Drug development is expensive and time consuming ranging from drug discovery to preclinical to Phase 1-3 clinical trials which too often fail because of safety issues and/or inadequate efficacy. Over the last decade, advances in biomedical engineering have demonstrated progress extending from molecules to cells to organoids and most recently to human-on-a-chip multi-organ systems. These devices promise to provide shortcuts to assessing pharmacokinetic and pharmacodynamic profiles of new molecules. This rapidly evolving science may be particularly relevant when barriers to testing and approval may be more challenging. This being my last Newsletter as interim vice chancellor for research at CU Denver | Anschutz I am particularly impressed with the work published in *Science Translational Medicine* (19 Jun 2019:Vol. 11, Issue 497) entitled ‘Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics’ (Figure 1). Here’s wishing the Office of the Vice Chancellor for Research best to follow.

**Multi-organ system for the evaluation of efficacy and off-target toxicity of anticancer therapeutics**

Christopher W. McAleer1 *, Christopher J. Long1 *, Daniel Elbrecht1, Trevor Sasserath1, L. Richard Bridges1, John W. Rumsey1, Candace Martin2, Mark Schnepfer2, Ying Wang2, Franz Schuler3, Adrian B. Roth3, Christoph Funk3, Michael L. Shuler1, James J. Hickman1,2†

*Hesperos Inc., 3259 Progress Drive, Room 158, Orlando, FL 32826, USA.

**NanoScience Technology Center, University of Central Florida, 12424 Research Parkway, Suite 400, Orlando, FL 32826, USA.

**Roche Pharma Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann–La Roche Ltd., Grenzacherstrasse 124, CH-4070 Basel, Switzerland.

†Corresponding author. Email: jhickman@hesperosinc.com

* These authors contributed equally to this work.

Hide authors and affiliations

A pumpless, reconfigurable, multi-organ–on–a–chip system containing recirculating serum-free medium can be used to predict preclinical on-target efficacy, metabolic conversion, and measurement of off-target toxicity of drugs using functional biological microelectromechanical systems. In the first configuration of the system, primary human hepatocytes were cultured with two cancer-derived human bone marrow cell lines for antileukemia drug analysis in which diclofenac and imatinib demonstrated a cytostatic effect on bone marrow cancer proliferation. Liver viability was not affected.
by imatinib; however, diclofenac reduced liver viability by 30%. The second configuration housed a multidrug-resistant vulva cancer line, a non-multidrug-resistant breast cancer line, primary hepatocytes, and induced pluripotent stem cell–derived cardiomyocytes. Tamoxifen reduced viability of the breast cancer cells only after metabolite generation but did not affect the vulva cancer cells except when coadministered with verapamil, a permeability glycoprotein inhibitor. Both tamoxifen alone and coadministration with verapamil produced off-target cardiac effects as indicated by a reduction of contractile force, beat frequency, and conduction velocity but did not affect viability. These systems demonstrate the utility of a human cell–based in vitro culture system to evaluate both on-target efficacy and off-target toxicity for parent drugs and their metabolites; these systems can augment and reduce the use of animals and increase the efficiency of drug evaluations in preclinical studies.

Research Corner

Christine Vohwinkel, MD, PhD is an Assistant Professor of Pediatrics. My laboratory’s research is focused on acute lung injury (ALI) an inflammatory lung disease characterized by its acute onset, severe hypoxia and pulmonary edema, which manifests itself in patients as acute respiratory distress syndrome (ARDS). We are specifically interested in how cell metabolism affects inflammation.

Most tissues energy demands are met by oxidative phosphorylation. However, a cell has the ability to divert pyruvate away from oxidative phosphorylation if it requires biosynthetic precursors and has rapid energy demands. This phenomenon has been intensely studied in cancer (Warburg-effect). Despite the potential relevance of these functions to ARDS pathophysiology, little is known about the impact of epithelial metabolism on lung injury responses. We observed, that alveolar epithelial cells demonstrate an up-regulation of key metabolic enzymes for anaerobic glycolysis, particularly phosphofructokinase-2/fructose-2,6-bisphosphatase (PFKFB) 3 in ALI. PFKFB3 is known for its critical role in enhancing downstream glycolytic enzymes particularly lactate dehydrogenase (LDH). We found that this glycolytic shift of the alveolar epithelium is protective mechanism in several murine models of ALI. We have now started to look deeper into the mechanism by which activation of epithelial glycolysis is protective in ALI and are focusing on the interactions between epithelium and airway macrophages. Macrophages surrounding tumors (that produce a lot of lactate) shift their phenotype more to an anti-inflammatory state (Arg1+, IL-10 producing). We found a similar effect in acute lung injury: mice which received intra-tracheal lactate 6 hours after onset of lung injury shifted the resident alveolar macrophages towards an anti-inflammatory state and improved resolution of ALI.

The overall goal of my research is to find the underlying pathways regulating metabolism and inflammation in order to harness those innate protective pathways for novel therapies of ALI.

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