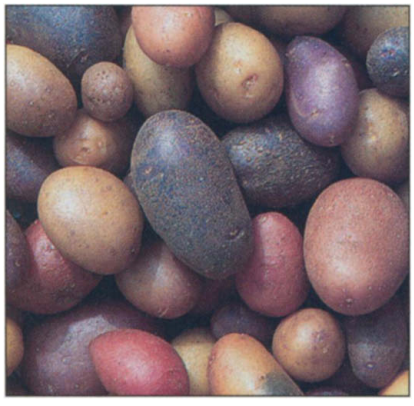
learning how some potatoes recognize the pathogen and elicit a defensive response. Of the two main types of resistance, hypersensitive response is the more straightforward—a process thought to involve "gene-for-gene recognition," in which a single resistance gene in the host recognizes a protein produced by a particular gene in the pathogen. The problem with single-gene resistance, says Deahl, is that *Phytophthora* is "an artful creature," and it can get around that kind of resistance with a simple mutation.



In reserve. Researchers are scanning all varieties for blight-resistance genes.

Considered more promising, therefore, is rate-reducing resistance, which is based on sets of genes that might collaboratively inhibit infection. And there's no dearth of resistant potatoes on which to draw.

The largest group addressing the challenge through molecular genetics is the Potato Functional Genomics program, funded by the National Science Foundation. It includes Barbara Baker, a molecular biologist at the University of California, Berkeley; plant pathologist William Fry of Cornell; John Helgeson, a U.S. Agricultural Research Service plant pathologist at the University of Wisconsin, Madison; and The Institute for Genome Research in Rockville, Maryland. The project has so far generated 60,000 ESTs from core potato tissues: shoots, leaves, stolons, tubers, and roots.

It might also be possible to learn something from "not-potatoes," says Sophien Kamoun of Ohio State University, Wooster. He is looking at *Arabidopsis*, for example, because he says it "exhibits active defense responses [including hypersensitive cell death] to *P. infestans*." And he wonders whether resistance genes from such nonhost plants can be transferred to the potato.

At the University of Victoria in British Columbia, molecular biologists William Kay and Santosh Misra say they have already achieved something of the sort. They've engineered potatoes with genes encoding segments of antimicrobial proteins from silkworm moths and honey bee venom—and the plants have shown late-blight resistance.

Some wild Mexican and South American potato species produce toxic glycoalkaloids that appear to help them resist insects. John Bamberg of the USDA Agricultural Marketing Service's Potato Project in Sturgeon Bay, Wisconsin, is studying how they work and whether these substances might confer resistance to late blight as well. A caveat, he acknowledges, is that the very toxins that make some potato varieties resistant to late blight might also make them poisonous to people and livestock. Some researchers are thinking about finding ways of designing plants to confine glycoalkaloids to the aboveground plant. One possibility might be to make them sunlight-activated, sparing the plant from disease without poisoning the tubers. And Dilip Shah, at the Donald Danforth Plant Science Center in St. Louis, is studying a vaccinelike procedure to see whether exposing the potato plant to the pathogen's proteins can stimulate generalized defenses.

Understanding the products of resistance genes and their biochemical interactions with the pathogen could put scientists a step closer to conferring resistance to plants that lack it. As Helgeson puts it, "What we need to know is, what's the product of these genes? What do they do? Look at the dialogue."

Whatever the dialogue, it's not likely to be produced by old-fashioned crossbreeding of potatoes. This has never been an easy affair, because many of the wild potatoes in which resistance genes have been found are genetically diploid (having two sets of chromosomes), whereas *tuberosum*, the world's beloved, is an unwieldy tetraploid (with four sets).

Helgeson sees hope in the news from Hamburg, however. Now that resistance genes have begun to be cloned, he says, it might be possible to put them "straight into a tetraploid." He thinks that in the next 5 years, researchers will clone and sequence three, four, or even more such genes. From there, it would not be long before those genes could be "pyramided" into a single supercultivar.

