Current preclinical testing using assays based on cancer cells and animal models often results in high failure rates for drug candidates in the clinic. Microphysiological systems like Altis's RepliGut® human intestinal tissue model more accurately reflect human physiological environments, enabling more efficient and cost-effective drug discovery and development.

ACCELERATING DRUG DEVELOPMENT WITH MICROPHYSIOLOGICAL SYSTEMS (MPS)

September 29, 2020

ALTIS BIOSYSTEMS

Using Human Tissue for Drug Screening

The inadequacies of current preclinical drug development methods have left the industry with an unacceptable clinical trials failure rate and nearly $200 billion spent every year on research and development. A key factor driving clinical failures is the use of tumor cell lines such as Caco-2 cells and animal usage in preclinical testing. Thus, too often ineffective

drugs reach clinical trials, while potentially efficacious medicines do not. An alternative and more promising approach to drug discovery, preclinical testing, and toxicity screening is the use of human tissue models.

Combining Engineering, Chemistry, and Physics

Altis Biosystems was spun out from the University of North Carolina at Chapel Hill; our company's goal is to apply engineering, chemistry, and physics to new strategies that lead to successful, faster drug development. We utilized methods from the semiconductor and electronics industries to build small-scale devices in an efficient, scalable, and cost-effective manner, seeking to marry this approach with stem cell technology.

We focused on the large and small intestines because they play crucial roles in the absorption and metabolism of drugs. Studies have proven that the bacterial composition in the colon can modulate immune responses and may play a role in many diseases, which also contributed to our interest.

Starting Simple

Capitalizing on research on growing organoids from human intestines, Altis has developed a next-generation intestinal platform for in vitro testing during drug development. The platform produces a layer of human intestinal stem and differentiated cells — either of the large or small intestine — that can be used for compound screening, disease modeling, and microbiome research.

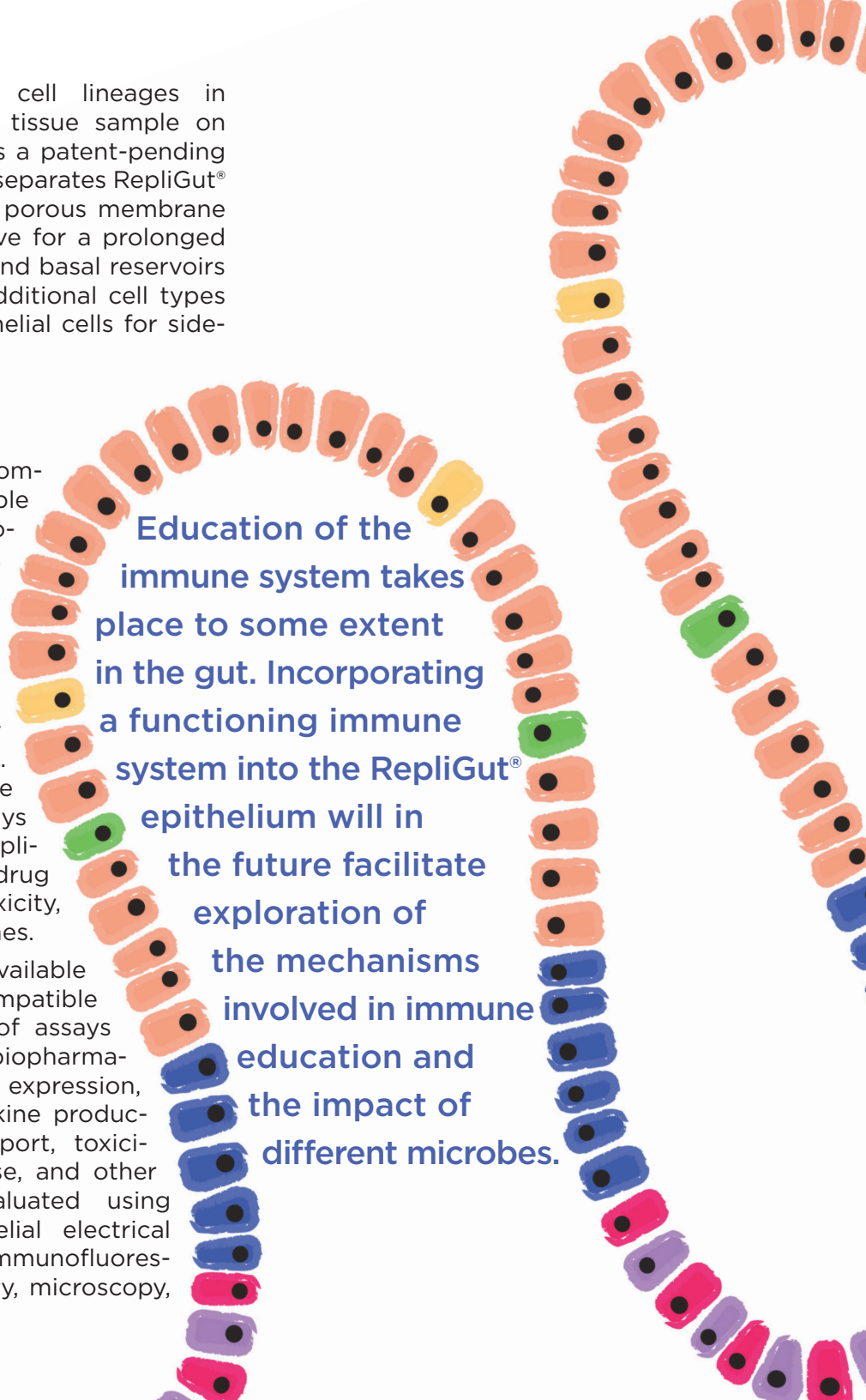
RepliGut® tissue constructs are polarized monolayers that express tight junction proteins and can be tailored to include stem/progenitor cells, differentiated cells, or both, representing all major cell lineages in physiologic ratios. Each tissue sample on the RepliGut® kit features a patent-pending biomimetic scaffold that separates RepliGut® cells from the cassette's porous membrane and allows cells to survive for a prolonged period of time. Luminal and basal reservoirs allow compounds and additional cell types to interact with the epithelial cells for side-specific assays.

