of an extrasolar planet, short missions won't do the trick. The lost hours spent at lower than optimal altitudes "really hit your science," says Harvard's Grindlay. But there is a way to stop the droop: seal the balloon. And that is exactly what NASA and the NSBF are doing with their superpressure ULDB balloon program.

The pumpkin-shaped ULDB balloons are about the same size as a large zero-pressure balloon. Because all the buoyant gases are sealed inside, the superpressure balloons being developed by Goddard at the Wallops Flight Facility in Wallops Island, Virginia, are impervious to the diurnal temperature changes that cause the droop that eventually grounds zero-pressure balloons. A ULDB should be able to stay at a constant altitude for at least 100 days. To maintain constant contact with a ULDB on its globetrotting journey, the NSBF will link these balloons to the constellation of three satellites that forms the Tracking and Data Relay Satellite System. The high-speed data link permits scientists to gather data from and send commands directly to the balloon over the Internet. "Now the scientists can just sit at home and watch the data flow in," says ULDB project manager Steve Smith of Wallops.

For Anspaugh, such high-tech frills are a needless luxury. Six hours after takeoff, his solar-cell experiment has parachuted safely into the west Texas desert, and the NSBF chase plane has flown him out to bring it back home. The crew seems buoyant, not just about one more successful mission, but about NSBF's future, as it prepares to open a new chapter in its history. As Grindlay says, "Ballooning is on a sharply upward trajectory." **–MARK SINCELL**

Mark Sincell is a science writer in Houston.

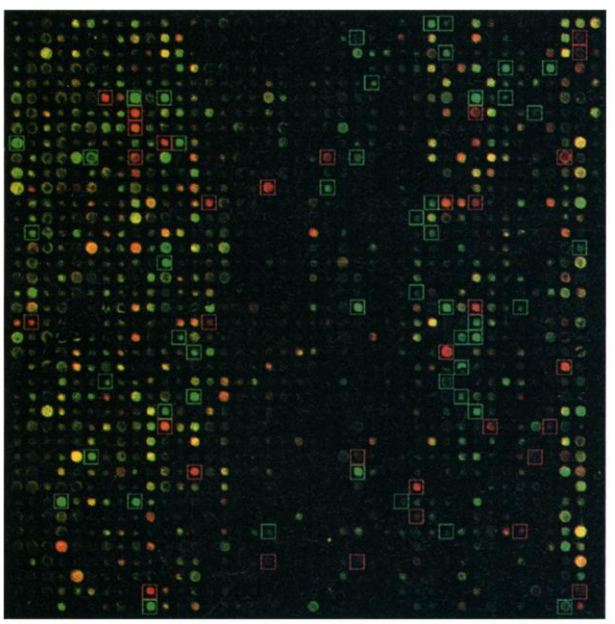
TOXICOGENOMICS

Toxicologists Brace for Genomics Revolution

Gene-array technology promises to deliver comprehensive profiles of toxic compounds, but validation will take years

ASPEN, COLORADO—Millions of animals are raised in the United States each year for routine toxicology tests, exposed to compounds in food additives, cosmetics, and industrial products, and then studied for ill effects. This is a time-honored way of identifying human health risks, but it can be an imprecise science. It's also expensive and increasingly under attack by animal-rights activists as wasteful. Now, according to researchers who gathered at a high-powered summit this month,* toxicology may be on the verge of changing the way it collects raw data—adopting a process that could reduce animal use and improve test results.

The new approach, called "toxicogenomics," grows out of the human genome project. Rather than using animal pathology to identify illnesses, it probes human or animal genetic material printed on plates, called DNA arrays. Cancer researchers have already been using such arrays for several years to compare gene expression in healthy and diseased cells (*Science*, 15 October 1999, p. 444). Toxicologists are using the same technology to profile gene expression in cells exposed to test compounds.



Gene scan. NIEHS researchers have developed a prototype array of 12,000 human DNA sequences, called ToxChip, to detect responses to known toxicants.

