



Alternatives Research & Development
F O U N D A T I O N

ARDF is pleased to announce the recipients of the

2008 Alternatives Research Grants

Michael J. Bouchard, PhD

Drexel University, Philadelphia, PA

A Novel Human Mini-liver Model for Studying Drug Toxicity

The challenge: Drug-induced liver toxicity (DILT) is the most common reason that new drugs fail. Currently, assessments of potential DILT are conducted in experiments using live animals or liver cells isolated from nonhuman mammals. In addition to the ethical objections, these are flawed models and do not consistently predict DILT in humans. There is a need for a human liver model that retains the essential structure and functions of the liver and uses a limited number of cells available from donated human livers.

The project: Dr. Bouchard's team has already started work fabricating authentically structured microchannel cultures. Using that system, this project will create co-cultures of the two predominant cell types of a functional liver. Then, the system will be tested by analyzing the toxicity of a well-characterized drug, and comparing it to known responses in a human liver.

David E. Cliffel, PhD

Vanderbilt University, Nashville, TN

Multianalyte Microphysiometry of Human Cell Lines to Replace Animal Toxicology

The challenge: Understanding how drugs or chemicals may adversely affect people's health and the environment is the main goal of the vast field of toxicology. Regulatory agencies in the U.S. and worldwide demand testing of many kinds to provide information, and much of that testing is done on animals, resulting in some of the most controversial experiments known. Some in vitro tests that simply measure if cells die or are visibly damaged upon exposure to a substance have limitations of use in answering more complex questions.

The project: Dr. Cliffel's research team has already engaged in initial experiments to perfect human cell-based toxicity measurements using a multianalyte microphysiometer. This device is particularly useful because it is able to quickly assess multiple measurable cell activities of interest, such as changes in overall cell metabolism, as well as specific changes in glucose, oxygen and lactate usage or production. Using human cells, this project will initially focus on detection of 'signatures' of cell activities, in sequence, demonstrating pathways of toxic effects. Then, by interpreting those signatures, predictive models of complex reactions to drugs and chemicals will be developed, potentially serving as an alternative to use of animals in many circumstances.

Qiao Lin, PhD

Columbia University, New York, NY

Microfluidic Selection of Synthetic Receptors for Affinity Extraction of Biomolecules

The challenge: A wide variety of research projects rely on purifying or identifying selected molecules by extracting them from a mixture of many other chemicals. Typically, antibodies are used for these 'affinity extractions' and the antibodies are generally produced in animals. There has been interest in moving away from antibody use, which, in addition to being inhumane, can also be inefficient, time-consuming and inconsistent, but the replacement technologies have been unsatisfying in some ways.

The project: Dr. Lin and his engineering colleagues have been working with new, miniaturizing technologies to run a system that can extract synthetic 'aptamers'. Aptamers are short sections of single stranded RNA or DNA that are designed to recognize and bind to specific molecules and can replace the functions of antibodies in affinity extraction. This fluid-based system of extraction is designed to be safe, reliable, and can be automated for ease of adoption. Possible applications are in fields as varied as drug discovery, diagnostic tests and even therapeutic treatments and therefore the potential impact on animal use is very significant.

Gail Jean Pyne-Geithman, PhD

University of Cincinnati, Cincinnati, OH

A Human Cell Culture-based Model of a Functional Blood Brain Barrier

The challenge: The Blood-Brain Barrier (BBB) is an area of intense research interest because: 1) when it breaks down, problems such as stroke and traumatic brain injury (TBI) are significantly worsened, and 2) it is a barrier to drugs that might otherwise access brain tissue and directly help treat brain diseases and conditions. Simple in vitro models of the BBB have been created and some are in limited use. However, there is still a need for a more complex (thus more predictive), yet practical in vitro model in order to gain acceptance as an alternative to the many animals that are used every year in this kind of research.

The project: Dr. Pyne-Geithman, a neurologist, and her team seek to develop an optimized, standardized model of the BBB which can be widely accepted. They will utilize human cell lines and commonly available lab products to make it attractive in terms of relevance and ease of use. Other key features are that the cell culture will be multi-layered and integrate four types of brain cells to more accurately simulate the actual conditions at the BBB. Dr. Pyne-Geithman sees immediate application in stroke and TBI studies and, with dissemination of the results, translation of the technology to many different fields of basic research and drug development.

Marcus Anton Wimmer, PhD

Rush University Medical Center, Chicago, IL

Response of Damaged Human Cartilage to Articular Motion**A Study Utilizing an Acute Trauma Model on Human Ankles**

The challenge: Joint injuries have long-term consequences including arthritis, which is a widespread health problem. Joint research often involves living animals, including dogs, in highly invasive procedures. In addition to the ethical concerns, there are problems in using the results of animal studies to understand what happens in human cells and tissues following injury.

The project: Dr. Wimmer proposes to use donated human cartilage tissue in a device that simulates the precise pressures that occur during an injury. This will allow his research team to identify the key factors at the cellular level that are involved in the initial stages of injury immediately following acute trauma to cartilage. Dr. Wimmer's project is extraordinary in its experimental design's extensive statistical foundation and its incorporation of 'tribology' in the design of the device which inputs the stress of physical motion into the injury parameters before measuring the result. Its complexity means that in research studies, responses such as inflammation might be able to be reversed utilizing different experimental treatments, allowing for a more rapid translation to clinical use.