

## Overview

Researchers at Wake Forest University School of Medicine have developed, manufactured and tested a number of new vaccines based on a platform of flagellin as an adjuvant and carrier of a range of protein antigens. Flagellin fusion protein vaccines against plague, *Pseudomonas aeruginosa*, drugs of abuse/addiction, cancer and pneumococcus efficiently elicit significant protective immune responses in animal models and are simple to make using recombinant DNA techniques. This new approach of using the proven adjuvant flagellin as an antigen carrier provides highly potent and cost-effective vaccines and is a versatile platform for developing multiple preventive and therapeutic vaccines.

## Plague vaccine (Patents issued)

Pneumonic plague is a rapidly progressing disease with a mortality rate approaching 100%. To date, there is no licensed vaccine for plague that is effective against the pneumonic form of the disease. Our plague vaccine is a safe alternative using a fusion protein which comprises flagellin and the F1- and V-antigens of *Yersinia pestis*.

Highlights:

- Phase 1 clinical trial will commence in first quarter of 2012.
- Vaccine is equally effective when given intranasally or intramuscularly to non-human primates and does not elicit any adverse reactions, providing multiple safe routes of administration.
- Vaccine elicits sterile immunity in mice challenged with *Y. pestis*, i.e. the vaccine promotes complete bacterial clearance.
- Vaccine is dramatically more potent than other plague vaccines, i.e. less vaccine is required to elicit a protective immune response, resulting in cost-effective treatment and production.
- GMP manufactured vaccine has a stability of over 10 months at 4°C, providing a shelf-stable vaccine.

## *Pseudomonas aeruginosa* vaccine (Patent pending)

There is currently no approved vaccine for *P. aeruginosa*, a major cause of morbidity and mortality in Cystic Fibrosis patients and ventilated patients (>\$1.5B market). Our vaccine targets this unmet need by producing a robust immune response using a fusion protein of flagellin and the OprI and OprF antigens.

Highlights:

- Vaccine produces a protective immune response in young African green monkeys and a dramatically enhanced *P. aeruginosa* clearance in mice with no lung damage.
- Multivalency of the vaccine creates a synergistic effect, giving an improved immunogenic response and better vaccine coverage compared to other *P. aeruginosa* vaccines in development.
- Vaccine is highly potent, resulting in efficacious low-dose vaccine formulations that are cost-effective to produce.

## Drugs of abuse vaccine (Patent pending)

Drug abuse is a global health problem. In the US alone, abuse of illicit drugs affects 9 % of the population and nicotine addiction affects 20 % of the population. Vaccine therapy has emerged as a promising tool for combating drug abuse (>\$1B market). However, current strategies need a large number of immunizations, large amounts of material and result in rapid decline in antibody titers. In contrast, a vaccine comprised of a drug-flagellin conjugate may promote long-lasting high levels of antibody production with small amounts of material, due to the powerful adjuvant activity of flagellin.

Highlights:

- Flagellin-cocaine conjugate vaccine has been constructed and is being tested *in vivo*.

## Cancer vaccine (Patent pending)

The cancer vaccine market (>\$500M) is a growing market with great opportunities for entry. Approximately 1.5 million Americans are being diagnosed with cancer annually, and an efficient treatment strategy is non-existing for many types of cancers. Our flagellin-based vaccine technology is a potential platform technology that may provide a preventive or treatment option for many of these cancers.

Highlights:

- Breast cancer vaccine, consisting of a fusion protein of flagellin and the Fra-1 antigen, elicits reduced tumor growth in mice.
- Vaccine is selective for breast cancer cells and not invasive, as compared to standard therapy such as surgery, radiation therapy and chemotherapy, which may lead to safer cancer treatment strategies.
- Any cancer antigen can be incorporated into the flagellin fusion protein, giving prospects of developing various cancer vaccine treatments and having a substantial market share.
- On-going research at Wake Forest is examining the effect of incorporating other cancer antigens into the fusion protein vaccine.

## Pneumococcal vaccine (Patent pending)

The incidence of pneumococcal disease is on the rise because current vaccines do not confer adequate protection against pneumococcal serotypes causing this disease. In fact, available vaccines fail to cover 10-15% of the pneumococcal serotypes responsible for pneumococcal disease, and as a result, an estimated 175,000 patients are hospitalized with pneumonia each year in the US alone. Our pneumococcal vaccine consisting of a fusion protein of flagellin and various *pspA* antigens is likely to have greater breadth of protection than the existing vaccines, resulting in better prevention of disease. Currently, the vaccine has been observed to induce a robust immune response in mice. (Market >\$3B)

## Additional Information

- US7,794,731: USE OF FLAGELLIN IN THE IMMUNOTHERAPY OF YERSINIA PESTIS
- WO2010107778: FLAGELLIN FUSION PROTEINS AND USE THEREOF TO INDUCE IMMUNE RESPONSES AGAINST PSEUDOMONAS AERUGINOSA
- WO2011028875: IMMUNOGENIC CONJUGATES FOR PRODUCING IMMUNE RESPONSES TO DRUGS OF ABUSE AND METHODS OF USE
- US20080220011A1: USE OF FLAGELLIN IN TUMOR IMMUNOTHERAPY
- WO2010141312: FLAGELLIN FUSION PROTEINS AND CONJUGATES COMPRISING PNEUMOCOCCUS ANTIGENS AND METHODS OF USING THE SAME
- Mizel SB et al. Flagellin-F1-V fusion protein is an effective plague vaccine in mice and two species of nonhuman primates. Clin Vaccine Immunol. 2009; 16(1):21-8.
- Weimer ET et al. Immunization of young African green monkeys with OprF epitope 8-OprI-type A- and B-flagellin fusion proteins promotes the production of protective antibodies against nonmucoid Pseudomonas aeruginosa. Vaccine. 2009; 27(48):6762-9.
- Weimer ET et al. A fusion protein vaccine containing OprF epitope 8, OprI, and type A and B flagellins promotes enhanced clearance of nonmucoid Pseudomonas aeruginosa. Infect Immun. 2009;77(6):2356-66.