neuroscientist Lou Reichardt of the University of California, San Francisco (UCSF). "My own feeling is that anything that even resembles a drug, like some of these neurotrophic factors, will be an improvement over these difficult and dicey surgeries and transplantations."

A long road to the clinic

Much as clinicians long for such success, however, it's a long way from tests on cultured rat neurons to clinical trials in humans. For one thing, notes UCSD neuroscientist Fred Gage, the Synergen workers have so far tested GDNF on only a few types of neurons. They haven't, for example, ruled out the possibility that it might also act on cholinergic neurons and on those that release the many regulatory peptides in the midbrain. Overstimulation of such nerve cells could lead to a kind of neurochemical babble in the brain. "Its effects on dopamine neurons are impressive," Gage says, "but to call it a dopaminergic-specific growth factor at this early stage strikes me as a little premature."

With the stakes so high, the Synergen group is already moving ahead with further studies. To find out whether GDNF is as specific as it appears, they've begun testing GDNF on a broader mix of cultured human neurons. And to learn more of its potential for Parkinson's, they've launched trials in rodents and primates. Collins is mostly close-mouthed about these important animal studies, but he says that in animals with neural deficits resembling Parkinson's, GDNF has had "a marked effect in reducing behavioral deficiencies."

Even if this therapeutic promise is borne out, however, another large problem would still have to be solved: that of delivering the drug to the right place. As proteins, neurotrophic factors are too big to cross the blood-brain barrier, and none of the options for getting them into the brain is especially attractive. The simplest approach would be to deliver GDNF directly into the gray matter via a permanently placed cannula. Swedish researchers have tried this technique in a few patients in trials of NGF for Alzheimer's and Parkinson's. "Technically, drilling a hole in the head is not that hard," says Ronald Lindsay, vice president for neurobiology at Tarrytown, New York-based Regeneron. "It's actually a lot easier than doing surgery on the heart." But there are other problems to worry about, he notes, not least of which is the potential for fatal brain infection from a permanently open site.

Researchers are also attempting to use carrier molecules to sneak proteins across the blood-brain border. Another possibility is to transplant cells genetically engineered to secrete GDNF into the brains of Parkinson's patients, either alone or with fetal neurons. But neither of these approaches is ready for the clinic.

Some skeptics, doubting that neurotrophic factors will ever make their way into the central nervous system, are setting their sights on a newly discovered class of smaller molecules that have many of the same properties as neurotrophic factors but with a lot less baggage. "The beauty of these small molecules is that they cross the blood-brain barrier," says Frank Baldino, president of Cephalon in Westchester, Pennsylvania, one of the companies taking the mini-molecule tack. "People who keep focusing on growth factors for central nervous system diseases are missing the boat."

But neuroscientist William Mobley of UCSF argues that neurotrophic factors, because they are already well characterized, are in a much better position to make a clinical difference in the next few years. As for GDNF, Mobley says, "It's really important and they've done a very good job. Best of all, it says there are still more factors out there to be found, and things are going to get incredibly interesting." And for the people suffering from neurodegenerative diseases, that word interesting can only translate as hope.

–Rick Weiss

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IMMUNOLOGY

Imanishi-Kari Says Her New Data Shows She Was Right

While the 15 April *Journal of Immunology* will never find itself on *The New York Times* bestseller list, it is capturing far more attention than might be expected for a regular issue of a specialized scientific journal. Is that because it contains a new method of attacking the AIDS virus, a novel strategy for cancer immunotherapy, or the discovery of an important autoimmune gene? Not at all. What has garnered the unusual level of interest are two papers addressing a small, complicated area of immunology that concerns few researchers today.

The curiosity about these manuscripts stems not just from the data they contain, but also from the presence of an author's name on both papers: Thereza Imanishi-Kari. She is the Tufts University immunologist who coauthored what may be the most controversial journal article ever written, a disputed (and since retracted) 1986 paper in *Cell* for which Imanishi-Kari has been accused of fabricating data. Now, she says, these new publications "confirm many of the original claims." And interviews by *Science* show that many in the immunology community are impressed. "These papers would suggest that what was observed in the first paper is reproducible. This is a very thorough piece of work, extremely well-documented," says immunologist J. Donald Capra of the University of Texas Southwestern Medical Center.

