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Halted trial renews questions about cancer vaccines

Citing ethics violations and 'important flaws' in methodology, Swiss authorities have ended a much-heralded cancer vaccine trial at Zürich University and will allow a second trial in the multicenter program to continue only after the errors have been corrected.

Coordinators of the trials—in Zürich and in five collaborating centers in Germany—are themselves considering whether to end the second trial because patient responses have been below expectations. The trials had been testing dendritic cells designed to carry antigens of melanoma tumors.

The problems once again call into question the viability of dendritic cell cancer vaccines, just months after a paper involving such a vaccine was retracted (*Nat. Med.* 9, 1221; 2003).

"There's very few people conducting careful, thoughtful clinical trials [with dendritic cell vaccines]," says Drew Pardoll, professor of oncology at Johns Hopkins University. Nearly all flashy pilot trials have later proven too good to be true, Pardoll points out. "Now, if I see dramatic results, I virtually just don't believe it."

Specialized in presenting foreign peptides to the immune system, dendritic cells loaded with antigens can amplify a specific immune response. Many researchers are trying to translate this principle into effective clinical treat-

ments. Although some immunologists doubt the immune system can successfully be deployed against the body's own tumors, the vaccines have proven successful in animal studies.

Frank Nestle and colleagues were among the first to report major success in human trials: of 16 patients treated with their vaccine, more than 30% showed shrinking tumors, they reported (*Nat. Med.* 4, 328–332; 1998). Because standard chemotherapy benefits 10–15% of melanoma patients, the announcement created a stir.

Nestle continued his pilot trial in Zürich. In 2000, along with five German hospitals, he also helped launch a randomized, multicenter trial in which 240 patients would receive either dendritic cells or chemotherapy as initial treatment. That trial would have yielded significant results if the response rates had been 30% with the vaccine, says trial coordinator Dirk Schadendorf, head of the dermatology clinic at Mannheim University, one of the German centers.

But in February 2003, internal accusations at Zürich University prompted investigations that ultimately brought several wrongdoings to light (*Nature*, 426, 484; 2003). One of the main complaints—that the Zürich dermatology clinic had charged study participants thousands of dollars—proved to be true.

Fueled by reports in the Swiss press, the investigations also revealed that response rates in the follow-up studies were far lower than anticipated, both in Zürich and at the collaborating German centers. Because of "massive public pressure" against enrolling patients without fresh, solid data on response rates, says Schadendorf, the multicenter trial was put on hold in September 2003.

Schadendorf says response rates have been "less convincing" than expected, but declines to reveal details. Statisticians are now busy calculating whether results from the first 107 patients make it likely the multicenter trial can still yield useful outcomes, he says. Depending on the results, the trial could be continued, expanded or terminated, he adds.

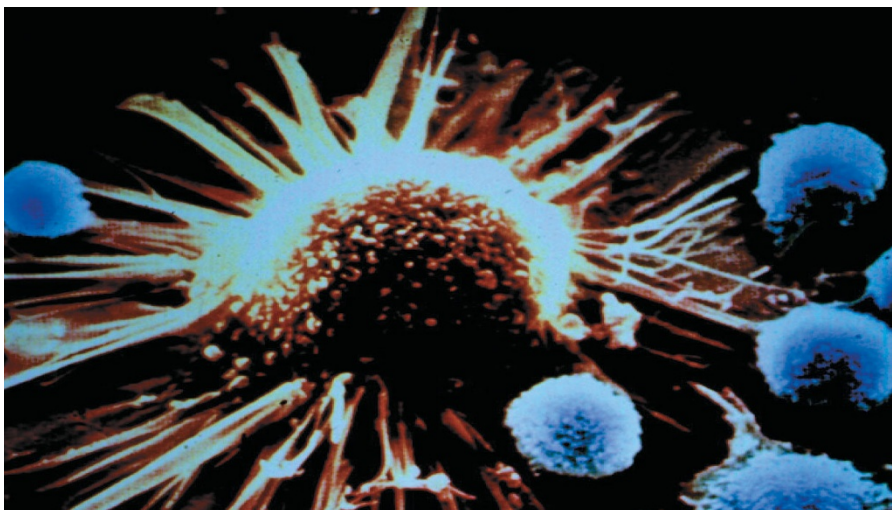
Controversy over the Swiss trial will only add to the image of a messy field, says Nina Bhardwaj, who studies dendritic cell vaccines at New York University. The main problem, Bhardwaj says, is the lack of standardized protocols for conducting trials with the vaccines. "People use different preparations, doses, frequencies, antigens and ways of loading them onto dendritic cells—they even use different ways to measure outcomes," Bhardwaj says. "We need to come together to strategize, or we will shoot ourselves in the foot."

Eli Gilboa, research director of the Center for Genetic and Cellular Therapies at Duke University, says there is "undue pressure exerted on researchers to engage prematurely in clinical trials and offer hopeful indications of success." Much more work—most of it unglamorous and unpublishable—will be needed to translate powerful results in animals to useful treatments in humans, Gilboa says.

Still, many in the field remain optimistic, citing a few ongoing trials that could validate the approach.

Dendritic cells are "one of the most promising approaches to stimulate protective immunity against cancer," says Gilboa. Even Nestle, beleaguered in Zürich, is upbeat. "Science is like the stock market—after excitement comes disillusion," Nestle says. "But in the long term, the trend is up. Don't declare this field dead too soon."

*Peter Vermij, Washington, DC
Martina Frei, Zürich, contributed to this report*



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Questionable cure: High hopes ride on dendritic cell vaccines to treat cancer, but the field remains fraught with problems.