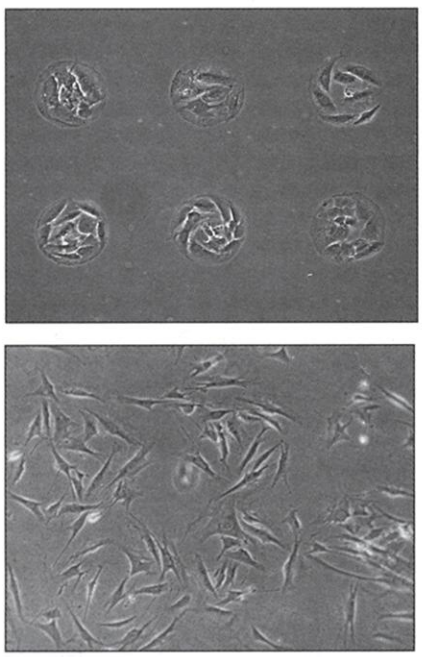
BIOCHEMISTRY

Ligand Chip Helps Manipulate Cells

Scientists at the University of Chicago have found an electrochemical way to control interactions between cells and a chip. It's an improvement over existing methods of influencing cell behavior, none of which allows control over cell-surface activities with chip-bound molecules. Researchers say the achievement could be a key step toward a wide variety of applications—everything from new drug assays to prosthetic aids that replace damaged neurons.

The behavior of cells is controlled by any of a large number of different receptors on their surfaces that respond to hormones, growth factors, and various other types of regulators. Chicago's Milan Mrksich and his colleagues devised a way to first attach certain peptide regulators, or ligands, to their chip, and then to release them, through electrical means. Because cells bind to the ligands, this allowed the researchers to turn the chip on for cell attachment or turn it off, thus releasing the attached cells. "The technique would be useful for studying subjects in cell biology like cell migration that depend critically on the cell's surface composition," says synthetic chemist George Whitesides of Harvard University, a former mentor of Mrksich. "In the longer term, it could serve as a basis for new types of assays for drug screening."



Moving pictures. Cells attached only to regions on the substrate coated with fibronectin (*top*) are able to spread and fill the entire surface (*above*) after electrochemical oxidation.

CREDITS: (LEFT TO RIGHT) MILAN MRKSICH/UNIVERSITY OF CHICAGO; NASA

Researchers have previously designed ligand-coated substrates for attaching cells, but these have been limited by the static composition of their surfaces. Mrksich wanted to develop a dynamic substrate—a chip that could actively modulate the behavior of attached cells. To achieve that, he and his colleagues coated a gold film with an alkanethiolate, a type of organic molecule that carries hydroquinone groups. Applying a tiny electric voltage to the film triggers an electrochemical reaction, converting the hydroquinone groups to quinones. When molecules containing a ligand bound to another organic group called cyclopentadiene are added to the chip, they will then react with the quinones. This reaction installs the ligand on the surface of the chip, thereby turning it on for cell attachment. Reapplying the electric voltage to the film converts the quinone groups back to hydroquinones, thus causing tethered ligands to break away and release the cells from the substrate—in effect, turning off the chip.

Mrksich and his colleagues have shown that they can induce cells to migrate on the chip by taking advantage of its switching-on aspect (see images). They first coated small circular regions on the gold substrate with a protein called fibronectin that causes connective tissue cells called fibroblasts to adhere to the spots, leaving the remaining areas covered with alkanethiolates. Then the researchers turned on the chip in the presence of a solution containing a conjugate of cyclopentadiene and a small peptide known to mediate cell adhesion. This caused the conjugate to bind to the chip and, as a result, the cells moved out from the circles and lodged themselves uniformly across its surface.

Such a system can be used, Mrksich says, to screen either for drugs that promote cell migration, which might be helpful in wound healing, or for drugs that inhibit it, which might have antimetastatic effects. For example, the team has tested two compounds, known for their antimigratory properties, and found that both blocked cell migration on the chip. "One goal of the work is to improve the design of cell-based sensors for drug screening," says Mrksich, whose results are in press at *Angewandte Chemie*.

Strategies for precise and selective cell attachments, such as the one used by Mrksich's group, should allow scientists to engineer small surfaces with multiple cell types. That could help in the miniaturization of cell-based sensors and thereby speed up drug screening. "The technology would enable us to screen drug candidates at a much more specific and fine level than what is possible with traditional assays," says Tom Schall, founder of ChemoCentryx Inc., a drug-discovery company based

ScienceScope

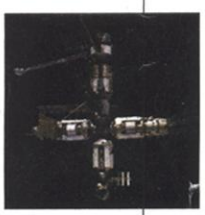
Frosted Biomedical researchers may be nipped by an early freeze this winter thanks to Congress's inability to pass a spending bill for the National Institutes of Health (NIH). Institute chiefs learned last week that the delay will probably force them to suspend cost-of-living increases for continuing grants due to go out early next month, and they plan to make cuts in new and competing grants as well.

Congress is considering a bill that would give NIH a 15% increase, but election year politics has stalled work until at least next month. Mary Hendrix, president of the Federation of American Societies for Experimental Biology, says the uncertainty "is a very serious threat to biomedical research" and could be "devastating" as faculty plan for research and staffing in the next year.

Sacked Indian scientists are in an uproar over the sudden removal last week of the head of the Indian Council of Agricultural Research (ICAR) for alleged financial mismanagement. Agricultural minister Nitish Kumar said that Rajendra Singh Paroda, a prominent scientist who has headed the $300 million ICAR for the past 6 years, was sacked to allow for an "independent investigation" of allegations that he mishandled the purchase of computers as part of a loan from the World Bank. But Narendra Gupta, executive secretary of the National Academy of Agricultural Sciences, says that he doubts the allegations will hold up. The unprecedented removal of a well-regarded technocrat, he says, makes scientists "like sacrificial lambs in the hands of politicians."

ICAR, with 5000 scientists, is India's premier agriculture research agency and has played a crucial role in ushering in the Green Revolution. An ICAR spokesperson said that "there was a deathly silence after the news of the removal broke."

MirCorpse? After numerous resurrections, Russia's Mir may finally be headed for a fiery death. President Vladimir Putin's cabinet agreed last week to deorbit the space station, launched in 1986, in February 2001. The decision is bad news for Amsterdam-based MirCorp, which wanted to lease the station for science and tourism. But company officials still hold out hope, with one noting that Russian officials have "killed the station at least four times" before.



Contributors: Eliot Marshall, Pallava Bagla, Andrew Lawler