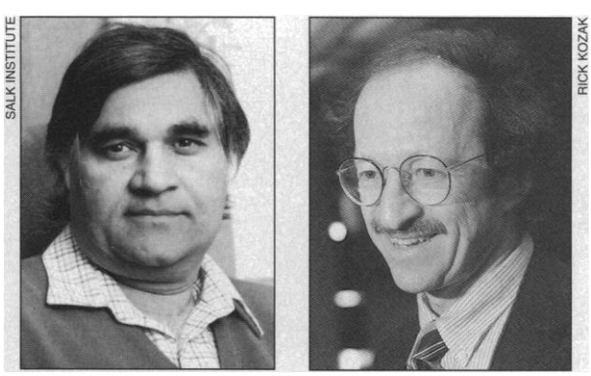
NATIONAL INSTITUTES OF HEALTH

Varmus Orders Up a Review of The Science of Gene Therapy

Almost 5 years have gone by since researchers at the National Institutes of Health (NIH) treated a crippling immune disorder in two young girls by injecting them with cells genetically altered to express an enzyme that their bodies did not produce naturally. The treatment ushered in the much-heralded era of gene therapy, and that pioneering experiment has since been followed by dozens of clinical trials, the majority aimed at developing gene therapies for cancer. Yet no definitive data on the efficacy of human gene therapy have been published in peer-reviewed journals; even that first test remains unpublished. And some researchers are quietly expressing concern that new clinical trials of dubious value or quality are being approved in the absence of hard data. Perhaps it is time, says Inder Verma, an expert in cancer genes at the Salk Institute in La Jolla, California, to "prick the balloon."

Verma, one of the most cited scientists at Salk, is in a good position to wield the needle. Since February, he has been chairing a special "ad hoc working group" conducting a wide-ranging review of NIH's methods of approving gene therapy trials. Verma took on this new assignment at the request of NIH Director Harold Varmus, who himself has expressed qualms about trends in gene therapy. Varmus gave Verma a broad mandate to take a hard look at the science and recommend how NIH should evaluate clinical research protocols. He also asked for advice on funding of new, extramural gene therapy centers. The review group* has met twice, most recently on 8 March, and hopes to draw up recommendations later this year.

The focus of its review is NIH's Recombinant DNA Advisory Committee (RAC). Its original task in the 1970s was to act as a safety check on recombinant DNA experiments. Then in the 1980s, it was given the task of reviewing human gene therapy protocols proposed by all researchers at NIH-funded institutions. RAC has been plagued "since its inception," says Executive Director Nelson Wivel, by a dilemma over "safety versus science." RAC's primary role is to review protocols for safety or ethical concerns, but scientists on the committee cannot resist asking scientific questions when they see gaps in the proposals. And they have learned that, because most projects they view are not funded by direct NIH grants, the principal investigators often haven't experienced stringent peer review. In this situation, says Wivel, the question is: "How hard do you push for scientific data?"



Looking beyond the hype. NIH Director Harold Varmus *(right)* and ad hoc working group chair Inder Verma.

Varmus, it seems, would like RAC to push a little harder than it has been. In a phone interview last week, Varmus told *Science* that he commissioned the Verma panel after realizing last fall that RAC's mission was surprisingly muddled. Varmus said that after he looked into RAC's handling of a colon cancer trial proposed last June by David Curiel of the University of Alabama, Birmingham, he found that RAC members were plainly "confused about whether they were reviewing for safety or science."

Curiel had proposed injecting patients with plasmid DNA for a specific antigen in the hope that it would stimulate an immune response against colon cancer. RAC members agreed that the experiment posed little risk, but many were skeptical about the science. Some felt that an inappropriate animal model had been used. Others were dissatisfied with the design of the trial and claimed it lacked supporting data. In the end, the RAC split, with a majority voting approval because they felt it wasn't their job to judge scientific merit.

They passed their approval to Varmus, but Varmus balked. Reversing the panel, he asked Wivel to inform Curiel that the proposal would be "deferred" until better data were submitted. In rejecting the proposal, he became the first NIH director ever to override a favorable vote by RAC. Curiel calls Varmus' action "extraordinary." "We were incredulous," he adds, noting that an NIH researcher, Jeffrey Schlom, was already conducting a similar trial. Curiel meanwhile has been collecting more data and plans to resubmit his application.

RAC's handling of the Curiel proposal prompted Varmus to establish the Verma panel, but he is apparently looking for more than just advice on how RAC should function. Varmus appeared before the Verma panel on 3 February to lay out some broad concerns about trends in gene therapy and NIH's involvement in the field. According to minutes of that session, Varmus raised six questions:

- Has the emphasis on safety rather than scientific merit at RAC "skewed the field" of gene therapy?
- Should RAC's charter be changed to state that it reviews proposals for merit?
- Is it appropriate for universities and companies to use RAC approval as a way of validating their research "and perhaps inflating the value of the companies' stocks?"
- Has this area of biomedicine been oversold?
- Should NIH fund extramural labs or "centers of excellence" to develop new gene therapy vectors? And how should it ensure high-quality science at these sites?
- Should RAC be concerned about the risk that inexperienced clinicians may be teaming up with companies to do gene therapy?

These are difficult and controversial questions, but the ad hoc panel has shown in its first two sessions that it is ready to tackle them. Last week, Verma told the panel that he thought the overall objective was to achieve "a higher notch of scientific evaluation" for gene therapy, and no one dissented.

Later, Verma told *Science* that it may be necessary to create a new study section at NIH to handle merit review of gene therapy protocols in private, allowing for more frank discussion. However, such a panel may have jurisdiction over only a fraction of the RAC's caseload: the 20% of gene therapy proposals funded by direct NIH grants. Finally, Verma said he hopes to arrange a public symposium that will review the results obtained so far from gene therapy trials aimed at treating cancer. The goal: to learn what techniques, if any, are succeeding. If the project gets approved, he would like to schedule it for September.

–Eliot Marshall

* In addition to Verma, the panel includes C. Estuardo Aguilar-Cordova of the Texas Children's Hospital in Houston; Helen Blau of Stanford University; Robert Desnick of the Mount Sinai Medical Center in New York; Charles Epstein of the University of California, San Francisco; Helen Heslop of the St. Jude Children's Hospital in Memphis, Tennessee; Susan Hirano of the University of Wisconsin, Madison; Albert Jonsen of the University of Washington School of Medicine in Seattle; Robertson Parkman of the Children's Hospital of Los Angeles; and Doris Zallen of the Virginia Polytechnic Institute and State University in Blacksburg.