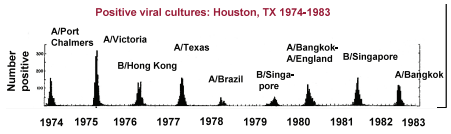
A Candidate Universal Vaccine for Control of Rapidly Emerging, Highly Virulent Influenza Viruses

The striking effectiveness of this vaccine in mice suggests that it is a candidate vaccine for emergency use during an influenza pandemic. It could be prepared in advance rather than hurriedly in response to events, since its design does not depend upon strain identification.

Novel Influenza Viruses Can Pose Serious Threats to Public Health

The sudden appearance of a novel influenza virus poses a potentially serious threat to public health, especially if the virus is highly virulent or spreads quickly among humans, most of whom will have no immunity to the novel virus. CBER researchers and their colleagues at the Centers for Disease Control and Prevention (CDC) are investigating a universal influenza vaccine that can be stockpiled for use during a sudden outbreak of a novel influenza virus. This universal vaccine would reduce illness and death until a strain-matched vaccine against the emerging virus was available.

Seasonal Influenza: Not the same virus every year



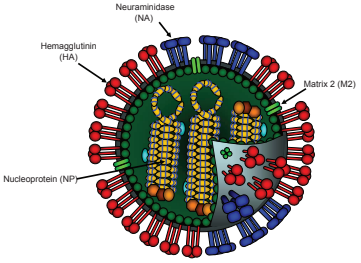
Edwin Kilbourne, Influenza, 1987, p. 289, with permission

Problem: Yearly strain changes of influenza virus require the development of new influenza vaccines each season. Development of a new vaccine each season takes six months, a delay during which new strains can spread.

Solution: A "universal" vaccine that provides significant protection against any influenza strain until a specific vaccine is ready.

Improving Immune Response by Taking Aim at Stable Targets

Seasonal vaccines target the influenza virus surface proteins HA and NA. The three most widely circulating (and disease-causing) influenza viruses worldwide each flu season are represented by their own specific HA and NA proteins in that year's influenza vaccine. But HA and NA proteins are highly variable among influenza viruses, so no one vaccine is sufficient to protect against all of them. Instead of using the variable HA and NA proteins, the CBER/CDC researchers developed a vaccine based on the surface protein M2 and the interior protein NP. These proteins are relatively stable targets, similar in all influenza A viruses and subject to only very slow mutation. These properties make them ideal targets for a universal influenza vaccine.



Seasonal vaccines against influenza viruses are based on the highly variable surface protiens HA and NA. A universal, off-the-shelf vaccine would target relatively stable proteins, such as NP and M2.

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Single-Dose Mucosal Immunization with a Candidate Universal Vaccine Provides Rapid Protection from Virulent H5N1, H3N2 and H1N1 Viruses

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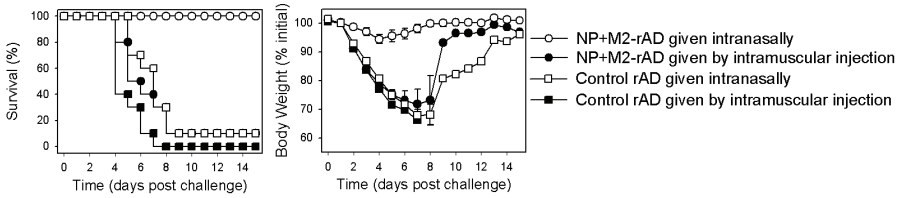
Nasal Vaccine: Putting Protection at the Site of Infection

The CBER/CDC team demonstrated that a single nasal (mucosal) administration of NP- and M2-expressing rAD vectors (adenovirus genetically modified to produce these stable influenza virus proteins) triggered rapid and lasting protection from highly virulent H3N2, H1N1 , and H5N1 ("bird flu") influenza viruses. This type of immunity, called heterosubtypic immunity, did not prevent infection, but it did demonstrate several important advantages in the animal model: 1) reduced signs of disease; 2) reduced mortality; 3) reduced the amount of virus in the lung leading to faster elimination of influenza viruses; 4) protection as early as two weeks after immunization and lasting at least 10 months; and 5) activation in the lungs of T-cells (cellular immunity), which participate in clearing virus.



Intranasal immunization with NP and M2 rAD protects mice from lethal influenza virus challenge. Mice were immunized intranasally or intramuscularly with NP and M2 rAD or with a control rAD expressing an irrelevant protein, and challenged with 100 LD_{50} of a highly virulent H1N1 influenza virus 3 weeks later. Mice immunized with the control rAD or NP and M2 rAD given intramuscularly lost significant weight and succumbed to infection. However, all of the mice immunized with NP and M2 rAD intranasally (open circles) lost little weight and survived the infection

The success of this vaccine in generating antibodies and T cells following nasal administration is a proof-of-concept. If comparable quick onset, long-term protection is induced in humans, such a vaccine could greatly reduce lung infection, virus spread, and the illness and mortality due to serious disease.