GENE THERAPY

New Clinical Trial Planned

A team of Michigan researchers is poised to begin an experiment that marks a new milestone in efforts to use gene therapy to treat human diseases. At a press conference on 13 April, team leader Gary Nabel of the Howard Hughes Medical Institute at the University of Michigan in Ann Arbor announced that his group has won Food and Drug Administration approval for the first clinical trial in which a potentially therapeutic gene will be injected directly into patients. The experimental therapy is aimed at treating malignant melanoma, a dangerous form of skin cancer.

In all the other human gene therapy trials conducted so far, researchers first remove cells from the patient, outfit them with the therapeutic gene, and then reimplant the cells in the patient. That approach is being used, for example, by W. French Anderson at the National Institutes of Health to try to correct the enzyme defect in children with a severe hereditary immunodeficiency disease. But if Nabel's approach works, it could be much less expensive and could involve fewer steps than the other methods currently being studied, says Anderson, who adds, "It is exciting that there are so many new avenues being explored in gene therapy."

In his Michigan trial, which is expected to start within a few months, Nabel and his colleagues will inject a gene encoding a histocompatibility protein directly into the tumors of melanoma patients who have not responded to conventional therapies. Histocompatibility proteins are the molecules on the cells of transplanted organs that trigger the immune responses leading to graft rejection. As Nabel describes his plan, "We're trying to mimic the case where you have organ rejection, but in an artificial way, by introducing the gene into a tissue where it isn't ordinarily expressed."

But the first challenge is to get the gene across the outer membranes of the tumor cells. To do this, Nabel's group will encase the gene copies in liposomes, tiny sacs made of lipids that can fuse with the lipids of the cell membranes, allowing the liposome contents to be dumped into the cell. Once the gene is inside, Nabel says, the hope is that the protein it makes will be displayed on the tumor cell surfaces where it can trigger an immune response.

Twelve to 15 patients are scheduled to receive the new therapy, which will be administered over a course of 6 weeks. And since the trial is a phase I clinical study, the goal is to determine the maximum dose of the liposome-encased gene the patients can tolerate without unacceptable side effects, as well as to see whether the gene is expressed by the tumor cells. Any clinical benefits would be a bonus at this stage. But if Nabel and his colleagues are satisfied with the results of the initial trial, they will seek FDA approval to move into a phase II study, in which they will try to refine the gene therapy procedure to get maximum efficacy. Ultimately, Nabel hopes that gene therapy will become routine. But for now, he is cautious. "We're really stepping into new territory," he says. "It's important not to take any unnecessary risks and to proceed systematically."

–Michelle Hoffman

HIGH ENERGY PHYSICS

Physics Facilities Come Under Fire

DOE Bites the Bullet

It has become a grim routine at the Department of Energy (DOE) in these days of budgetary pinch. A panel of eminent scientists gathers to set priorities for a research program using various budgetary scenarios. After weeks of anxiety within the community, the panel produces its report. That leaves the affected research community to agonize over the projected tradeoffs. So it went, this week, for DOE's high-energy physics program.

On the positive side, the report—issued on 13 April by a panel chaired by Michael Witherell, a physicist at the University of California at Santa Barbara—strongly supports the Superconducting Super Collider (SSC) and a major upgrade to Fermilab's Tevatron. But it also exacts a severe price from other national laboratories. And that's only under a scenario that assumes a flat budget, adjusted for inflation. Under a "low scenario," amounting to a real funding decline of about 3.5% a year, even Fermilab would begin to feel the ax.

In either case, the Stanford Linear Accelerator Center (SLAC) would undoubtedly be hardest hit. The flat scenario calls for SLAC to shut down its only operating accelerator, the Stanford Linear Collider, by October 1993, and does not allow SLAC to begin building its heartily desired "B factory" until late 1995. The low scenario is even worse: Under those conditions, the panel agreed, DOE should close SLAC down in 1995. "The damage to particle physics would be severe," said Witherell.

The SSC, however, escaped unscathed in the panel's deliberations, thanks to its status as a protected presidential initiative. That's a source of frustration for some of the physicists on the exercise's receiving end. "We're creating a monster," said Mel Schwartz, an official at Brookhaven National Laboratory. But short of congressional cancellation of the SSC or a miraculous return to moderate growth in the high-energy physics budget, physicists are going to have to live with their monster and the choices it has forced on them.

Whacking at the SSC

Members of a House oversight panel last week opened fire on the Superconducting Super Collider (SSC), claiming that its builder, the Department of Energy (DOE), has managed the project poorly and hidden the news that it is over budget and behind schedule. The 9 April hearing was the latest round in an ongoing struggle between subcommittee chairman Howard Wolpe (D–MI) and DOE.

For nearly every complaint raised in the hearing, however, SSC officials are ready with an explanation. An official from the General Accounting Office, for instance, testified that a previously unrevealed analysis by an SSC subcontractor showed that construction costs will exceed the $1.5 billion budget by $73 million to $383 million. But SSC project manager Edward Sisken says that analysis resulted from the subcontractor's eagerness to undertake more work than DOE wanted, and that once the agency reined in the company the cost estimates returned to normal.

In another salvo, Wolpe released a 24 January letter by then DOE deputy secretary W. Henson Moore that criticizes SSC lab director Roy Schwitters and his employer, SSC contractor University Research Associates (URA), for their failure to control costs. After asking for a detailed plan for correcting the problems, Moore wrote: "If your plan is not satisfactory to me, I intend to instruct our attorneys to examine our contract to see what remedies are available to the department." But SSC spokesman Russ Wylie claims that Moore was threatening a URA subcontractor, not URA itself.

Representative Sherwood Boehlert (R–NY), however, may have offered one criticism the department cannot rebut. "We are told that the SSC will not be built at the expense of other science; the truth is that the other labs—Fermi, SLAC (Stanford Linear Accelerator Center), Brookhaven—will be cannibalized in the effort to find money to build the SSC." Coming just a few days before a DOE advisory panel recommended closing SLAC if high-energy physics budgets do not keep pace with inflation (see related story), Boehlert's complaint may be the one that comes back to haunt DOE.

–David P. Hamilton