strategies has been described in detail. However, challenges in directional



control of vessel growth within 3D scaffolds, and the planarity of 2D microfluidic channels limit their physiological geometry.

Biological printing has the potential to surpass traditional scaffold-based tissue engineering. The invention describes a more advanced printing technique that allows continuous free-form printing of biological material within a self-healing hydrogel to assemble complex omnidirectional microvascular networks that range from micron to millimeter in diameter. This technique will allow the growth of microvascular networks with spatial physiological morphology, as well as an understanding of tissue assembly and nutrient diffusion requirements to maintain long-term tissue survival.

Notably, the tissue systems, networks, etc. are physiologically-relevant, i.e. exhibiting one or more characteristics indicative of physiological relevance, such as a substantially fractal geometry, inter-vessel spacing, cellular composition, dermal structure, concentric multi-layered structure, etc.

Applications

- Improved drug development as vascular network exhibits physiologically relevant conditions
- Basic research,
- 3D printing
- De novo tissue/organ printing

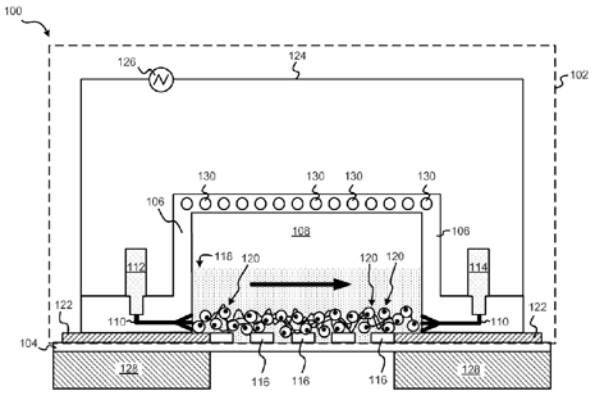
IL12755: MINIATURIZED, AUTOMATED IN-VITRO TISSUE BIOREACTOR (US Patent Application US2014/0322701)

Currently, development of new therapeutics takes over a decade and in excess of $2B. Less than 1% of potential new pharmaceuticals reach market and greater than 10% of those demonstrate serious unanticipated adverse effects that cause market withdrawal and significant costs in litigation. This process is a result of an antiquated system that involves testing without consideration of mechanism of action in animal models that often do not reflect human biology. New methods are needed to efficiently assess potential new drug entities directly in human tissues.

This invention describes a novel system that combines primary human cells, tissue engineering, and novel microfluidics, creating an *in vitro* platform to reproduce *in vivo* physiological response to study the effects of exposure to toxins. This platform provides a highly-integrated, multi-organ, human-relevant tissue reactor for rapidly assessing and predicting the toxicity, safety and efficacy of new drug entities with the goal of accelerating both development and regulatory approval of drugs. This advancement could shorten the development time by an estimated 50% and reduce the cost of human clinical trials through earlier selection of winning therapeutic candidates. The technology demonstrates an assembly of computer-controlled reactors designed to support living human cells and tissues enabling precise control of environmental conditions to maintain long term cell functionality, imaging, stimulation and recording with electrophysiological multi-electrode arrays, and biochemical sensing.

