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**Live Attenuated Influenza Vaccines Using the Biology of NS1**

**Vivaldi Biosciences Inc.** is developing live attenuated influenza vaccines (LAIVs) to address the most pressing public health issues of influenza – the need for vaccines that provide greater protection for children and seniors against seasonal influenza, and the need for a rapid and effective response to emerging pandemics with vaccines that are easily administered, safe, and protective. Vivaldi's LAIV technology platform provides a new vaccine approach with the potential for superior safety, efficacy, and broad cross-protection. Vivaldi's strategy is to demonstrate this potential in early clinical studies, and pursue further development by partnering with leading pharmaceutical companies.

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

**Nonstructural Protein 1**

**Nasal spray administration** of Vivaldi's LAIVs elicits an immune response in the nasal passages, generating a first line of defense at the natural point of entry of circulating viruses, and a robust systemic immune response. Vivaldi's LAIVs stimulate the body's production of interferon, which acts as a natural adjuvant, activating the cellular immune response and enhancing production of antibodies, including neutralizing antibodies cross-reactive with variant or drifted influenza strains.

**Four completed clinical studies** demonstrate safety and efficacy of deltaFLU, Vivaldi's lead LAIV candidate. deltaFLU LAIVs are composed of attenuated vaccine strains with fully deleted NS1. deltaFLU LAIVs for 5 different influenza strains including H5N1 ("bird flu") have been evaluated in randomized, double-blind, placebo-controlled clinical trials enrolling a total of 245 healthy adult volunteers. Vivaldi plans to undertake a Phase 2 study of a monovalent deltaFLU LAIV in healthy adult volunteers challenged with a heterologous (mismatched) influenza strain. Vivaldi also is planning a Phase 2 study of deltaFLU Quadrivalent LAIV for seasonal influenza in children 6 months to 11 years of age. Subsequent studies will evaluate deltaFLU Quadrivalent in older age groups.

**deltaFLU Quadrivalent LAIV Target Product Profile**

- Broad age range
- Cross-protective
- Replication-deficient
- Adjuvant-free
- Preservative-free
- Single dose
- Nasal spray administration
- Sterile, pre-filled spray device
- Vero cell-based manufacture

**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, between 5% and 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 double-digit growth in the world market for seasonal influenza vaccines, valued at $5.5 billion.

Elderly adults and young children are the most vulnerable to seasonal influenza and its serious complications. However, these age groups are poorly served by conventional inactivated influenza vaccines. Conventional vaccines ("flu shots") show only modest efficacy in the pediatric population and inadequate efficacy in seniors. The licensed LAIV shows good efficacy in the pediatric population, but is not licensed for children younger than 2 years of age or adults older than 49 years.

**Focus on Pediatric Influenza**

- Children are the main reservoir and vector
- Incidence of influenza is more than twice that of adults
- 90 million cases / year worldwide in children younger than 5 years
- 20,000 hospitalizations / year in US in children younger than 5 years
- Children younger than 2 years at greatest risk of severe disease

**Pandemic influenza** is a relentless global public health threat. A pandemic may occur when an influenza virus undergoes genetic changes that enable human infection and direct human-to-human transmission. 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), initially was reported to cause disease in humans in 2013. 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 LAIV candidate against H7N9. The company is seeking additional government support for clinical development of LAIV candidates for seasonal and pandemic influenza.

**Vivaldi LAIV Technology for Pandemic Preparedness**

- Rapid response to emerging strains using proprietary reverse genetics and plasmid rescue
- Dose-sparing, without requiring adjuvant; potential protection with a single dose in naïve subjects
- Nasal spray dosage form amenable to self-administration and mass use

**Vivaldi's patent portfolio** provides exclusivity and broad freedom to operate using reverse genetics and plasmid rescue technologies for development and manufacturing of LAIVs with modifications of NS1, including exclusivity on issued patents covering LAIVs with intermediate and full deletions of NS1, and manufacturing methods in interferon-deficient substrates.

**Vivaldi's management team** and advisors have significant experience in the pharmaceutical industry, and expertise in virology, immunology, and influenza vaccine development and production. Company founders Drs. Peter Palese and Adolfo García-Sastre at the Icahn School of Medicine at Mount Sinai, and Dr. Elliott Kieff of Harvard Medical School, provide ongoing technology leadership and expert advice. Vivaldi has raised over $32 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 |
|---|---|
| Douglass Given, MD, PhD, MBA, *President, CEO, Chairman* | Bay City Capital, Mallinckrodt, Schering Plough, Monsanto |
| William Wick, MBA, *COO* & *CFO* | Vision Capital, ZoZa, National City Corporation |
| Thomas Muster, PhD, *CSO* | Blue Sky Vaccines, AVIR Green Hills |
| Manfred Reiter, PhD, *Vice President, Manufacturing* | Hookipa Biotech, Baxter Bioscience, Immuno AG |
| Peter Johann, PhD, *Director* | NGN Capital, Boehringer Ingelheim, Hoffmann-LaRoche |
| John Costantino, JD, *Director* | NGN Capital, Walden, Conair, Touche Ross |
| **Scientific Founders and Advisors** | **Affiliations** |
| Peter Palese, PhD, *Scientific Founder, Advisor* | Icahn School of Medicine at Mount Sinai |
| Elliott Kieff, MD, PhD, *Scientific Founder, Advisor* | Icahn School of Medicine at Mount Sinai |
| Adolfo García-Sastre, PhD, *Scientific Founder, Advisor* | Brigham & Women's Hospital, Harvard Medical School |

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