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## Gazetteer

### RESEARCH

# Preparing for Smallpox ... Again

**For most Americans**, concerns about smallpox and other forms of bio-terrorism came only in the aftermath of September 11. Researchers at Penn and other universities, not to mention the Centers for Disease Control, have been thinking about ways to combat it for a good deal longer than that.



Illustration by William Hood

Last January, two Penn scientists—Dr. Stuart N. Isaacs, assistant professor of medicine in the Division of Infectious Diseases; and Dr. John D. Lambris, professor of pathology and laboratory medicine—received a \$1.1 million grant from the National Institutes of Health (NIH) to investigate ways of protecting against smallpox. They had responded to the

NIH's October 1999 request for applications to prepare against various forms of bio-terrorism, a list that included smallpox. Even though the disease has been effectively eradicated (the last known case was in 1977), the deadly virus still exists in laboratories, and only limited quantities of vaccine are available. And the very fact that people are no longer vaccinated against it makes the population vulnerable.

“Being prepared will, potentially, prevent the problem from

ever happening,” says Isaacs. “There are various pieces of the pie that scientists and the government will try to fill in.” Those pieces include: treatments for those infected with smallpox, treatments for complications from smallpox vaccine, and rapid diagnostic techniques. Isaacs and Lambris are focusing on the second aspect.

“One of the most often-asked questions is, ‘Once we have enough vaccine available, why not start vaccinating everybody again?’” Isaacs notes. “But with every treatment in medicine, there are risks and benefits.” And at this point, “the risk of the vaccine still outweighs the potential benefits.”

The vaccinia smallpox vaccine is a live-virus vaccine, he points out, and while it has been highly effective in eradicating smallpox, complications have sometimes developed. Some were “life-threatening complications where people, most commonly with abnormal immune systems, would die from the vaccine itself.” Other, more common, side effects included “brain inflammation” that can lead to “neurological deficit,” and “skin complications that could potentially leave bad scarring.”

At present, the only available treatment for such complications is a blood product known as vaccinia immunoglobulin, which has a high level of antibodies against the vaccinia virus. But it is difficult to produce.

“What Dr. Lambris and I—and other labs—are trying to come up with is laboratory-generated antibodies that will neutralize or turn off the virus from replicating, and prevent it from getting into cells,” explains Isaacs. “By having it as a lab-based product, you don’t have to worry about blood products—bleeding people to get material. It can be made or synthesized in the laboratory. So it will be a potentially renewable resource whose quantity is only limited by how much you want to make.”

To produce those antibodies, they are targeting specific proteins produced by the virus. One is VCP—vaccinia complement-control protein—which inactivates the human complement system of proteins that attack invading organisms. “We thought that if we could block the activity of that protein, it would then allow the person’s immune system to overcome the vaccine or infection,” says Isaacs. Another is B5R, a surface protein “that we think is important for the virus attaching onto and getting into the cell.”

Those proteins “are going to be important targets for developing monoclonal antibodies” that will replace the vaccinia immunoglobulin, he says. “The other point is that since both proteins—B5R and VCP—are also encoded in smallpox virus, these monoclonal antibodies might be useful in the treatment of smallpox” itself, not just in the treatment of vaccinia complications.

And the results of their efforts so far? “With the events of September 11 and the bio-terrorism with anthrax, we wish we had made more progress,” sighs Isaacs. “But these are long-term goals, and we’re not going to have instant progress.”■

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