

# Broadband Influenza Vaccine PEV8

Current influenza vaccines are based on the genetically variable hemagglutinin antigen. The protection mediated by these vaccines is restricted to the virus strains included in the vaccine. As a consequence, the vaccine composition has to be updated annually to match the circulating virus strains. Pevion Biotech is developing a broadband influenza vaccine aimed at overcoming these weaknesses by including an additional viral component which is highly conserved among strains from season to season. Formulated on the market-approved virosomes, this component showed excellent results in preclinical tests and achieved proof of concept in animals.

## MEDICAL NEED

Influenza is one of the main viral diseases in humans. Influenza virus typically infects 10-20% of the total global population during seasonal epidemics, resulting in 3-5 million cases of severe illness and 250,000-500,000 deaths per year. Vaccination is the most effective measure to prevent influenza disease and provides an overall protection rate of about 85%. However, all current influenza vaccines are based on the envelope proteins hemagglutinin (HA) and neuraminidase (NA) and thus, their protective effect is restricted to the virus strains included in the vaccine. At the same time, influenza viruses continuously change their antigenic properties, thereby evading both natural and vaccine-induced immunity and protection. As a consequence, good protection is only achievable by yearly immunization with a vaccine adapted in its composition to match the circulating strains. Every year the WHO defines three strains, which are then included in the seasonal trivalent influenza vaccines (TIV) by multiple manufacturers.

## RATIONALE FOR VACCINE DESIGN

A broad spectrum influenza vaccine which protects independently of its match with the circulating virus strains may be more attractive than current vaccines and may thereby contribute to an increased use of an influenza vaccine. In addition, such a vaccine may be considered for stockpiling as a precaution against new influenza pandemics.

The influenza A M2 protein and especially its ectodomain (M2e) have been extensively studied as candidate broadband vaccines. In humans, antibodies against M2e are inconsistently induced by natural infection and not at all by current inactivated vaccines. However, such antibodies exhibit significant protective activity against influenza A strains in animal models.

Since the peptide itself is a very weak immunogen, a number of approaches have been developed to enhance the antibody response to M2e including fusion with various proteins, coupling to carrier proteins and delivery in viral vectors or in virus-like particles. In almost all cases these vaccines protected mice against a lethal challenge by a mouse-adapted influenza strain. However, experimental M2e vaccines did not mediate a sterile immunity but reduced morbidity, suggesting that they may be inadequate as a stand-alone vaccine.

Pevion Biotech aims at developing a tetravalent influenza vaccine which contains a virosome-formulated M2e component in addition to an established trivalent vaccine. The use of a synthetic peptide antigen is a fast and cost-efficient approach. However, it requires proper presentation by a suitable

### Key advantages of Pevion Biotech's broadband influenza vaccine

- Broader protection range of tetravalent vaccine in comparison to marketed trivalent vaccines, especially against heterologous influenza A strains, including emerging pandemic strains
- Demonstrated efficacy of carrier & adjuvant system for high-quality antibody responses to small peptide antigens
- Market-approved safety and local tolerability of carrier & adjuvant system, especially in elderly people and other vulnerable populations
- Established GMP manufacturing on a commercial scale
- No requirement of cold chain and long shelf life due to option of lyophilized vaccine form

vaccine platform in order to elicit a relevant immune response. Pevion Biotech's virosome technology responds extremely well to the combined needs of a designed peptide antigen such as M2e and its use in vulnerable populations. It is therefore a prime candidate platform for the development of an M2e-based vaccine.

Using a market-approved technology allows fast development at reduced risk. In addition, combination of the M2e component with pandemic strains such as the 2005 H5N1 (avian) or the 2009 H1N1 (swine) strains is possible and represents opportunities for the vaccine's further life cycle management. Moreover, Pevion Biotech has developed a proprietary process which allows lyophilizing the vaccine (i.e. a dry storage form), offering the option for an extended shelf life.

The M2e component is based on a repeat configuration of the M2e peptide. Several configurations were screened for immunogenicity in mice and for robustness in synthesis. In addition, sera from immunized animals were assayed for their ability to inhibit binding of the protective monoclonal anti-M2e antibody 14C2. Thereupon, a tandem repeat with N-terminal lipid anchor for formulation with the virosomes was chosen for further development.

## VACCINE PROFILE

Pevion Biotech is developing a state-of-the-art tetravalent influenza vaccine (PEV8) for elderly people >60 years of age, who have a particular safety and efficacy demand, and healthy adults. The primary goal is to confer superior protection against heterologous influenza A strains, compared to a conventional trivalent vaccine. In addition, an improved protection against the homologous influenza A strains is expected. The secondary goal is to achieve a superior local tolerability profile compared to adjuvanted trivalent vaccines, which also claim broader protection. In a later stage of development, indication of the vaccine may be extended to infants, children, and chronically ill or immunocompromised individuals, i.e. to vulnerable subpopulations with similar needs.