> **"These papers suggest that what was observed in the first paper is reproducible."**
>
> **—J. Donald Capra**

But even so, the papers won't put an end to a long-running federal investigation into the paper or to the charges of misconduct. The new papers "deal with many of the scientific questions with the *Cell* paper, but they don't speak to fraud," admits Tufts immunologist and Imanishi-Kari supporter Henry Wortis. The official verdict in the case, which has also marred the career of Noble laureate David Baltimore, a coauthor on the 1986 paper, should come this summer, when the Public Health Service Office of Research Integrity (ORI) issues its final report.

Even in the absence of misconduct allegations, the 1986 manuscript would have been controversial to the small cadre of immunologists familiar with its topic because its observations were used to argue for conclusions about the immune system that most researchers were unwilling to accept. Imanishi-Kari (who was then at MIT), Baltimore, and their four coauthors created transgenic mice by introducing into the animals a gene encoding a particular form of an antibody protein, a version the mice did not normally produce.

Active antibody genes have to be assembled from separate bits and pieces of DNA in the genome, and to ensure that the foreign gene would be functional, the group introduced it in its "arranged" version. The expectation was that the added gene would prevent the arrangement, and thus the expression, of the animal's own gene, which produces a slightly different variation of the an-

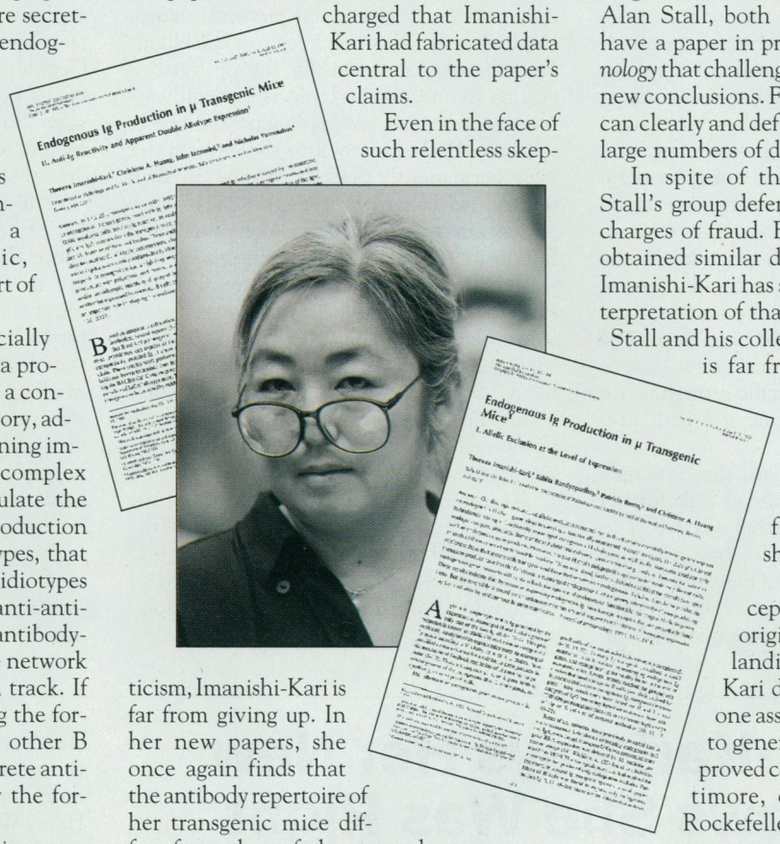
tibody protein. This phenomenon, known as "allelic exclusion," is a well-established property of these immune system genes.

Readers of the *Cell* paper were therefore startled to find the authors presenting data suggesting that while some hybridomas, long-lived fusions of tumor cells and antibody-producing B cells taken from the transgenic mice, made antibodies with the foreign gene product, roughly three-quarters were secreting only antibodies made with the endogenous gene protein even though the hybridoma cells contained the apparently functional foreign gene. Adding to the bewilderment, tests with biological reagents—various antibodies—implied that these endogenous antibodies now carried a unique structural characteristic, known as an "idiotype," that was part of the foreign gene's protein.

In the eyes of the authors, especially Imanishi-Kari, this bewildering data provided the strongest evidence yet for a controversial notion: the "network" theory, advanced in 1974 by Nobel Prize–winning immunologist Niels Jerne. Jerne's complex theory suggests that idiotypes regulate the immune system by eliciting the production of antibodies, known as anti-idiotypes, that recognize the idiotypes. The anti-idiotypes in turn elicit the production of anti-anti-idiotypes and so on until many antibody-producing cells are linked in a large network that keeps antibody production on track. If true, B cells in the mice expressing the foreign idiotype gene should induce other B cells, without the added gene, to secrete anti-anti-idiotype antibodies that carry the foreign idiotype shape.

