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Recombinant Newcastle disease viruses and uses thereof for the prevention of RSV disease or human metapneumovirus disease

Abstract

Described herein are recombinant Newcastle disease viruses ("NDVs") comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a respiratory syncytial virus ("RSV") F protein or human metapneumovirus ("hMPV") F protein. Also described herein are recombinant NDVs comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises (i) an RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains; or (ii) an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. The recombinant NDVs and compositions thereof are useful for the immunizing against RSV or hMPV as well as the prevention of RSV disease or hMPV disease.

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Background/Summary

(1) This application is a U.S. National Stage Application under 35 U.S.C. § 371 of International Patent Application No. PCT/US2019/046837, filed Aug. 16, 2019, which claims the benefit of U.S. Provisional Patent Application No. 62/765,242, filed Aug. 17, 2018, the disclosure of each of which is incorporated by reference herein in its entirety. (2) The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on Jul. 31, 2019, is named 6923-280-228_SL.txt and is 375,809 bytes in size.

1. INTRODUCTION

(1) In one aspect, described herein are recombinant Newcastle disease virus (“NDV”) comprising a packaged genome, wherein the packaged genome comprises a transgene encoding respiratory syncytial virus (“RSV”) F protein. In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding RSV F protein. In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In some embodiments, the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence. Also described herein are compositions comprising such recombinant NDV and the use of such recombinant NDV to induce an immune response to RSV F protein. In another aspect, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding human metapneumovirus (hMPV) F protein. In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding hMPV F protein. In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a

transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In some embodiments, the ectodomain of the hMPV F protein is encoded by a codon optimized nucleic acid sequence. Also described herein are compositions comprising such recombinant NDV and the use of such recombinant NDV to induce an immune response to hMPV F protein.

2. BACKGROUND

(2) 2.1 RSV

(3) Human respiratory syncytial virus (RSV), a negative sense RNA virus in the Pneumoviridae family (Afonso et al., 2016, Arch. Virol. 161: 2351-2360), is the major cause of bronchiolitis and pneumonia in infants (Hall C B, Long C E, Schnabel K C. Respiratory syncytial virus infections in previously healthy working adults. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 2001; 33(6):792-6. Epub 2001/08/21. doi: 10.1086/322657. PubMed PMID: 11512084; Paramore L C, Ciuryla V, Ciesla G, Liu L. Economic impact of respiratory syncytial virus-related illness in the US: an analysis of national databases. PharmacoEconomics. 2004; 22(5):275-84. Epub 2004/04/06. PubMed PMID: 15061677). RSV outbreaks occur on an annual basis and essentially all persons are infected within the first two years of life. While RSV infection is limited to the upper respiratory tract in most healthy adults and children, severe, even fatal, RSV pneumonia occurs in young infants 2 to 4 months of age, transplant recipients and the elderly (Hall et al.). Secondary RSV infections, which are generally limited to the upper respiratory tract, present with mild, cold-like symptoms in healthy adults, but are commonly associated with otitis media in young children (Alper C M, Winther B, Mandel E M, Hendley J O, Doyle W J. Rate of concurrent otitis media in upper respiratory tract infections with specific viruses. Archives of otolaryngology—head & neck surgery. 2009; 135(1):17-21. Epub 2009/01/21. doi: 10.1001/archotol.135.1.17. PubMed PMID: 19153302; Hall C B, Walsh E E, Long C E, Schnabel K C. Immunity to and frequency of reinfection with respiratory syncytial virus. The Journal of infectious diseases. 1991; 163(4):693-8. Epub 1991/04/01. PubMed PMID: 2010624; Simoes E A, Carbonell-Estrany X. Impact of severe disease caused by respiratory syncytial virus in children living in developed countries. The Pediatric infectious disease journal. 2003; 22(2 Suppl):S13-8; discussion S8-20. Epub 2003/04/03. doi: 10.1097/01.inf.0000053881.47279.d9. PubMed PMID: 12671448). In addition, RSV has been associated with the development of asthma, and exacerbation of wheezing in asthmatic patients (Korppi M, Piippo-Savolainen E, Korhonen K, Remes S. Respiratory morbidity 20 years after RSV infection in infancy. Pediatric pulmonology. 2004; 38(2):155-60. Epub 2004/06/24. doi: 10.1002/ppul.20058. PubMed PMID: 15211700; Pelaia G, Vatrella A, Gallelli L, Renda T, Cazzola M, Maselli R, et al. Respiratory infections and asthma. Respiratory medicine. 2006; 100(5):775-84. Epub 2005/11/18. doi: 10.1016/j.rmed.2005.08.025. PubMed PMID: 16289785; Sigurs N, Bjarnason R, Sigurbergsson F, Kjellman B. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. American journal of respiratory and critical care medicine. 2000; 161(5):1501-7. Epub 2000/05/12. PubMed PMID: 10806145; Sigurs N, Gustafsson P M, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. American journal of respiratory and critical care medicine. 2005; 171(2):137-41. Epub 2004/11/02. doi: 10.1164/rccm.200406-7300C. PubMed PMID: 15516534).