Applications

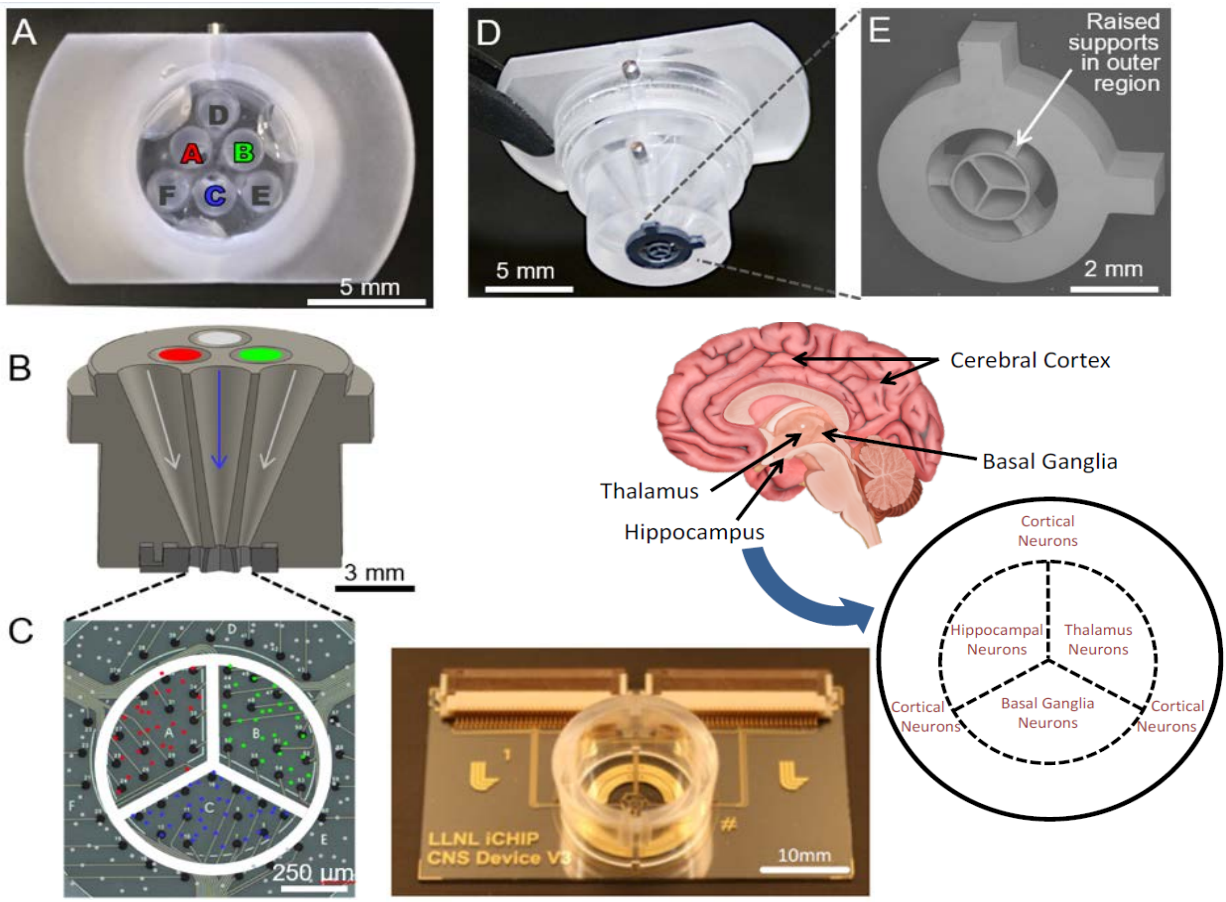
- Rapid and accurate prioritization of drug candidates for human and animal testing
- Interrogation/monitoring of neurotoxicity effects on up to 100 cells as opposed to one at time
- Predicting the toxicity, safety and efficacy of new drug entities in order to accelerate both development and regulatory approval
- Medical countermeasures against chemical, biological, and radiological (CBR) agents
- Study of host-pathogen reactions on human tissue and organ systems in a manner not previously possible



IL12910: FUNNEL FOR LOCALIZING BIOLOGICAL CELL PLACEMENT AND ARRANGEMENT (US Patent 9,909,093)

The present disclosure relates to a funnel apparatus for channeling cells onto a plurality of distinct, closely spaced regions of a seeding surface

The funnel apparatus has a body portion having an upper surface and a lower surface. The body portion forms a plurality of flow paths, at least one of which is shaped to have a decreasing cross-sectional area from the upper surface to the lower surface. The flow paths are formed at the lower surface to enable cells deposited at the upper surface of the funnel apparatus to be channeled into a plurality of distinct, closely spaced regions on the seeding surface positioned adjacent the lower surface.



This iCHIP (in vitro Chip-based human investigational platform) method and device allows segregation or selective placement of cells, without using chemicals or permanent physical surface modifications, to grow freely on an unconfined space. It is applicable to any cell type derived from any organ system. It provides better resolution and smaller separation distances (tens of microns) between different cell types used for localized cell placement. It overcomes limitations of PDMS "stencils." PDMS stencils' wells are too small to insert micropipette tip that often leads to flooding of the entire stencil, which is suitable for placing only one type of cells but does not work when multiple cell types need to be seeded.

Applications

Neuronal communication, cell migration, cancer metastasis, quorum sensing, growth factor effects, organ-on-a-chip, tissue engineering, and developmental biology. The device could also be used to study bacterial cell interactions (microbiome), cell signaling in proximity without physical contact, disease models (e.g., Alzheimer's), and early stage drug development.

Reference: https://doi.org/10.1371/journal.pone.0188146

Development Status

LLNL is seeking industry partners with a demonstrated ability to bring such inventions to the market. Moving critical technology beyond the Laboratory to the commercial world helps our licensees gain a competitive edge in the marketplace. All licensing activities are conducted under policies relating to the strict nondisclosure of company proprietary information.

Contact

Yash Vaishnav

Vaishnav1@llnl.gov