Providing Diversity

With our donor bank comprising tissue from multiple donors of different demographic backgrounds, Altis is able to make realistic models that recapitulate many different physiologies and thus provide a faithful representation of the diversity of the human population. We have developed a suite of platforms and assays tailored for specific applications to investigate drug absorption, transport, toxicity, and inflammatory cytokines.

Our commercially available RepliGut® system is compatible with the vast majority of assays commonly used in the biopharmaceutical industry. Gene expression, protein expression, cytokine production, permeability, transport, toxicity, inflammatory response, and other attributes can be evaluated using ELISA, PCR, transepithelial electrical resistance (TEER), immunofluorescence, mass spectrometry, microscopy, and other techniques.

Education of the immune system takes place to some extent in the gut. Incorporating a functioning immune system into the RepliGut® epithelium will in the future facilitate exploration of the mechanisms involved in immune education and the impact of different microbes.



Differentiated from Other Organs-on-a-Chip

Unlike most other human intestinal tissue models, Altis has included both stem cells and differentiated cells. The presence of stem cells is important for evaluating tissue repair and drugs to treat cancer. The RepliGut® platform can also include cells that secrete hormones, cytokines, and other biochemicals involved in the proper function — and dysfunction — of the large and small intestine. Most other models do not have this capability. We also include mature enterocytes, goblet cells, and enteroendocrine cells. These combined features result in a more sophisticated system than other tissue models, allowing for more faithful predictions of the impact of drug candidates.

Fits into Existing Workflows

In addition to providing a human tissue model for the large and small intestines that faithfully recapitulates the behavior of these important organs from a wide array of demographic groups and for many different applications, Altis has focused on developing a platform technology that is easy for researchers to use.

Unlike many microfluidic devices that require the purchase of large, specialized instruments and the connection of tubes and pumps, the RepliGut® system has been designed in a footprint that slots into existing workflows that the biopharmaceutical industry already uses.

The RepliGut® kit includes a Transwell multiwell plate comprising 6, 12, 24, or 96 wells, with each well containing a Transwell insert with an individual tissue sample. Each kit also includes the materials needed to culture the cells, including stem cells and media. To populate the device, the stem cells are placed on the scaffold, and a few media changes are completed via pipetting. The tissue structure self-assembles into the lineages populating the intestinal epithelium.

Moving to the Next Level

Microbiome-based therapeutics is a rapidly growing field that would benefit greatly from access to better preclinical testing methods. It is clear that bacteria in the colon influence every aspect of human body functions, from mentation and satiety to metabolism and response to chemotherapeutics.

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The intestine also plays a significant role in the nervous system. One of the largest sites for the production of serotonin — a neurotransmitter — is in the gut. Combining aspects of the nervous system into the RepliGut® system is an exciting avenue currently under investigation at Altis.

Leaky gut is a significant problem from the neonate to the adult. A robust and reliable human tissue model that enables the investigation of this phenomenon and drugs that can prevent or treat gut damage holds tremendous promise.

Developing RepliGut® models specifically designed to enable investigation of treatments for colon cancer presents yet another opportunity for Altis. Among all types of cancer, colon cancer causes the third most deaths among both men and women.[1]

In the near term, Altis has much interesting work ahead of us as we add other types of tissues and features to the RepliGut® human tissue model for the large and small intestines. Our hope is to eventually supplant old tumor cell (Caco-2) models with models like our RepliGut® platform that more accurately reflect what occurs in the human body, enabling more efficient and accurate drug discovery and development.

Reference

"Key Statistics for Colon Cancer." American Cancer Society. 29 Jun. 2020. Web.

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Nancy Allbritton is an international expert on multiplexed single cell assays, microfabricated platforms for high-content cytometry combined with cell sorting, and microengineered stem cell–based systems for recapitulating human organ-level function. Four companies have been formed based on her research discoveries: Protein Simple, Intellego, Cell Microsystems, and Altis Biosystems. She has an M.D. from the Johns Hopkins University School of Medicine and a Ph.D. from the Massachusetts Institute of Technology and is Emeritus Professor at the University of North Carolina, Chapel Hill.