New technology for boosting vaccine efficiency

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One of the most pressing biomedical issues is the development of techniques that increase the efficiency of vaccines. In a paper published on April 24, 2008 in the journal *Vaccine*, a Massachusetts's biotechnology company, Cure Lab, Inc. has proposed a new technology for anti-viral vaccination.

This technology consists of two major elements. First, each vaccine antigen should be made in two forms. One is easily processed within the organism's cells by an intracellular "chopping machine" called the proteosome, while another is resistant to the "chopping". Thus both these forms of an antigen would be used in combination to elicit a much stronger immune response than either of them would be able to do alone.

Imagine a vaccine that could make a cell within our body produce a viral protein. This is called a recombinant vaccine. Recombinant vaccines give the most hope today as anti-viral and anti-cancer vaccines. They train the immune system to recognize and eliminate first infected or cancerous cells, preventing a disease progression. In order for a recombinant vaccine to be effective, the produced viral protein must be presented by the cell to our immune system. This antigen presentation process is very complex and remains poorly understood.

"A few years ago the situation seemed to be simple- said Dr. Alex Shneider, Founder and CEO of Cure Lab, Inc. - Vaccinologists believed that a recombinant vaccine makes the cell able to produce a viral protein. The proteosome cuts this protein into pieces. These pieces are then

presented on the cell surface and stimulate immunity. If this was the complete story, life-saving solutions would be so close." A lot of research groups rushed to enhance their vaccines by fusing different viral proteins used in vaccines with specific transport signals directing the proteins to the proteosome. The logic was pretty straightforward. The more protein that would be targeted to a proteosome, the more protein segments generated for presentation to the immune system. This would then result in an elevated immune response.

However, these hopes did not materialize. One of the reasons was that the proteosome could not effectively cut the viral proteins used in vaccines. Dr. Shneider and his team hypothesized that viral proteins have such a shape that the proteosome can not efficiently "chew" them. To test this hypothesis, they introduced changes into viral proteins thereby disrupting their structures. As a result, proteosomes are able to "cut" into segments viral proteins that were once resistant to proteosome processing.

"After we established the technology allowing us to create a form of viral protein that would be easily processed inside the cell, we thought that victory would be rather straightforward - commented Dr. Petr Ilyinskii of Cure Lab.- A modified protein with disrupted structure would provide protein segments for antigen presentation and thus be a stronger immunogen. However, the disappointing news was just ahead". The readily proteosome degradable proteins were not better vaccines than their wild type counterparts. The same problem was encountered by other research groups as well. These unsuccessful attempts temporarily put an end to great hopes for the future of vaccine development based on proteosome degradation.

"Based on the most recent scientific findings- explains Dr. Alex Shneider- we hypothesized that there are two mechanisms which present a viral protein to the immune system. One requires peptides derived

from the antigen protein, while the other presents the entire intact protein. Therefore, by creating a form of a protein which would be rapidly degraded by the proteosome we enhance this first mechanism and, at the same time, reduce or eliminate the second. If both of these mechanisms are necessary to establish an immune response, we have to combine two forms of a protein: one “chopped” into many peptides and optimal for the first mechanism, and the other resistant to “chopping” and good for the second mechanism.”

Cure Lab tested this assumption on two proteins of influenza (flu) virus, M1 and NS1. Vaccines with both of these proteins were shown to elicit a much higher immune response when the two forms of the protein were mixed together than if any of these forms was used alone.

Most of the vaccines in-use today must be administered more than once, with the initial shot called “prime” and the following one- “boost”. It became apparent lately that prime and boost are not simply a repeat of each other, but mobilize different immunological mechanisms. Following this logic, Cure Lab tested if two forms of the protein (proteosome resistant and degradable) may constitute a better prime or boost. Indeed, this turned out to be the case.

This research provides a great example of collaboration between industry and academia as well as international scientific partnerships. Scientists from Cure Lab are co-authors on this paper with researchers from Boston University, and the Ivanovsky Institute of Virology in Moscow, Russia.

Source: Cure Lab, Inc.