Vivaldi Biosciences

Bellevue Hospital Center
462 First Avenue
Building A, 9th Floor
New York, New York 10016
Tel: 646-381-6680

Research Innovation Center
3185-A Rampart Road
Campus Delivery 0922
Fort Collins, Colorado 80521
Tel: 970-492-4365

www.vivaldibiosciences.com

Live Attenuated Influenza Vaccines Using the Biology of NS1

Vivaldi Biosciences Inc. is developing live attenuated influenza vaccines (LAIVs) that address the most pressing public health issues of influenza – the need for a vaccine for seasonal influenza that protects older individuals, and a means of rapid response to an emerging pandemic with fast, efficient production of vaccines that are easily administered and effective with a single, small dose.

NS1 (nonstructural protein 1) is a key virulence factor of influenza produced by the virus in infected cells to evade the host immune response. Using proprietary reverse genetics and plasmid rescue technologies, Vivaldi scientists have engineered a precise, stable deletion in a section of the gene encoding influenza NS1, generating a LAIV strain with the requisite balance of potent immunogenicity and safety. Vivaldi is using this master NS1-attenuated LAIV strain to develop vaccines that provide greater protection for the elderly against seasonal influenza, and vaccines to address the need for pandemic preparedness.

NS1 Protein

Vivaldi's NS1-Attenuated LAIVs

- Genetically modified for attenuation and safety
- Antigens delivered in their native state
- Strong local interferon response, for potent protection, without replication, without adjuvants
- Mucosal and systemic immunity; antibody and cell-based
- Cross-protection against drifted / unmatched strains
- Single, low-dose nasal spray administration (needle-free)
- Highly efficient production feasible on egg and cell-based commercial platforms

NS1-attenuated LAIVs have a unique mode of action that confers potent, protective immunity without viral replication, and without the need for adjuvants. Vivaldi's NS1-attenuated LAIVs stimulate the body's production of interferon, which acts as a natural adjuvant, enhancing antibody production and activating the cellular immune response. This robust immune response has been demonstrated in animal models to protect against matched and unmatched influenza strains, indicating the potential for broad cross-protection. NS1-attenuated LAIVs are administered as a single-dose nasal spray, eliciting an immune response in the nasal passages as a first line of defense at the natural point of entry of circulating viruses, and a strong, durable systemic immune response.

Vivaldi has demonstrated efficient manufacturing of its NS1-attenuated LAIVs with industry-established egg substrate technology, which provides cost and yield advantages in live vaccine production. The company also has demonstrated manufacturing feasibility on Vero and MDCK cells, addressing strategic and evolving commercial needs. Vivaldi is preparing to file an Investigational New Drug (IND) application and begin clinical testing of its lead candidate for seasonal influenza. Vivaldi also is planning a clinical development program for its NS1-attenuated LAIV for pandemic influenza.

Seasonal influenza ("flu") is a serious viral disease and significant public health problem. Worldwide, one billion cases of seasonal influenza and up to 500,000 influenza-related deaths occur annually. In the US, influenza and pneumonia together are the 8th leading cause of death. 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 $4 billion.

Elderly Market Focus

- Standard flu vaccines are less effective or not approved for adults ≥ age 49
- Efficacy of widely used trivalent inactivated vaccines is reduced up to 50% in elderly
- Influenza + pneumonia are the 6th leading cause of death among individuals ≥ age 65
- Adults in the US ≥ age 65:
  - Account for > 90% of flu-related deaths
  - Have the highest vaccination rate
  - Are the fastest-growing age group

The elderly suffer disproportionately from influenza, accounting for over 90% of influenza-related deaths annually. Adults age 65 and older are poorly protected by conventional vaccines. Efficacy of conventional trivalent inactivated vaccines is reduced as much as 50% in this age group due to the weakened immune system of older adults. Vivaldi's NS1-attenuated LAIV is positioned to address the major unmet medical need and commercial opportunity for a more potent influenza vaccine providing greater protection in the elderly.

Pandemic influenza, occurring when a novel strain such as H1N1 or H5N1 emerges, is a real and significant threat, requiring a rapid response with a specific monovalent vaccine. Governments have placed a high priority and budgeted significant funding to meet this need, though vaccines developed to date are inadequate. Vivaldi's NS1-attenuated LAIV technology is uniquely suited to addressing the pandemic threat. Advances in development and production of the NS1-attenuated LAIV for seasonal influenza provide synergies in Vivaldi's pandemic program. The company is seeking government funding for its pandemic program, and has a biosafety level 3 (BSL-3) facility for development and production of NS1-attenuated LAIVs for pandemic strains.

Vivaldi's patent portfolio provides exclusivity and broad freedom to operate using reverse genetics and plasmid rescue technologies for development and manufacturing methods for viruses with modifications of NS1. Vivaldi has exclusive rights to issued patents covering NS1-attenuated vaccines based on partial or intermediate deletions of NS1, and co-exclusivity on compositions with fully-deleted NS1. Vivaldi has rights in the US and major international markets to more than 25 issued patents in the fields of NS1-attenuated vaccines and cell substrates for LAIV production.

NS1-Attenuated LAIVs 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
- Cell-based manufacturing

Vivaldi's management team has significant experience in the pharmaceutical industry, and expertise in virology, immunology, and vaccine development and production. The company was founded by preeminent virologists, Drs. Peter Palese and Adolfo García-Sastre of Mount Sinai School of Medicine, and Dr. Elliott Kieff of Harvard Medical School, who provide ongoing technology leadership and expert advice. Vivaldi's investors, led by Bay City Capital and NGN Capital, have provided the company with $26 million through a Series A financing.

Management and Directors	Affiliations / Experience
Douglass Given, MD, PhD, MBA, *President & CEO, Director*	Bay City Capital, Mallinckrodt, Schering Plough, Monsanto
David Liebowitz, MD, PhD, *CSO*	Amgen, Immunex, Univ. of Pennsylvania, Univ. of Chicago
William Wick, MBA, *CFO*	Vision Capital, ZoZa, National City Corporation
Brendan Rae, PhD, JD, *CBO (Consulting)*	VIA Pharmaceuticals, Purdue Pharma, Hoffman-LaRoche
Bin Lu, PhD, *Vice President, R&D*	MedImmune / AstraZeneca
Peter Johann, PhD, *Director*	NGN Capital, Boehringer Ingelheim, Hoffmann-LaRoche
William Gerber, MD, *Director*	Bay City Capital, Epoch, DiaDexus, Onyx, Chiron, Cetus
Georg Nebgen, PhD, *Director*	NGN Capital, MPM Capital, Schering-Plough
Victor Schmitt, MBA *Director*	Bay City Capital, Baxter Healthcare
Scientific Founders and Advisors	**Affiliation**
Peter Palese, PhD, *Scientific Founder, Advisor*	Mount Sinai School of Medicine
Elliott Kieff, MD, PhD, *Scientific Founder, Advisor*	Brigham & Women's Hospital, Harvard Medical School
Adolfo García-Sastre, PhD, *Scientific Founder, Advisor*	Mount Sinai School of Medicine
Robert Belshe, MD, *Advisor*	St. Louis University School of Medicine
Ann Arvin, MD, *Advisor*	Stanford University School of Medicine
Paul Mendelman, *MD, Advisor*	LigoCyte Pharmaceuticals