"Of course," says Helgeson, "getting McDonald's to accept a 'transgenic' potato is another matter." **–GLENN GARELIK**

Glenn Garelik is a writer in Falls Church, Virginia.

REGULATORY RESEARCH

A Centennial Letdown for FDA's Biologics Group

A planned overhaul of CBER that would take away its special status as both a regulator and a researcher has staff members threatening to quit

Do regulation and research mix? New leaders at the Food and Drug Administration (FDA) are pushing a big shakeup of the division that oversees biologics in a way that seems to de-emphasize research, although they cite other reasons for making changes.

With little advance warning and no input at all from his scientific advisory panel, FDA Deputy Commissioner Lester Crawford declared on 6 September that much of the Center for Biologics Evaluation and Research (CBER)—which regulates therapies ranging from monoclonal antibodies to gene transfer—would be transferred to the Center for Drug Evaluation and Research (CDER), which regulates more conventional, chemically derived small-molecule drugs. Crawford said the consolidation—the precise details of which have not been worked out—will make the review of new drugs more efficient and consistent.

Over the past few weeks, however, many CBER researchers and outside scientists have begun arguing that the real purpose of the move is to strip away CBER's special status as a regulator that also supports substantial intramural research. This self-directed program, which is based on the campus of the National Institutes of Health (NIH), is supposed to keep regulators at the cutting edge of fast-moving areas of biotechnology. The research effort is the envy of other FDA divisions that don't enjoy such free rein, and some FDA observers—including drug companies that help pay FDA's costs—have long argued that intramural research should be trimmed.

The overhaul came as a complete surprise to most CBER staffers. They were planning to celebrate the division's 100th anniversary this fall and had already prepared a history, passed out commemorative coffee mugs, and scheduled a symposium for late September. Then the FDA bosses rained on their parade.

CBER's friends on the outside were shocked. "There is no good rationale for what is being proposed," says Leslie Benet, a professor of biopharmaceutical sciences at the University of California, San Francisco, who chaired an FDA advisory committee

CREDIT: ARS

that strongly endorsed CBER's researcher-regulator model 4 years ago.

Under decisions that Crawford has made so far, CBER will lose authority over a wide array of therapeutic biologics, including monoclonal antibodies, cytokines, growth factors, enzymes, interferons, proteins extracted from animals or microorganisms, and some immunotherapies. These products have moved into the medical mainstream, says FDA Principal Associate Commissioner Murray Lumpkin, who co-chairs a working group that is hammering out the details of the consolidation, and they "need to be under one management umbrella and need to be overseen from a clinical perspective"—although with due attention to the special manufacturing problems posed by biologics.

CBER Director Kathryn Zoon strongly disagrees. "The science behind these [biologics] and the scientific issues with these products are not all solved," she told the FDA Science Board—an advisory committee of non-FDA scientists—on 25 October. "And the need for having a research-reviewer model to deal with these issues continues to be important."

CBER will retain authority over the transferred biologics when they are used as reagents or as part of the manufacturing process, as well as its responsibility for such areas as blood and blood-related products, cellular therapy, vaccines, antitoxins, allergenics, xenotransplantation, and gene therapy (see table).

"They're basically gutting CBER," says Benet, even though it is meeting its performance goals, and "there's no evidence" that the move will improve efficiency or consistency. Benet also warns that the plan will retard biowar defense by driving away people with expertise that FDA needs to help develop and approve countermeasures. (Benet has just been named chair of a National Research Council–Institute of Medicine study committee on accelerating the research, development, and acquisition of medical countermeasures against biological warfare agents.)

Whether CBER will, in fact, be "gutted" is an open question. Benet says the consolidation could sweep out 30% to 40% of CBER's roughly 900 employees and its $147 million budget. But staffing decisions haven't been made yet, says Lumpkin: "I'm not sure if that's in the ballpark or not."

