Firm tried to block report on failure of AIDS vaccine

Scott Gottlieb *New York*

A Californian biotechnology company tried to block publication of a major AIDS study that found that the experimental treatment the company was developing failed to improve the health of patients, the scientists conducting the research said.

The Immune Response company of Carlsbad, California, opposed publication of the study because it did not include a sub-analysis it believed showed that the treatment boosted the immune systems of some patients.

But despite the objections of the company, the researchers, led by James Kahn of the University of California at San Francisco, submitted their results to *JAMA*, which published them.

The study, of 2527 patients at 77 hospitals, tested a therapeutic vaccine, marketed under the trade name Remune, designed to boost the immune systems of people infected with HIV. The researchers concluded that Remune failed to show any advantage in survival or in slowing progression of AIDS. The number of people whose health had worsened after two years

was exactly the same as that in a placebo group. The findings were disappointing to patients and researchers, who had hoped that the substance, manufactured from killed and dismantled HIV, would attenuate the course of the disease (*JAMA* 2000;284:2193-202).

"Companies are frantic to get out positive results, but not neutral or negative results," Dr Kahn said. "It's very hard to publish a study that's either neutral or negative on a commercial product."

Drummond Rennie, the deputy editor of *JAMA*, said that the journal had gone ahead with publication to "prevent the bias that comes from reporting only those results favorable to sponsors' products."

At issue was whether an analysis of data from 250 patients out of the 2527 in the study should have been included in the published report. The vaccine's manufacturer believed that the subanalysis would not change the outcome of the trial but was highly informative and should have been included. Dr Kahn believed the analysis was misleading and

should have been excluded.

In September the vaccine's manufacturer refused to provide all the study data to Dr Kahn and his colleagues, and Dr Kahn refused to put what the company wanted in the paper.

The analysis that Dr Kahn and his colleagues performed showed no benefit, as measured by survival or health improvement rates, between the vaccine and placebo groups. This was also true of a subpopulation of 250 patients, in whom blood samples had been taken more frequently than in the others. In that group, however, the patients taking Remune had a more vigorous immune system response than those taking the placebo.

Dr Kahn's paper reported these results, but the company's researchers believe that Dr Kahn and his team should have noted that patients in the subpopulation taking Remune had a steeper drop in viral load than those taking placebo.

Dr Kahn and his colleagues viewed that analysis as "data dredging." The statistical test that the company used to show

James Kahn

the connection between Remune and viral load in the subpopulation was not specified in advance in the experiment's protocol, Dr Kahn said.

Ronald Moss, vice president of medical affairs at Immune Response, said: "The published article excludes the full presentation of results showing that Remune did cause enhanced immune system activity." He said the company tried to stop publication "only because we think there was important information excluded." He said the company still planned to publish such data from the study. □

BAX gene needed for NSAIDs chemoprotection

Abi Berger *BMJ*

Scientists have discovered how non-steroidal anti-inflammatory drugs (NSAIDs) can prevent colorectal cancer. Dr Lin Zhang and colleagues at the Howard Hughes Medical Institute and Johns Hopkins University in Baltimore have shown that a vital key to

chemoprevention is the presence of the BAX gene (*Science* 2000;290:989-92).

Long term use of NSAIDs is known to be effective in preventing colorectal cancer in those who are at high risk of developing it. These drugs induce apoptosis (programmed cell death), but until now very little was known about the mechanisms involved. Now Dr Zhang's team has provided convincing evidence that the key to drug induced apoptosis is the presence of the BAX gene. Dr Zhang, a molecular geneticist working in human cancer, and his team began investigating the BAX gene

because it is the first pro-apoptotic gene to have been described.

Cell death is triggered when pro-apoptotic genes are expressed. In this new set of experiments, the team created two cell lines of human epithelial cells. The first cell line had the BAX gene knocked out; the second had an intact BAX gene (resulting in normal levels of the BAX protein being produced). When the cells with the BAX gene were treated with sulindac (an effective chemopreventive NSAID), 100% cell death occurred. When the cells without the BAX gene were similarly treated, no apoptotic

cell death was observed.

Dr Bert Vogelstein, who works with Dr Zhang, said that this clearly shows that the efficacy of the drug depends on the presence of a single gene. "We don't usually see such black and white results," he said. This knowledge will help to rationalise chemopreventive regimens for high risk patients. "It is likely, as with other chemotherapy regimens, that the best course of preventive treatment will involve more than one drug," says Dr Vogelstein. "We should now look at other NSAIDs and ascertain which rely on the BAX gene and which don't." □