Outfoxing pox: Developing a new class of vaccine candidates

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Dr. Sykes' team has used functional screening of cowpox to identify new vaccine candidates against similar viruses. Credit: Biodesign Institute at Arizona State University

In the annals of medicine, Edward Jenner's 1796 vaccination of a young boy against smallpox, using fluid from cowpox blisters, remains a landmark case. In a new study, Kathryn Sykes, a researcher at Arizona State University's Biodesign Institute and her colleagues have taken a fresh look at cowpox. Their findings, appearing in the advanced online issue of *Virology*, demonstrate that this ancient pathogen still has much to teach us, and may hasten development of novel vaccines against smallpox and other pox-like diseases.

Sykes explains that poxviruses, in addition to their importance for human health, provide an ideal framework for investigating protective antigens—parts of the virus that can be used to develop a vaccine—by means of modern, high-throughput genomic and proteomic screening technologies.

"If you study viruses like ebola or HIV, their genomes contain a small number of genes—maybe just 3-9," she says, noting that this is too small for the purposes of demonstrating a capacity for high-throughput functional screening. Other pathogens like malaria, which boast tens of millions of nucleotides, are too large. "We wanted something in the middle that could demonstrate our high-throughput technologies but not blow us away before we had a few protocols in place," she says. "Poxviruses are the Goldilocks case. At around 220 genes, they are just right."

In the current study, Sykes' team used functional screening of cowpox to identify new vaccine candidates against similar viruses. These were compared with 4-pox—a vaccine comprised of 4 protective genes from a close genetic relative of cowpox called the vaccinia virus. The team found that the identified antigens offered superior protection in a cowpox challenge compared with the 4-pox vaccine. (See figure 1) The 4-pox vaccine was developed by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) as an alternative to the licensed vaccine against smallpox, known as Dryvax, (which is made from live vaccinia and presents significant risk for those with suppressed immune systems).

By rapidly screening the whole viral genome, Sykes' group attempts to isolate genes necessary for an effective vaccine. This subunit vaccine approach is in contrast to traditional vaccine methods, where scientists use a weakened form of a live, whole-virus strain. "The dogma among old fashioned vaccinologists is that you want to make a vaccine that

recreates the immune responses that happens upon natural infection," Sykes explains. But pathogens like poxviruses also contain elements that can help the virus evade or in some cases, subvert the host's immune system. Subunit vaccines make use of only those genomic segments known to be immunogenic, provoking a robust immune response without the danger of initiating disease.

The tricky part is identifying the effective subunits. Using a process known as expression library immunization, the entire cowpox genetic library was separated into pools and tested in comparison with the 4-pox vaccine for protective effect in a mouse model. In all, the team identified 9 new protective components. Sykes stresses that the majority of new candidates would not have been identified through traditional methods, where scientists focus on a viral gene because of its function or surface exposed location. "The power of this technology is that it's assumption-free with respect to what should be a vaccine candidate."

To further boost the immune response, Sykes recommends using a gene gun to deliver the subunit vaccines, a process in which protective antigens are shot directly into the cytoplasm of immunogenic skin cells, (rather than injected by needle into muscle cells, which are not themselves immunogenically active). Such gene gun delivery provides a highly effective mechanism for delivering antigens to the immune system.

Sykes emphasizes that a single viral subunit will likely not offer comprehensive protection. Rather, suites of antigens must work together synergistically. Further high-throughput, rapid vaccine development research will focus on identifying such cooperative antigen groups. "We need to come up with empirical ways of determining which antigens are working together," Sykes says. "There's your highly effective subunit vaccine."

The application of subunit component vaccine strategies for other diseases, including tularemia, African swine fever virus, and even cancer is also under investigation. "If you think of a tumor cell as a pathogen, then you want to take that tumor cell and treat it the same way we treated cowpox—by screening all of its potential antigens and testing them. "

More information: dx.doi.org/10.1016/j.virol.2009.09.008

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