Although they suggested other interpretations of their surprising data, the authors concluded that this "idiotypic mimicry" was the "most appropriate" explanation for their observation that in the B cell hybridomas where the foreign gene was not expressed, the antibodies secreted still carried its idiotype. But other researchers were skeptical about this conclusion and were unwilling to accept that the presence of a foreign gene could so perturb the whole immune system. Indeed, they've mostly lost interest in the notion of idiotype networks in view of a vast amount of evidence showing that antibody production is regulated jointly by immune cell interactions and regulatory molecules such as cytokines.

To the skeptics then, there were other, more mundane explanations for what Imanishi-Kari was seeing. Some immunologists, for example, disputed whether the *Cell* paper had established that the introduced gene had indeed been silenced. If the hybridomas were "double-producers," making both the endogenous and the foreign antibody protein, it would explain why Imanishi-Kari detected the foreign idiotype. Frustrated by her inability to replicate the results, former Imanishi-Kari postdoc Margot O'Toole, whose questions about the paper triggered the investigations into scientific misconduct, also argued that the reagents used to detect the foreign idiotype were flawed and therefore provided false-positives. Doubts about the paper mushroomed when O'Toole then charged that Imanishi-Kari had fabricated data central to the paper's claims.



Even in the face of such relentless skepticism, Imanishi-Kari is far from giving up. In her new papers, she once again finds that the antibody repertoire of her transgenic mice differs from that of the controls, an observation she and Baltimore now contend was the crucial one in the 1986 paper. But she backs away from the controversial notion that this is due to idiotypic mimicry. Compared to normal mice, the authors assert, transgenic mice produce more antibodies whose reactivity is similar to those produced by a specific group of B cells, those found in fetal mice. "This finding could account for the so-called 'double producer' cells found in [certain] transgenic mice," they write, since these fetal-like antibodies can apparently bind to the reagents designed to detect the foreign idiotype as well as to those used to reveal the antibody that incorporates the endogenous gene protein. Imanishi-Kari offers these results as corroboration of her original data that appeared to show the presence of an endogenous antibody containing the foreign gene's idiotype.

In her other paper, Imanishi-Kari continues her effort to dismiss the notion of double producers by doing a reanalysis of the original hybridomas, as well as looking at new ones. Her results show, she says, that hybridomas that appear to produce both the foreign and endogenous antibodies are in fact mixtures of cells, some of which produce only the foreign antibody protein while others make only the endogenous version.

Don't expect Imanishi-Kari's latest research to be the final word on this complicated topic. Immunologists Leonore Herzenberg of Stanford and Kong-Peng Lam and Alan Stall, both of Columbia University, have a paper in press at *International Immunology* that challenges many of Imanishi-Kari's new conclusions. For instance, says Stall, "we can clearly and definitely show that there are large numbers of double producers."

In spite of the scientific differences, Stall's group defends Imanishi-Kari against charges of fraud. Both camps have actually obtained similar data, his team argues, and Imanishi-Kari has simply offered her own interpretation of that data—an interpretation Stall and his colleagues dispute but believe is far from misconduct. Indeed, Stall says his group's latest paper will be the strongest replication yet of the original *Cell* data: "From our data, we confirm virtually everything she found."

So does this growing acceptance that the data in the original *Cell* paper is not outlandish prove that Imanishi-Kari did not commit fraud? No one asserts that yet. "It is possible to generate false data and later be proved correct," acknowledges Baltimore, currently a professor at Rockefeller University, where this controversy forced him to step down as president. Nevertheless, Baltimore says the new results have helped convince him there was nothing wrong with the original *Cell* paper, and he is only waiting for the final ORI report to withdraw officially his retraction. "To my mind it is a valid contribution to science. NIH will realize that there was never anything wrong with the paper."

That may be an overly optimistic view, however. Hints from the staff of John Dingell, the congressman whose interest in the topic led to federal hearings and widespread media attention, suggest that the final report due out this summer may contain an even stronger condemnation of Imanishi-Kari than did a 1991 draft report that concluded she had committed fraud and scientific misconduct (*Science*, 29 March 1991, p. 1552). Even Imanishi-Kari does not think the new papers will clear her name. "I cannot prove I didn't commit fraud by repeating the [research]," she says. Indeed, while her latest research may answer some relevant scientific questions, the verdict on the issue of misconduct is still out.

–John Travis