

3. Rationale for FuMist Development

3. RATIONALE FOR FLUMIST DEVELOPMENT

Vaccination with FluMist mimics the natural immunobiology of influenza. This is accomplished by administering the cold-adapted, live, attenuated vaccine to the nasal mucosa via large particle aerosol in the form of a nasal mist. FluMist induces both serum and mucosal antibodies. Thus, immunity should be comparable to natural infection. In addition, the delivery of FluMist via intranasal spray rather than by injection may increase compliance with vaccination and lead to enhanced utilization of vaccine.

FluMist is based on the cold-adapted master donor strains derived by Dr. H.F. Maassab at the University of Michigan, and cold-adapted vaccine candidates (CAIV) have been tested since 1976 in clinical trials sponsored by the National Institutes of Health (NIH). In those trials, monovalent and bivalent Type A vaccine, monovalent Type B vaccine, and trivalent vaccine was administered to more than 8,000 subjects whose ages ranged from 2 months to more than 100 years. In 1995, Aviron signed a Cooperative Research and Development Agreement (CRADA) with the National Institute of Allergy and Infectious Diseases (NIAID) and a licensing agreement with the University of Michigan to develop a commercial vaccine based on the Maassab master donor strains (cold-adapted A/Ann Arbor/6/60 and cold-adapted B/Ann Arbor/1/66).

Master donor virus (MDV) strains were derived by serial passage of influenza viruses at successively lower temperatures to generate strains that would replicate efficiently at 25°C, a temperature that was restrictive for the replication of the wild-type parental viruses. These virus strains are cold-adapted (replicate efficiently at 25°C), temperature sensitive (growth is restricted at 37°C for the Type B and 39°C for the Type A strains), and attenuated in ferrets. The influenza A and B master donor strains developed by Dr. Maassab are stable donors of attenuating genes for the production of live influenza virus vaccine candidates.

To generate and select a live, attenuated, cold-adapted, reassortant virus vaccine strain, reassortant viruses are produced from the Maassab master donor strains, A/Ann Arbor/6/60 or B/Ann Arbor/1/66, and newly emergent virulent wild-type virus strains. Reassortant viruses are selected that contain the six internal genes from the cold-adapted master donor strain and the genes for the two protective antigens, the hemagglutinin and neuraminidase surface glycoproteins, from the wild-type virus. These live, attenuated, reassortant viruses are referred to as 6:2 reassortants. Like the MDV strains, the 6:2 reassortants retain the cold-adapted (*ca*) phenotype, that is, they replicate at 25°C to a titer that is within 100-fold of the titer at 33°C. The two additional phenotypes of the MDV strains are also retained by the 6:2 reassortants:

temperature sensitivity (*ts*), which limits replication at higher temperatures and attenuation (*att*), which limits replication in the lungs of ferrets. In summary, for 6:2 reassortants, the hemagglutinin and neuraminidase genes define the vaccine antigenicity and the remaining six genes encoding internal viral proteins are responsible for the *ca*, *ts*, and *att* phenotype.