AUSTRALIA

Engineered Mouse Virus Spurs Bioweapon Fears

Efforts to find a better pest-control agent lead to a potentially deadly surprise for a team of Australian researchers

MELBOURNE, AUSTRALIA—The surprising virulence of a virus genetically altered to reduce rodent infestations in Australia has raised alarm over whether such research could be hijacked to produce biological weapons. In an unusual twist, those sounding the alarm are not environmental activists but the scientists themselves. Despite their warning, released with the research results this month in an electronic version of the *Journal of Virology*, it's not clear whether the unexpected result, which turned a vector into a potent killer, could be duplicated in viruses that affect humans. But scientists say it should serve as a warning to the community to be more aware of the potentially harmful consequences of their work.

The goal of the research was certainly benign. The scientists were attempting to sterilize rodents by using a virus to trigger an antibody attack against mouse egg proteins. But when the researchers attempted to beef up this virus by incorporating the immune system hormone interleukin-4 (IL-4) into its genetic payload, the virus turned into a killer, wiping out all the animals. Even vaccination offered little protection.

The potency of this modified virus startled officials at the Co-operative Research Center (CRC) for the Biological Control of Pest Animals in Canberra, whose scientists had teamed up with the John Curtin School of Medical Research at the Australian National University in Canberra. So on 16 January the CRC issued a press release timed to accompany the article that pleaded for stronger measures to combat the threat of biowarfare arising from such good intentions. Not surprisingly, the press release triggered sensational warnings in the Australian media and elsewhere.

"This is the public's worst fears about GMOs [genetically modified organisms] come true," says CRC director Bob Seamark, who led the research. Adds Annabelle Duncan, a former deputy head of the United Nations team of inspectors in Iraq and now chief of molecular science at the Commonwealth Scientific and Industrial Research Organization (CSIRO), "This shows that something we had thought was hard—increasing the pathogenicity of a virus—is easy."

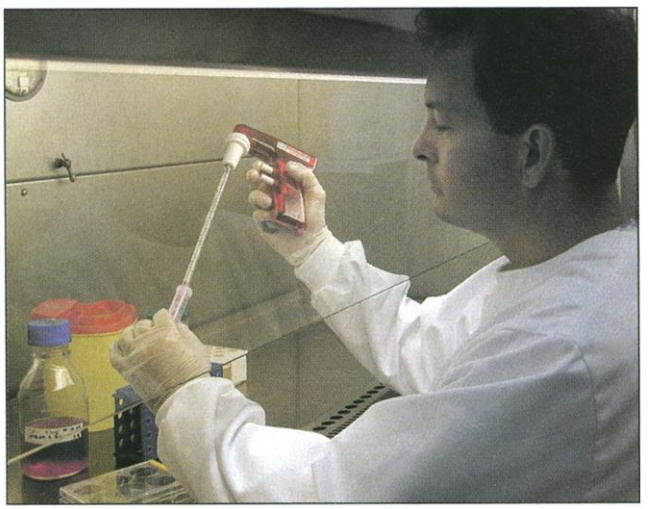
The focus of all this attention is a mousepox virus that had been engineered to carry the mouse egg shell protein ZP3, or zona pellucida 3, as a mouse contraceptive. The foreign protein triggers an antibody response that within several months destroyed eggs in female mice, at least in one laboratory strain of mice. But when Seamark's group tried the technique on a second strain of mice, known as Black 6, it was ineffective.

To boost the antibody response, Seamark called on the immunological expertise of Ian Ramshaw's group at the Australian National University. In previous work, they had shown that adding IL-4 to the genetic payload of the vaccinia virus increased the antibody-producing response in mice and toned down the effectiveness of virus-clearing killer T cells.

Hoping to take advantage of this shift, Seamark's team inserted the IL-4 gene into the mousepox virus. They expected only to strengthen the antibody response in the resistant Black 6 strain, but instead the virus overwhelmed the mice, proliferating out of control and destroying their livers. Even mice that had been vaccinated against the virus fared poorly, with half dying immediately and the remainder developing a chronic abscess at the site of infection. "This was a shock to us," says Seamark, who worries about the close relationship between mousepox and smallpox, once a scourge to humans. "We [also] had shown that a commonly used technology could overwhelm resistance and render vaccination useless."

The team spent the next 18 months confirming the data and debating whether to go public with them. In the end, disclosure won out over concerns about educating future bioterrorists and alarming the public. "We need the public to trust us if we are going to seek their approval to release pest-control viruses down the track," says Seamark, the driving force behind a consensus conference on GMOs held 2 years ago in Canberra (*Science*, 5 March 1999, p. 1427). But any intentional release, he hastens to add, won't involve viruses carrying the IL-4 gene. "These are confined to the high-security lab," he says.

Such fears may be overrated, says Ron Jackson, the CRC virologist who carried out much of the work. Jackson suspects that the findings may be peculiar to the mousepox virus, which naturally carries other proteins, such as interferon γ binding protein, that weaken the antiviral response. He notes that the result did not occur with the vaccinia virus in Ramshaw's lab.



Handle with care. CRC's Ron Jackson would like to know if his findings are peculiar to the mousepox virus.

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At the same time, he and other scientists point out that many viruses employ immune system modifiers as part of their arsenal, including the human Epstein-Barr virus and primate cytomegaloviruses. "I wouldn't say that mousepox is an exception," says immunologist Chris Burrell of the University of Adelaide in South Australia. "The more we look, the more we find viruses that carry these types of genes."

The implications of this finding are of intense interest to organizations such as the Federation of American Scientists, which has formed a working group to develop a protocol that would add verification powers to the currently toothless international convention on biological weapons. "Until now, we considered genetically engineered organisms little threat compared to the naturally occurring ones," says microbiologist Mark Wheelis of the University of California, Davis, a member of the working group. "But with genomics and proteomics, we're going to see a lot more of this sort of thing." **–ELIZABETH FINKEL**

Elizabeth Finkel writes from Melbourne.