In a first stage, Pevion Biotech is focusing on the development of the M2e peptide component of PEV8 and demonstrating its protective potential. The final product is planned to be a tetravalent influenza vaccine including the M2e component on virosomes and classical trivalent components that are based on the three seasonal, WHO-defined influenza strains. The M2e component of PEV8 is suited to be combined with any kind of trivalent vaccine, because the virosomes are the only adjuvant included in the vaccine. This is in sharp contrast to most of the M2e-based vaccines currently in development, which require the addition of alum salts or even combinations of adjuvants to achieve sufficient immunogenicity. The use of these adjuvants virtually excludes their combination with market-approved TIV, because the vast majority of the currently used trivalent influenza vaccines do not contain any adjuvants, except for those intended for elderly individuals or pandemic vaccines.

Therefore, the virosome-based M2e component is unique in that it is readily compatible with any TIV. The combination with virosome-formulated trivalent influenza vaccine would be an ideal match and could be easily incorporated into the development pathway. The final tetravalent vaccine will be produced in either liquid or lyophilized form according to specific market requirements. The product is suited for combination with Pevion Biotech's RSV vaccine candidate (PEV4).

## EXCELLENT PRECLINICAL RESULTS

Results from preclinical studies with Pevion Biotech's influenza vaccine candidate (PEV8) in mice are very promising. The vaccine was able to confer 100% protection against a lethal influenza challenge (see figure below). The viral load in lungs of immunized animals was significantly reduced, as was

disease severity and duration. The protective effect of the vaccine exceeded the effect of the treatment with monoclonal anti-M2e antibody 14C2 and clearly added to the immunity conferred by the HA and NA-based component. The latter aspect is essential, since the M2e component is intended to broaden the protective range of a classical TIV vaccine based on the envelope antigens.

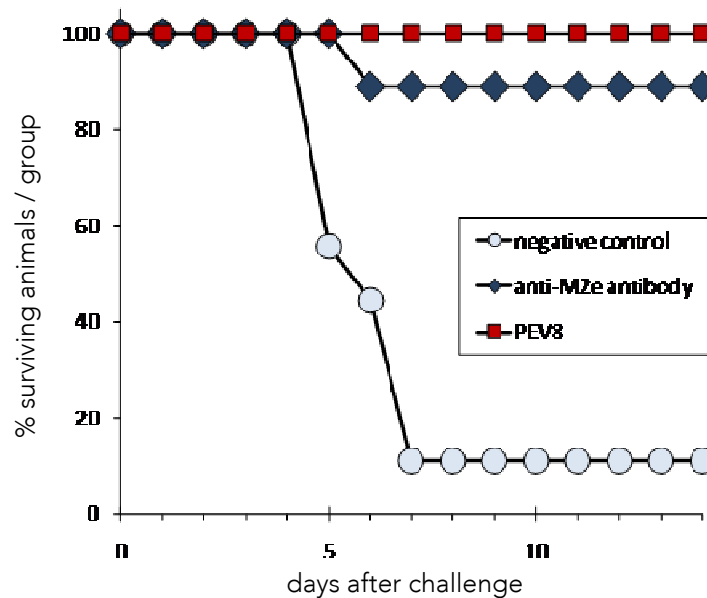


Figure: Challenge study in mice. Mice were immunized with the broadband (M2e) component of the tetravalent vaccine (PEV8) and then challenged with a lethal dose of influenza virus. Immunized mice were protected and showed 100% survival, whereas only 11% of unvaccinated mice survived (negative control). A third group of animals, which received a passive immunization with a monoclonal antibody against M2e, given immediately before challenge, showed 89% survival.

In summary, the key findings are as follows:

- Immunization with PEV8 elicited anti-M2e antibody levels higher than the protective level of monoclonal anti-M2e antibody
- Animals immunized with PEV8 showed 100% survival after a lethal challenge with influenza virus
- The viral load in the lungs of animals immunized with PEV8 was significantly reduced as compared to unvaccinated animals
- Animals immunized with PEV8 developed disease, but in milder form and of shorter duration than unvaccinated controls

#### DEVELOPMENT STATUS

Currently, the M2e component is in late preclinical development. Proof of concept in an animal model has been achieved and will be confirmed with additional challenge studies in ferrets, which will commence in April 2010. The GMP manufacturing process of the vaccine has been established. The production of GMP vaccine and toxicology studies are planned for H2 2010. Pevion Biotech expects to enter a first clinical trial in early 2011. The company plans to conduct a combined clinical phase I/II study in healthy volunteers with a controlled virus challenge. The combined study design will enable rapid achievement of proof of concept in humans.

## IP SITUATION

Pevion Biotech has a complete patent portfolio of virosomes covering all aspects and applications of the virosome technology platform.

## SELECTED REFERENCES

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