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Innovations

Surface Logix

Mini Disease Models for Maximum Impact

Surface Logix is on a fast track to revolutionizing the arts of pharmacological screening and cell biology. Scientists using traditional cell-based protocols continually grapple with the problem that data generated from such assays can be difficult to interpret and unreliable. "From the pharmaceutical standpoint, what is really a black box is [how to look] at cells in an in vitro environment and get comfortable with the information that comes from assays or experiments so that you can really count on the data," comments Carmichael Roberts, President of Surface Logix. To address this pervasive issue, Surface Logix is developing tools to conduct cell-based assays that are well-defined, standardized, and controllable. This 50 person, Brighton, Massachusetts-based company is engaged in building ex vivo models of human disease containing cells that accurately and robustly mimic cellular environments and tissues from healthy and diseased humans. Building these disease models is a tremendous challenge, but Surface Logix has tackled the problem head-on by harnessing the diverse technologies of soft lithography, microfabrication, and customized surface chemistry. Additionally, detailed physiological profiles of different kinds of cells are being produced by the research team to better understand what makes each individual cell type "tick."

Soft lithography, which is a critical element of the pioneering Surface Logix technology, was initially conceived by George Whitesides (Harvard University). Whitesides envisioned systems where elastomers and polymers could be used as a backbone or template for patterning a wide range of kind of chemistries to reveal uncharacterized aspects of protein biochemistry and cell biology. This initial ideal blossomed into a simple and elegant method due to the efforts of Enoch Kim, the principal coinventor of soft lithography, who was a graduate student in the Whitesides lab in the early nineties. The basic principle behind the method starts with designing a mold using CAD software to include specified topographical and geometrical features required for a particular experiment. This mold is then generated from a wafer of glass or silicon by a mask aligner and photolithography, which burns the microfeatures into the surface. A layer of polymer is then placed into the mold to create an irreversibly bonded 3D surface ready for further chemical manipulation. Kim saw great commercial potential in the technology that he had created and consequently was the nucleating factor for the enterprise, which was cofounded by Roberts and Whitesides in 1999. The initial goal of Surface Logix was to industrialize or commercialize a research tool or application centered around soft lithography that would be of relevance to the drug discovery process; an idea that ultimately led to the concept of the development of complete ex vivo disease models (Figure 1).

"Cells are really smart in terms of recognizing their microenvironment. We saw a huge opportunity to take soft lithography (that allows you to work down to the micro to nano scale) and tune that microenvironment in a way that the cells actually become much more comfortable in that in vitro environment."
–Carmichael Roberts, President, Surface Logix

This technique has distinct advantages over other microfabrication technologies. It is fast and flexible and easily interfaced with the laboratory. The silicon and glass formats commonly used to make biochips are expensive and are not easily accommodated by a typical pharmaceutical laboratory's equipment. Furthermore, the time needed for the fabrication of biochips is too long for research that needs rapid data turnaround. Another significant benefit to using soft lithography is that silicon or glass is not always the best material to mimic a biological condition. This is emphasized by Roberts, who feels that it is unrealistic to consider cells cultured by standard protocol as representative of "normal" cells. "Cells are really smart in terms of recognizing their microenvironment," he explains. "We saw a huge opportunity to take soft lithography (that allows you to work down to the micro to nano scale) and tune that microenvironment in a way that the cells actually become much more comfortable in that in vitro environment. We can look at the typical phenotypic responses of cells and show that they are behaving similar to the way that they would in their natural environment."

