

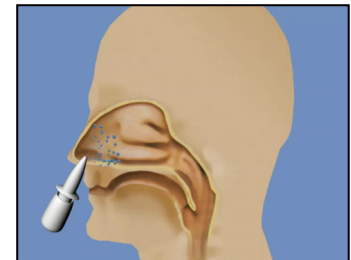
deltaFLU Genetically Attenuated Influenza Vaccine Clinical-Stage Influenza Vaccine for Greater Efficacy and Broad Cross-Protection

Vivaldi Biosciences Inc. is developing its deltaFLU influenza vaccine to provide greater efficacy and broad cross-protection against multiple influenza strains. Vaccination is the primary means of preventing influenza infections and their spread, but conventional influenza vaccines (“flu shots”) are only moderately effective when well matched to circulating influenza strains. These vaccines are poorly effective (0-20%) when not matched to the circulating viruses, as is often the case.

All licensed flu shots aim to provide protection against influenza by stimulating serum antibodies to the neuraminidase (NA) and / or hemagglutinin (HA) surface proteins of the influenza strains from which they’re composed. Influenza viruses have a high rate of genetic mutation, causing changes in the HA and NA proteins that impede the immune system’s ability to recognize and defend against such “drifted” virus strains. These changes cause a mismatch between vaccine strains and circulating influenza viruses, leading to reduced or even negligible vaccine efficacy.

NS1 (nonstructural protein 1) is a virulence factor of influenza produced by the virus in infected cells to counter the host immune response. Vivaldi uses proprietary reverse genetics and plasmid rescue technologies to delete the gene encoding influenza NS1, generating vaccine strains that are safely attenuated, replication-deficient, and induce a more effective immune response, including broad cross-protection against variant influenza strains. Vivaldi has developed a high-efficiency, high-yield Vero cell production process for deltaFLU vaccines that is expected to provide significant advantages over traditional egg-substrate influenza vaccine manufacturing technologies in terms of speed, reliability, efficiency, and cost.

Nasal spray administration of deltaFLU elicits broadly cross-neutralizing antibodies in the nasal mucosa, generating a first line of defense directly at the point of entry of circulating viruses. deltaFLU also stimulates a robust systemic immune response. deltaFLU induces interferon, which acts as a natural adjuvant, activating the cellular immune response and enhancing production of antibodies. Thus deltaFLU generates a robust immune response from multiple components of the immune system, while flu shots rely only on a limited facet of the immune system – serum antibodies specific for certain proteins on selected vaccine strains. deltaFLU candidate vaccines for seasonal and pandemic influenza strains have been evaluated in a total of four Phase 1 and 2 clinical trials enrolling 245 healthy adults.



deltaFLU Target Product Profile

- Broadly cross-protective
- Replication-deficient
- Self-adjuvanting
- Nasal spray administration
- Broad licensure (all ages)
- Vero cell-based manufacture

The superior efficacy and broad-cross protection potential of deltaFLU vaccines is evident from completed preclinical and clinical studies that provided data enabling comparisons of deltaFLU with licensed vaccines evaluated in similar studies. A nonclinical study in ferrets is in progress providing a head-to-head comparison of deltaFLU with a leading licensed vaccine. Immunized ferrets will be challenged with matched (homologous) or unmatched (heterologous) influenza strains. This study is expected to indicate that deltaFLU is a superior vaccine approach that overcomes the problems of low efficacy and protection against unmatched strains.

Vivaldi's goal is to develop a deltaFLU influenza vaccine licensed for all age groups, including children as young as 6 months and elderly adults. Vivaldi has developed detailed plans for an 18-month Phase 2 program in the EU that will enroll adults and children. The pediatric segment presents unique unmet needs and strong near-term growth potential. Addressing the pediatric market with a safe and effective vaccine is a high priority for the pharmaceutical industry. The company plans to undertake late-stage development and commercialization through a partnership or license.

Seasonal influenza is a serious disease and a significant public health problem. Worldwide, one billion cases of seasonal influenza and up to 500,000 influenza-related deaths occur annually. Each year 5-20% of the US population contracts influenza, leading to as many as 226,000 hospitalizations and 36,000 deaths. Increased awareness of the need for vaccination against influenza, broader recommendations for vaccination, and aging populations are fueling growth in the world market for seasonal influenza vaccines, currently valued at \$5.6 billion.

Focus on Pediatric Influenza

- Children are the main reservoir and vector
- Incidence of influenza is >2x that of adults
- 90 million cases / year worldwide in children <5 years
- 20,000 hospitalizations / year in US children < 5 years
- Children < 2 years are at greatest risk of severe disease
- Recommendations for universal pediatric influenza immunization are increasing

Pandemic influenza is a relentless global public health threat. Three influenza pandemics in the 20th century caused over 50 million deaths in total. The 2009 H1N1 influenza pandemic led to over a quarter of a million deaths worldwide. An emergent strain with pandemic potential, influenza A(H7N9), has been reported in humans. The risk of a pandemic will be great if this strain acquires the ability for direct human-to-human transmission. Governments and international health organizations have placed a high priority and budgeted significant funding for development of vaccines for pandemic preparedness. Vivaldi successfully completed a Cooperative Research and Development Agreement (CRADA) with the National Institute of Allergy and Infectious Diseases for preclinical development of a vaccine candidate against H7N9. The company is seeking additional government support for clinical development of deltaFLU candidates for seasonal and pandemic influenza.

deltaFLU Advantages for Pandemic Preparedness

- Rapid response to emerging strains using reverse genetics and plasmid rescue
- Dose-sparing, without requiring adjuvant
- Nasal spray dosage form amenable to self-administration and mass use

Vivaldi's management team has significant experience in the pharmaceutical industry, and expertise in virology, immunology, and influenza vaccine development and production. Vivaldi's co-founders Drs. Peter Palese and Adolfo García-Sastre at the Icahn School of Medicine at Mount Sinai are pioneers in the fields of influenza genomics and NS1. They support Vivaldi on an ongoing basis as scientific advisors. The company has raised over \$34 million in institutional venture capital, led by NGN Capital. Vivaldi has operations in Fort Collins, Colorado; its European affiliate Vivaldi Biosciences AG is located in Vienna, Austria.

Management and Directors	Affiliations / Experience
William Wick, MBA, <i>CEO</i> Thomas Muster, PhD, <i>CSO</i> Manfred Reiter, PhD, <i>Vice President, Manufacturing</i> John Costantino, JD, <i>Chairman</i> Peter Johann, PhD, <i>Director</i> Douglass Given, MD, PhD, <i>Director</i>	Lumendi, Vision Capital, ZoZa, National City Corporation Blue Sky Vaccines, AVIR Green Hills Hookipa Biotech, Baxter Bioscience, Immuno AG NGN Capital, Walden, Conair, Touche Ross NGN Capital, Boehringer Ingelheim, Hoffmann-LaRoche Health2047, Bay City Capital, Mallinckrodt, Lilly, GD Searle