CREDIT: R. PAULES

The advantages of these DNA tests are legion: They are fast, efficient, and reduce live-animal expenses, which can range as high as $3000 per week, per animal, when nonhuman primates are used. Some of the biggest gains may come in cancer toxicology; New tests may be able to spot the metabolic precursors of slow-developing diseases without holding up research for the months or years it takes for tumors to develop. If adapted for use in tissue cultures, these tests might even eliminate the need to sacrifice animals.

Toxicogenomics is advancing so rapidly as a specialty that the National Institute of Environmental Health Sciences (NIEHS) this spring opened a new National Center for Toxicogenomics in Research Triangle Park, North Carolina. Its express purpose is to spur the development of gene-based toxicity studies. But some leaders in the field warn against rushing too quickly to embrace DNA tests, which are still difficult to interpret. Doing so, they say, could exaggerate some risks and understate others—halting research on promising new products while overlooking life-threatening toxicities that would have shown up on traditional bioassays. "We have to be careful we don't drive beyond our headlights and run into a wall," cautions Joseph DeGeorge, a pharmacologist at the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research.

Mountains of data

The basics of toxicogenomics are straightforward, although details vary from lab to lab. The hardware uses gene arrays bearing such names as "ToxChip" or "ToxBlot" that contain thousands of genes that might be affected by toxic chemicals. These genes, arranged on plastic or glass plates about the size of microscope slides, bind to matching genetic material extracted from animals or cell cultures exposed to the substance being tested. The extracted genetic material, called messenger RNA, comes only from genes that are currently active; it is reverse transcribed and tagged with a radioisotope or a fluorescent marker to simplify detection. Researchers sometimes use a red marker for material from treated cells and a green one for untreated controls. When labeled sequences are tested on a single array, both treated and untreated types bind to a gene site, with the resulting color at each site showing the degree to which that gene has been turned on or off by the putative toxicant.

* 26th Annual Summer Meeting, The Toxicology Forum, 10 to 14 July.

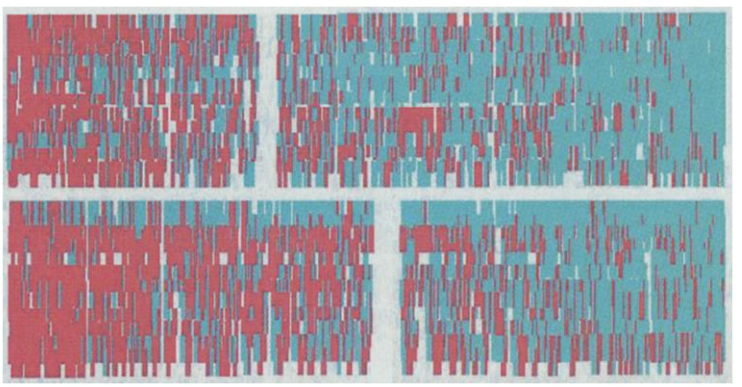
The great promise of toxicogenomics is that it might be used to scan the entire human genome to see which genes are affected by specific chemicals. "Right now, that's not feasible," in part because not all the genes can be placed on arrays, says Richard S. Paules, toxicogenomics facilitator at NIEHS, "but at some point it may be."

The immediate goal, Paules says, is to look at different classes of compounds and identify groups of genes that are tightly correlated with known classes of toxicants. These "very informative" genes could then be used to generate a next-generation array with a small number of genes. The condensed set could be used routinely to determine if a test chemical exhibits any of several common toxicities.

After a critical gene set is identified, the real work of sifting wheat from chaff begins. DNA arrays generate mountains of data. A single experiment, Paules says, can produce 300,000 data points; computer pattern-recognition programs must be used to tease out the meaning—a job that researchers describe as "mind-bogglingly complex." But Paules doesn't see it as impossible. Toxicogenomics is just in its infancy, he says, like clinical pathology before doctors learned how to recognize biopsy samples as benign or cancerous: "It takes years of experience" to make such distinctions. Once the appropriate databases are assembled, toxicogenomics will become something like digitized pathology. "It's like taking the field of pathology from the Wright brothers to the moon, from a subjective art to measuring thousands of parameters," Paules says. "But to do that, you need a very robust database."