This, however, is just the beginning. Creating microworlds that are representative of diseased or healthy cells and tissues that can be used as human disease models is much more complex. Although it is a lofty goal, it seems to be well within the grasp of the company. "Let's say we look at inflammation," explains Greg Kirk, Vice President of Technology, "we can break down any number of relevant cellular events that are of interest to companies doing inflammation research. If you look at those events and you map out what the cells are actually doing, it is not trivial to duplicate that in the microenvironment." Paul Sweetnam, Chief Scientific Officer, continues, "First, cells in the body don't exist on glass or plastic, they exist in the extracel-

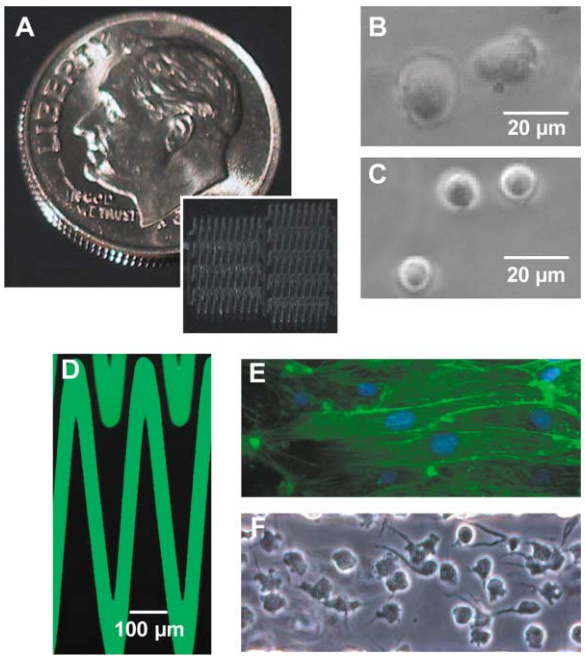

Figure 1. Model of an Ex Vivo Biosystem

Primary leukocytes can be activated under shear flow on a bed of endothelial cells. Motion and morphological changes can be quantitatively measured in these microenvironments. Media flow is controlled in the model microscale capillary bed (compare the size of the dime in [A] relative to the size of the capillary bed in the inset), and the surfaces are engineered and patterned with immobilized biomolecules to support endothelial cell growth. The capillary bed is magnified in (D), which shows a fluorescent dye flowing through the engineered channels. The combination of flow and surface biochemistry causes the endothelial cells to align, elongate, and differentiate (E). A different set of surface chemistries cause primary leukocytes to activate and adhere to the synthetic capillary walls (B), or their adhesion can be inhibited entirely (C). Chemokine gradients are also established that cause leukocytes to migrate and change shape (F).

lular matrix (ECM), so in our devices we have to mimic the ECM. We do this using a blend of synthetic polymers, hydrogels, and biomaterials. Second, we have "stealth surface technology"—we have to hide traditional surfaces because we don't want cells interacting with glass or plastic—those [surfaces] have to be invisible—and each protein in each cell has a profile of what it considers to be inert. Then we have to dial in chemistries to make [the cells] comfortable." There are two primary areas of surface chemistry employed by Surface Logix to create an optimal microenvironment for the cells. The first is surface engineering, where the glass or polymer of the 3D microenvironment is coated with single molecular layers. These molecules are designed to meet the cells' physical "needs," or they can simply be inert. The second area was developed based on a technology that the company licensed from Milan Mrksich at the University of Chicago which provides links that bind peptides, carbohydrates, or proteins in a predetermined orientation to hook cells in specific immobilization schemes. Using the Mrksich technology as a starting point, the company has vastly expanded its biosurface chemistry platform to more effectively design microenvironments that mimic the ECM.

Geometry and space also play a huge role in cell behavior. "If you squeeze a cell into a very small space, some cells will want to die in that space, some will want to divide, and some will just be happy," says Sweetnam. "Each cell has a personal space that it likes, and what we do is we define that personal space." Interestingly, physical space can directly influence the function of a cell, as Sweetnam elaborates, "by changing their geometry, we can change how the cell responds, what it makes, and what the cell actually does." For example, in the case of inflammation, endothelial cells provide the vascular lining through which the white blood cells travel, and these cells can be either cuboidal or elongated in appearance. Cuboidal endothelial cells are important for modeling the pathology of atherosclerosis, but the long, polarized endothelial cells play a role in inflammation.

