CLINICAL RESEARCH

Less Hype, More Biology Needed for Gene Therapy

It's not often that a federal agency throws cold water on its own hot prospects. But that's what the National Institutes of Health did last week in releasing a tough review of gene therapy, a field on which NIH spends about $200 million a year. Private industry also spends about the same amount, the review said. The authors of this report,* 14 experts hand-picked by NIH Director Harold Varmus, concluded that gene therapists and their sponsors are "overselling" the technology, promoting the idea that "gene therapy is further developed and more successful than it actually is."

Chaired by geneticist Arno Motulsky of the University of Washington, Seattle, and hematologist Stuart Orkin of Harvard University, the review panel concluded that, contrary to the general impression, the field is still in its infancy. "Clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol," the report says—"despite anecdotal claims of successful therapy" and despite NIH's approval of more than 100 human studies. Researchers, Orkin said, have repeated similar noninformative experiments in one study after another, with slight variations. Many suffer from a weak design, he said, yielding scant data. Moreover, he and his colleagues found that "significant problems remain in all basic aspects of gene therapy." In particular, the report says, all the "vectors" used so far to transfer genes into target cells are inefficient. Little is known about how these vectors interact with human cells. The result, the report says, is that the rate of gene transfer has been "very low."

This report, which reaches conclusions like those of a Special News Report in *Science* last August (25 August, p. 1050), was presented last week to the NIH director's advisory committee. It accompanied a separate report on NIH's procedures for vetting gene therapy proposals, released last month (*Science*, 24 November, p. 1287). In discussing his panel's conclusions with Varmus's committee, Orkin warned that turning a blind eye to the hype could lead to serious consequences: "This goes beyond PR," he said. Orkin said that basic science was being neglected as enthusiasts race to join the gene therapy club. He and Motulsky argued that researchers, including those in NIH's intramural programs, should be paying more attention to basic questions about stem cell function, gene regulation, and disease pathophysiology. They also warned that the hype could give patients the wrong idea about what is currently feasible.

Although they had reservations about the quality of many studies, the panelists affirmed the value of clinical research, noting that animals often aren't valid substitutes for humans, and that human studies can open new avenues of research. But it recommended that NIH resist pressure to rapidly increase the number of federally funded clinical studies by underwriting gene therapy centers at many new sites, distributing vector material, or creating a special grant review committee for this field, as some clinicians have advocated. The panel laid out some general recommendations:

■ *No entitlements.* Current NIH funding of gene therapy—$200 million per year—is "appropriate," but should continue to compete with other fields under "stringent peer review." Protocols should be held to "the same high standards" applied to other fields, according to the Orkin-Motulsky report, and reviewers should insist that studies have "specific hypotheses" that permit an investigator to interpret negative as well as positive findings. The reviewers said NIH should not create a new study section devoted to gene therapy, nor should it expand existing gene therapy centers.

■ *More coordination.* Noting "duplicative" projects, the panel urged NIH institute directors to avoid the temptation to "round out the portfolio" of intramural research with studies that appear " 'hot' but may lack a strong scientific basis." Directors should support gene therapy "only when there are compelling scientific reasons" and "await further developments in vector technology before expanding gene therapy programs."

■ *Postdocs and vectors.* The panel made a plug for "vigorous support" of postdoctoral grants for researchers who wish to combine clinical and basic studies. It also advocated targeting research on vector development, animal models, and stem cells.

Members of Varmus's advisory panel made no objection to these suggestions. One or two even endorsed a point made by Paul Marks, president of the Memorial Sloan Kettering Cancer Center in New York, that NIH should "bite the bullet" and begin an immediate review of ongoing gene therapy projects. (Like NIH, Marks explained later, his own institution has come under pressure to do gene therapy.) Other members of the panel suggested that NIH should "volunteer" to review the quality of industry-funded studies, a suggestion Varmus declined.

Although the panel gave gene therapy a tough review, leaders in the field contacted by *Science* took the criticism well. James Wilson, director of the University of Pennsylvania's gene therapy center, said he agreed "absolutely" with the report: "You've got to know your weaknesses if you're going to be successful." Like many researchers, he said, he was "naive" when he set out in this field in the 1980s, not appreciating its complexity. "The focus on basic research is what we need," he said, and he hopes these recommendations will "rejuvenate areas of virology that have been underfunded."

Dusty Miller, a virologist and gene therapy researcher at the Fred Hutchinson Cancer Research Center in Seattle, felt the report was on target, although he differed with its finding that no experiment had yielded evidence of efficacy; he felt that a child with adenosine deaminase deficiency had been helped by an NIH protocol. Gene therapist W. French Anderson of the University of Southern California, a celebrated proponent of gene therapy, also felt that the report was harsh in expecting that preliminary clinical trials should yield hard efficacy data. But he agreed "totally" with its emphasis on improving the quality of research.

When the reviewers had finished presenting their reports last week, Varmus said he would put one recommendation into effect right away. He plans to create a new "gene therapy coordinating group" composed of select institute directors and intramural leaders to see that NIH actually makes use of all the new advice it has received.

–Eliot Marshall

RICK KOZAK

Strong medicine. Panel co-chairs Stuart Orkin *(left)* and Arno Motulsky issue tough report.

* "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy," available from NIH or the World Wide Web at <http://www.nih.gov/news/panelrep.html>.