Researcher-reviewers who are transferred to CDER will be able to continue their current projects for at least a year, says CDER Director Janet Woodcock. She also indicates that there are no plans "at this time" to move them out of their labs on the NIH campus.

That doesn't strike CBER scientists as very reassuring. Amy Rosenberg, director of the Division of Therapeutic Proteins in CBER's Office of Therapeutics Research and Review (OTRR), told the FDA Science Board that many will simply quit. In a poll of OTRR laboratory personnel, about 90% said they would look for other jobs if the consolidation plan is carried out, she said. (Eighty-six of the 140 to 150 people involved replied to the poll.)

However, Lumpkin's working group still has not determined precisely how many people and how much funding will be transferred to CDER, nor has it settled on a schedule for the transition. Lumpkin hopes to complete a transition plan in early January.

Why is FDA pushing such a controversial plan now? "That's a big Washington mystery, frankly," says one Washington lobbyist. After all, Crawford had been on the job only about 7 months when he ordered the consolidation, and incoming FDA Commissioner Mark McClellan—who was sworn in 14 November—had not even been formally nominated. McClellan, who was then a member of President George W. Bush's Council of Economic Advisers, was kept informed, however.

Crawford declined to comment. But in a memo to FDA staff, Crawford said the issue had been under study since last fall, and that a consultant's report laying out possible options was given to him soon after he arrived in February. Then, during negotiations on extending the Prescription Drug User Fee Act—under which pharmaceutical companies will pay FDA an estimated $1.2 billion over the next 5 years—Crawford said industry representatives complained about "consistency" of FDA decision making. (Whoever they were, these industry reps left no fingerprints. Neither the Pharmaceutical Research and Manufacturers of America nor the Biotechnology Industry Organization admits to pushing for the change.) Crawford finally concluded that transferring therapeutics to CDER would produce "less duplication of effort and greater consistency."

FDA Science Board members were clearly miffed that Crawford didn't ask for their views. They didn't formally oppose the CBER-CDER consolidation at their 25 October meeting, but they made a point of not supporting it. "Before you move something, somebody's got to present a very logical and rational reason for doing that," said Martin Rosenberg, retired senior vice president of GlaxoSmithKline. "I certainly haven't heard that."

Science Board Chair Robert Langer, a professor of chemical and biomedical engineering at the Massachusetts Institute of Technology, reported to Crawford that the board "is concerned that the science not [be] disrupted and wants to understand better the reason for this move." But Langer sees little chance that the consolidation plan will be blocked. After talking privately with FDA officials, "I think it is a done deal," he says.

Lumpkin suggests that CBER scientists' initial dismay will pass. "It's not like CBER is going away, or CBER is somehow being minimized," he says. "On the contrary, this incredible cutting-edge stuff—gene therapy, cellular therapy, stem cells—that's still in CBER, and it's going to get all the attention that CBER can give it." Maybe Lumpkin is right; but right now, much of CBER's staff would prefer to be celebrating their 100th anniversary with an undiminished mandate.

–BRUCE AGNEW

Bruce Agnew is a writer in Bethesda, Maryland.

FDA'S NEW STRUCTURE

CBER will lose authority for some therapeutics:

- monoclonal antibodies
- cytokines, growth factors, enzymes, interferons
- proteins extracted from animals or microorganisms
- some immunotherapies

CBER will retain authority for:

- processes using monoclonal antibodies, cytokines, growth factors, and proteins for products under CBER's jurisdiction
- viral-vectored gene therapy
- products composed of human or animal cells or their parts
- blood and components, including recombinant versions
- plasma expanders
- allergen patch tests and allergenics
- antitoxins, antivenins, and venoms
- toxoids and toxins intended for immunization
- vaccines
- in vitro diagnostics

Dissent. CBER's Kathryn Zoon thinks biologic products need scientific oversight.

CREDIT: FDA