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Michael L. Shuler is the Eckert Professor of Engineering, Emeritus in the Meing Department of Biomedical Engineering and in the Smith School of Chemical and Biomolecular Engineering at Cornell University, and was director of Cornell's Nanobiotechnology Center. Shuler has degrees in chemical engineering (BS, Notre Dame, 1969 and Ph.D., Minnesota, 1973) and has been a faculty member at Cornell University since 1974. Shuler's research includes development of "Body-on-a-Chip" for testing pharmaceuticals for toxicity and efficacy, creation of production systems for useful compounds, such as paclitaxel from plant cell cultures, and construction of whole cell models relating genome to physiology. Shuler is CEO and President of Hesperos, a company founded to implement the "Body-on-a-Chip" system. Shuler and F. Kangi have authored a popular textbook, "Bioprocess Engineering; Basic Concepts" now in its third edition. He has an honorary doctorate from the University of Notre Dame. Shuler has been elected to the National Academy of Engineering and the American Academy of Arts and Science and is a fellow of numerous professional societies.

BODY ON A CHIP: CONCEPTION TO PRACTICAL APPLICATIONS

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Introduction

The preclinical drug development process is inefficient at selecting drug candidates for human clinical trials, since only 11% of drug candidates selected for clinical trials exit with regulatory approval. Current technology is based on isolated human cells and animal surrogates. A "human" multiorgan model based on physiologically based pharmacokinetics-pharmacodynamic (PBPK-PD) models that house interconnected modules with tissue mimics of various organs could lead to more accurate preclinical assessment of a drug or of human toxicity for cosmetics, foods, or chemicals. (1)

Discussion

Integrated, multi-organ microphysiological systems (MPS) based on human tissues (also known as "body-on-a-chip") such microscale systems combine organized human tissues with the techniques of microfabrication (2). In particular, I will describe such systems that are guided in their design by a PBPK model. Our systems are "self-contained" in that they can operate independently and do not require external pumps as is the case with many other microphysiological systems. They are "low cost", in part, because of the simplicity and reliability of operation. They maintain a ratio of fluid (blood surrogate) to cells that is more physiologic than in many other in vitro systems allowing the observation of the effects of not only drugs but their metabolites. While systems can be sampled to measure the concentrations of drugs, metabolites, or biomarkers, they also can be interrogated in

situ for functional responses such as electrical activity, force generation, or integrity of barrier function. Operation up to 28 days has been achieved allowing observation of both acute and chronic responses with serum free media.

We have worked with various combinations of internal organ modules (liver, fat, neuromuscular junction, skeletal muscle, cardiac, bone marrow, blood vessels and brain) and barrier tissues (eg skin, GI tract, blood brain barrier, lung, and kidney). We have achieved unidirectional flow in a pumpless system which is important for mimicking the response of vascular tissues (3) and constructed blood brain mimics with human in vitro like characteristics (4. The use of microelectrode arrays to monitor electrically active tissues (cardiac and neuronal) and micro cantilevers (muscle) have been demonstrated (2,5). While most systems use 5 or fewer organ modules, we have demonstrated that a 13 “organ” compartment device can be constructed (6) demonstrating the potential to address a wide range of problems in pharmacology and toxicology in a low cost system. Most importantly these technical advances allow prediction of both a drug’s potential efficacy and toxicity (side-effects) in pre-clinical studies. (6, 7)

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