A major focus of Surface Logix's energies and talents is in inflammation; the second key area is ADMET (absorption, distribution, metabolism, excretion, and toxicity) or pharmacokinetics: looking at how drugs act in the body. Developing human-based models of these systems that will expand on traditional experimental results and studies in animal models is the cornerstone of the Surface Logix scientific and business plans. "As the number of targets and the chemistries improve, it is becoming clear that animals don't often reflect human physiology and that compounds made by the industry often don't interact with animal receptors or enzymes," states Sweetnam. Furthermore, he emphasizes that it is essential for researchers to understand that they could be working with the wrong cells in the first place: "The industry typically works with continuous cell lines, and since when is a tumor or immortal cell line ever normal? You are testing noncancer diseases against tumor cells and that's inappropriate." Surface Logix made a logical decision to move away from cell lines and genetically engineered cells and use the most appropriate cells for their biosystems, which are primary cells isolated directly from patients. The major limitation with primary cells is the number of cells that one can acquire. However, this problem is greatly aided by the innate beauty of their miniaturized, microscale systems, since fewer cells are needed for each assay. Therefore, more assays can be conducted using the cells from each individual patient. Surface Logix has also established a growing pool of over 100 donors from whom they regularly harvest cells of interest for their inflammation program. "We are in the process of characterizing that donor pool and putting it into batches. All people are different, and we are in-

terested in things such as age, race, sex; these are all key issues in what cells do. In that regard, we are looking at population dynamics as well as the individual for every disease state," explains Sweetnam. "What we are doing now is looking at an individual patient and running a breadth of assays. More information gives you a better chance of making a better decision on what compounds to bring forward and for what disease. Inflammation actually has a broad disease spectrum, so if you run twenty assays, one can start to target clinical trials more effectively." By conducting several drug assays using cells from donors with well-defined disease profiles, the company will avoid the common pitfalls of drug development that currently face the pharmaceutical industry. Says Sweetnam, "If you look at failures in the clinic, there are an increasing number of [drug] failures at phase II. [Companies] get beautiful drug-like molecules that are not toxic and show beautiful pK parameters, but they have no efficacy because they had the wrong assays to predict what [disease] they should have targeted in the clinic."

Within the current glut of biotech companies, Surface Logix stands apart, occupying a niche filled with little competition. Few other companies are capable of combining surface chemistry, microfabrication, cell biology, and 3D analysis in the same way. Their true competition lies within the biological disease research that is going on within the pharma companies themselves. Regardless, Roberts is enthusiastic: "We are biology driven, we use biology expertise in-house, and we are extremely fast and flexible around the biology as it relates to disease. In the short term, over the next couple of years, what we would really like to do is to effectively apply our ex vivo disease models to two or three disease areas and develop these ex vivo disease models to offer a platform around each disease. In the long term, we would like to be considered an essential component of the drug discovery process." In fact, the team's primary goal is for Surface Logix to become a premier research and development house, using the ex vivo disease models to develop their own expertise in drug discovery and collaborating with pharma to aid in their drug discovery pipelines. Establishing alliances with the intent of selling these tools is a secondary goal. One possible pitfall for Surface Logix lies in the availability of primary cells if the company wants or needs to move into other disease areas (like neurobiology or particular cancers) where the cell source is limited—sources such as tumor biopsies. However, they plan to play it safe for the immediate future by sticking to inflammation as their field of interest, since there is still a need for additional therapeutics to treat inflammatory disease, and both blood and endothelial cell collection are now routine practices.

The potential value and impact of the Surface Logix ex vivo disease models is obviously great. These microscale systems are capable of providing scientists with more pharmacological information from more assays in a shorter time frame: a long-awaited breakthrough that will surely mark a turning point in drug development.

***Chemistry & Biology* invites your comments on this topic. Please write to the editors at chembiol@cell.com.**

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