

Introduction

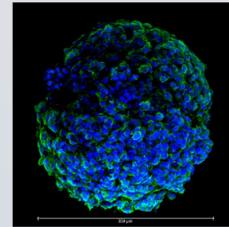
In order to better predict human toxicity following chemical exposure, it is necessary to develop models which more closely represent the human response. Animal models are not always predictive of human physiology and can be very costly and are becoming less desirable to use for research because of ethical reasons. Also, traditional 2D cell culture methods, even when using human cell lines, may not accurately represent whole organ responses to chemical exposure. Members of the Molecular Toxicology Branch here at ECBC are currently collaborating with investigators from several universities to address this problem. A model system utilizing human 3D spheroid cultures has been developed and is currently being tested. The objectives are to identify biomarkers and other endpoints in order to better predict human toxicity. Our lab is currently testing human 3D cardiac, lung and liver spheroid cultures. However, because this novel, integrated system is modular, 3D human spheroid cultures from other organ cell types such as the vasculature and brain/neural tissues can easily be included.

Objectives

- Develop a microfluidic module with on-board monitoring capabilities: optical imaging (including fluorescence), photodiodes, micro-electrodes, immunoassay capture.
- Create 3D, multicellular organoids that mimic the function of the *in vivo* human organs.
- Evaluate the system using chemical agents known to exert effects on humans, and compare derived data with that extrapolated from animal exposures, human exposures and computer modeling.

Approach/Work Flow

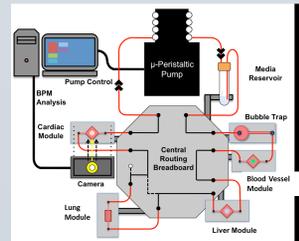
Wake Forest



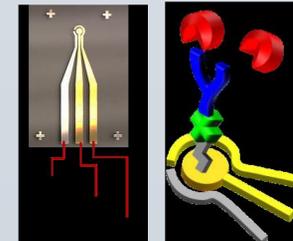
Organoids are 3D and contain all of the major cell types found in the native organ.



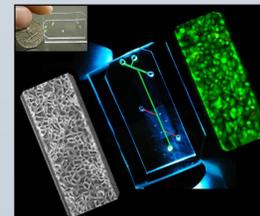
3-D bio printer for manufacture of human tissue



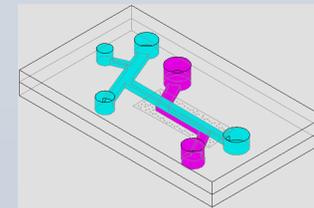
Microfluidics platform for organoid support and linking organs systems



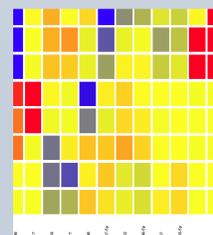
Inline metabolite sensing



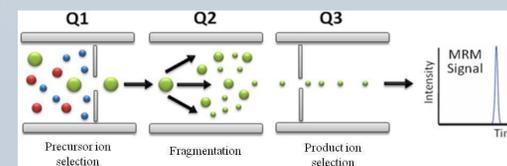
Lung module for detecting mechanical injury



Lung module with air liquid interface



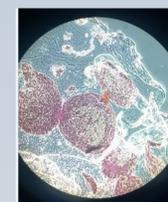
Offline analysis and biomarker discovery with micro RNA



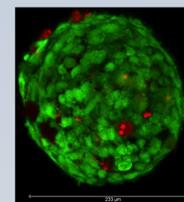
Offline analysis and biomarker discovery using metabolomics



Human on a chip evaluation and additional endpoint analysis



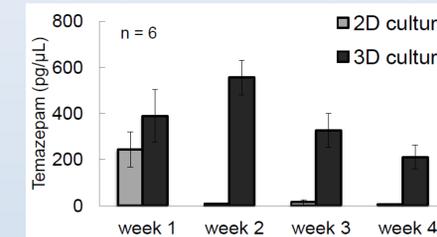
Organoid thin sections



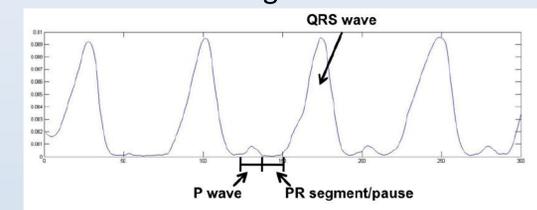
3-D image analysis

Results

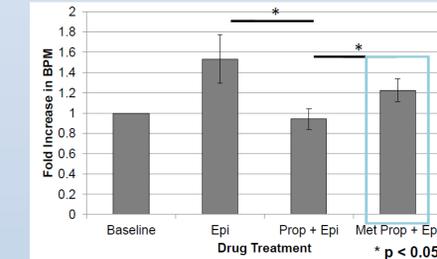
Longevity of 2D vs 3D Hepatocytes



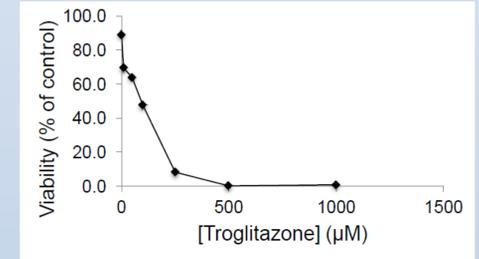
Cardiac Organoid "EKG"



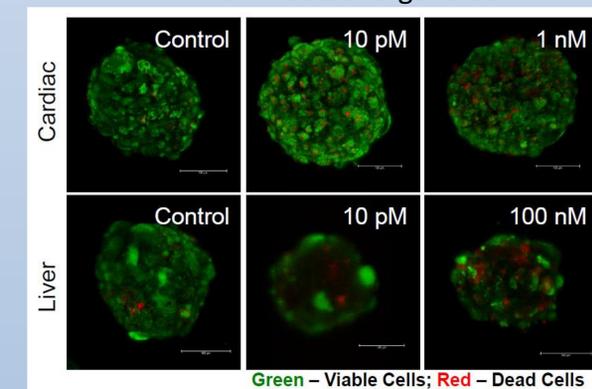
Epinephrine + Propranolol on Heart Rate



Troglitazone (rezulin)



Ricin Treated Organoids



Conclusions

- A system has been designed that is able to create multiple bioprinted human organoid types that have a high degree of functionality long-term.
- A microchip/biosensing system is able to monitor function and allows for the interaction of many different organ systems in parallel or in series.
- The system can be used for drug screening and toxicity testing.

Acknowledgements

This work was funded by the Defense Threat Reduction Agency's Chemical and Biological Defense Program.

TECHNOLOGY DRIVEN. WARFIGHTER FOCUSED.