The biggest challenge will be interpreting the results of these analyses. Simply observing that a chemical changes a cell's gene expression is meaningless: Virtually any change in the environment will do that. The body makes complex cellular-level adjustments, for example, just to cope with waking up in the morning or moving to a higher elevation. One of toxicologists' greatest fears is that people with antichemical axes to grind will obtain gene-array results and create public hysteria. For that reason, toxicologists agree that it's not enough simply to compare a test chemical's effects on gene expression to those of known toxicants. It's also necessary to validate the entire process by correlating such changes to actual illnesses.

It may be years before gene arrays are widely accepted for routine chemical screening. But they're already being used in research, where they help identify biochemical pathways that are vulnerable to chemical interference. In the past, toxicologists learned to identify such pathways by becoming expert in each step in the process—a method that Bill Pennie, head of investigative toxicology at Zeneca Central Toxicology Laboratory in Macclesfield, U.K., refers to as the "one gene, one postdoc approach." It sometimes took an army to do the job. Gene arrays are streamlining this process by revealing which genes are affected by various categories of chemicals. Researchers can then turn to conventional techniques for a detailed analysis.



Snapshot of toxicity. Zeneca's Bill Pennie exposed cultured liver cells to cytotoxic damage, yielding an image with about 70,000 data points. Computer scanning and analysis produces a detailed response pattern.

CREDITS: W. PENNIE

Scientists are now using this mixed strategy to probe a class of chemicals known as peroxisome proliferators, which includes certain herbicides, pharmaceuticals, and plasticizers. Animal bioassays reveal that these compounds cause liver tumors in rodents, but by a mechanism that most toxicologists believe isn't relevant for humans. Not surprisingly, researchers would like to know more about how these chemicals affect liver metabolism.

NIEHS has run several of these compounds through its own gene-array process, called ToxChip. The research is preliminary, but it is revealing that many of the affected genes have already been identified in the toxicological literature—a useful validation of the test. Just as important, however, is the discovery that about half the genes identified by ToxChip weren't previously known to be involved in peroxisome proliferation.

Pennie's research team has been making similar use of gene arrays to study the mechanisms by which estrogenlike chemicals affect organs as disparate as the brain, uterus, ovaries, and testes. It's not yet a precise technique—Pennie calls it "stamp collecting"—but the gene data help researchers generate hypotheses about how biochemical pathways work—hypotheses that they can then test in gene-altered mice.

A coming boom?

These near-term uses are not what thrill toxicogenomics fans, though. Their Holy Grail is to develop routine gene-array screens that can be used to catalog the risks of previously untested chemicals. And despite traditionalists' concerns, this dream is drawing near.

Drug companies are among the most enthusiastic about the vision, because they're interested in finding ways to speed the process of toxicological testing to keep pace with new R&D techniques that have vastly increased the rate at which candidate drugs are being developed. The industry would like to weed out potentially dangerous ones early in the expensive development process, says David Essayan, an assistant professor of medicine at Johns Hopkins University. Health officials also would like to find tests that can reduce toxic drug reactions, estimated to cost the nation $77 billion a year, Essayan says.

Support for toxicogenomics may flourish outside the technical community, too. Penelope Fenner-Crisp, senior science adviser to the director of the U.S. Environmental Protection Agency's Office of Pesticide Programs, says animal-rights advocates like the technology because they see it as a way to pursue the "three R's" of conscientious animal research: replacement, refinement, and reduction. "There will be pressure to use these technologies, probably sooner than the scientists think they're ready," she predicts. Already, she adds, European countries have imposed legislative constraints on animal research, and similar U.S. proposals are always "hovering" in the background.

Given these pressures, toxicogenomics isn't going to wait demurely in the wings while scientists validate it, says FDA's DeGeorge. Fenner-Crisp agrees, advising scientists to expect to be pushed to use these tests sooner than they would like. And, she adds wryly: "We'll probably be among those who press you."

Jay Goodman, a professor of pharmacology and toxicology at Michigan State University in East Lansing, however, urges scientists not to be coerced into using the new techniques before they've been properly "anchored" by comparison to known toxicological responses. Whatever the pressures from animal-rights organizations, he says, "we need to be true to the science and let this sort itself out in the peer-reviewed literature."

–RICHARD A. LOVETT

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