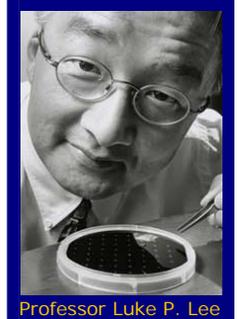


PINHEAD PETRI DISHES

by David Pescovitz

During the 1970s, UCB pioneered the tools and techniques that enabled hundreds of thousands of components to be packed onto a tiny computer chip. Thirty-years later, a similar revolution is taking place on campus. Bioengineering professor Luke Lee and graduate students Paul Hung and Philip Lee are developing integrated circuits for biology rather than bits. The new technology could lead to automated "laboratories" the size of fingernails that accelerate drug discovery, synthetic biology, stem cell research, and the development of new biomaterials for implants.

Rather than use transistors to switch voltages racing through wires, these laboratories-on-a-chip employ microscopic valves, pumps, cellular manipulators, and other tiny components to test hundreds of biological samples in parallel. Lee's latest creation shrinks a workhorse of cell biology, the standard petri dish, so that 100 of them fit into a 2 mm square device. It's a tour-de-force in microfluidics, hair-thin plumbing systems capable of transporting nanoliter volumes.

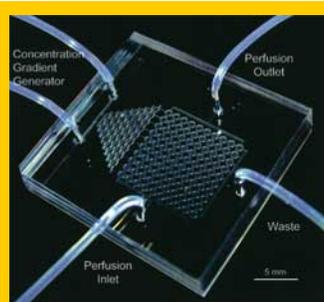


Professor Luke P. Lee

"The array could enable 100 different cell-based experiments to run in parallel," he says. "For example, a biopharmaceutical company might watch how tumor cells respond to various concentrations of a drug to help determine the correct dosage for the desired response. It's true quantitative biology."

To use Lee's device, several cells are loaded into each of the millimeter-sized chambers riddling the plastic chip. Nutrients are continuously pumped through the array while waste flows out. Various kinds of chemicals, a new drug for example, can then be injected in highly specific amounts into each chamber. Eventually, the chip might be outfitted with Lee's nanoscope that would automatically analyze the biochemical reactions. Right now though, he says, desktop microscopes are good enough for scientists to observe how the cells differentiate or react to the infusions. "Our initial aim is just to speed up currently-available bioassays," he says.

Today, these kinds of experiments involve growing cells in standard Petri dishes and then adding chemicals to the mix using pipettes. Not only will the microfluidic approach be much faster and precise, Lee explains, but "the continuous flow of nutrients through the channel makes feeding more uniform, similar to our own physiological conditions."



A 10x10 microfluidic cell culture array of microchambers was fabricated on a 2x2 cm device. The port at the left provided continuous perfusion of medium uniformly across the array. The port at the right was the outlet for the medium. Reagents and cells were loaded from the top and flow out through the bottom port.

Along with dramatically improving drug development and screening, the high-throughput cell culture array promises to be a godsend for bioengineers developing new biologically-compatible materials for medical implants and other in vivo applications. For instance, biomaterials that are candidates for the construction of artificial bones or heart valves could be introduced into Lee's chip by the dozens. Studying their impact on the cells could then aid in the identification of the most biologically compatible material.

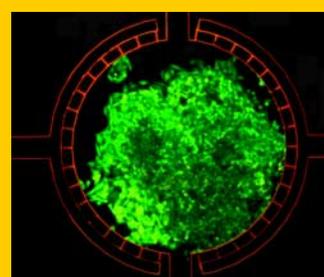
Currently, Lee is designing his next-generation large scale microfluidic cell culture array. The new model is based on a 16 x 24 array of chambers, enabling nearly 400 separate assays to be conducted in one shot. Meanwhile, Lee's developing other devices in his arsenal of Biologic Application Specific Integrated Circuits (BASICs), named for ASICs, computer circuits design, customized, or programmed for a specific application. The goal of BASICs, Lee says, is to create a standardized library of tools for quantitative systems biology.



A SEM photo of a single microfluidic culture unit before bonding to a coverglass. Multiple perfusion channels surround the main culture chamber. Micro-chamber is 1 mm in diameter.

For example, one device that measures how cells communicate might provide insight into Alzheimer's disease or someday inform the engineering of a bioartificial retina. Already, Lee is collaborating on such efforts with synthetic biologists in Berkeley's Department of Molecular and Cell Biology and College of Chemistry and the University of California, San Francisco. In the future, Lee says, multiple BASICs might be microfluidically linked to manipulate and prepare biological samples for a variety of "on-chip" assays.

Berkeley electrical engineers led the way in computer chips," Lee says. "Now we have the opportunity to distinguish Berkeley as the leader in new biological labs-on-chips too."



Human cancer (HeLa) cell culture in the microfluidic device. Cancer cells were fluorescently labeled with a live cell dye after 7 days in culture (green) depicting high cell viability & multilayer morphology.

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