(4) Immunity to RSV is remarkably ineffective, allowing for repeated infection of immunocompetent children and adults (Buchman C A, Doyle W J, Pilcher O, Gentile D A, Skoner D P. Nasal and otologic effects of experimental respiratory syncytial virus infection in adults. American journal of otolaryngology. 2002; 23(2):70-5. Epub 2002/03/15. PubMed PMID: 1189397; Mills Jt, Van Kirk J E, Wright P F, Chanock R M. Experimental respiratory syncytial virus infection of adults. Possible mechanisms of resistance to infection and illness. Journal of immunology. 1971; 107(1):123-30. Epub 1971/07/01. PubMed PMID: 5091954; Habibi M S,

Jozwik A, Makris S, Dunning J, Paras A, DeVincenzo J P, et al. Impaired Antibody-mediated Protection and Defective IgA B-Cell Memory in Experimental Infection of Adults with Respiratory Syncytial Virus. American journal of respiratory and critical care medicine. 2015; 191(9):1040-9. doi: 10.1164/rccm.201412-22560C. PubMedPMID: 25730467; PubMed Central PMCID: PMCPMC4435460). Unlike other viral pathogens, serum antibody levels are very slow to rise following RSV infection, with a gradual accumulation of protective antibodies only after multiple re-infections (Wagner D K, Muelenaer P, Henderson F W, Snyder M H, Reimer C B, Walsh E E, et al. Serum immunoglobulin G antibody subclass response to respiratory syncytial virus F and G glycoproteins after first, second, and third infections. Journal of clinical microbiology. 1989; 27(3):589-92. Epub 1989/03/01. PubMed PMID: 2715331; PubMed Central PMCID: PMC267370; Welliver R C, Kaul T N, Putnam T I, Sun M, Riddlesberger K, Ogra P L. The antibody response to primary and secondary infection with respiratory syncytial virus: kinetics of class-specific responses. The Journal of pediatrics. 1980; 96(5):808-13. Epub 1980/05/01. PubMed PMID: 7365579). The inability of RSV to induce robust immunity following repeated natural infections likely underlies the difficulties encountered in attempts to design effective, attenuated vaccine strains (Crowe J E, Jr. Respiratory syncytial virus vaccine development. Vaccine. 2001; 20 Suppl 1:S32-7. Epub 2001/10/06. PubMed PMID: 11587807).

(5) A recent study suggests that the ability of RSV to re-infect immunocompetent adults is correlated with a defect in B cell memory. Neutralizing serum and nasal antibody levels in experimentally infected healthy adult volunteers increased post-infection, but returned to baseline levels 6 months later (Habibi M S, Jozwik A, Makris S, Dunning J, Paras A, DeVincenzo J P, et al. Impaired Antibody-mediated Protection and Defective IgA B-Cell Memory in Experimental Infection of Adults with Respiratory Syncytial Virus. American journal of respiratory and critical care medicine. 2015; 191(9):1040-9. doi: 10.1164/rccm.201412-22560C. PubMed PMID: 25730467; PubMed Central PMCID: PMCPMC4435460). This differs markedly from the lifelong persistence of influenza specific IgG that follows this infection (Fujimoto C, Takeda N, Matsunaga A, Sawada A, Tanaka T, Kimoto T, et al. Induction and maintenance of anti-influenza antigen-specific nasal secretory IgA levels and serum IgG levels after influenza infection in adults. Influenza Other Respir Viruses. 2012; 6(6):396-403. doi: 10.1111/j.1750-2659.2011.00330.x. PubMed PMID: 22226319; PubMed Central PMCID: PMCPMC4941696). Thus, it is important that any RSV vaccine candidate induce both systemic and mucosal RSV-specific antibodies, but do so in a manner that induces a B cell memory response superior to that induced by RSV infection.

(6) While an effective RSV vaccine has been eagerly sought, no licensed vaccine yet exists. RSV vaccine development has focused primarily on live-attenuation, a strategy with demonstrated safety in infants, the target population for most RSV vaccines. Unfortunately, live-attenuated RSV vaccines evaluated clinically to date have been poorly immunogenic, an outcome that could be predicted from the poor immune response to natural RSV infection (Gomez M, Mufson M A, Dubovsky F, Knightly C, Zeng W, Losonsky G. Phase-I study MEDI-534, of a live, attenuated intranasal vaccine against respiratory syncytial virus and parainfluenza-3 virus in seropositive children. The Pediatric infectious disease journal. 2009; 28(7):655-8. Epub 2009/06/02. doi: 10.1097/INF.0b013e318199c3b1. PubMed PMID: 19483659; Wright P F, Belshe R B, Kim H W, Van Voris L P, Chanock R M. Administration of a highly attenuated, live respiratory syncytial virus vaccine to adults and children. Infection and immunity. 1982; 37(1):397-400. Epub 1982/07/01. PubMed PMID: 7107009; PubMed Central PMCID: PMC347542; Wright P F, Shinozaki T, Fleet W, Sell S H, Thompson J, Karzon D T. Evaluation of a live, attenuated respiratory syncytial virus vaccine in infants. The Journal of pediatrics. 1976; 88(6):931-6. Epub 1976/06/01. PubMed PMID: 178852). Disappointing immunogenicity of live-attenuated RSV vaccines has led investigators to diversify RSV vaccine strategies (reviewed in Mazur N I, Martinon-Torres F, Baraldi E, Fauroux B, Greenough A, Heikkinen T, et al. Lower respiratory tract infection caused by respiratory syncytial virus: current management and new therapeutics. Lancet Respir Med. 2015; 3(11):888-900. doi:

10.1016/52213-2600(15)00255-6. PubMed PMID: 26411809).
(7) An important goal of pre-clinical vaccine evaluation is to establish the safety profile of a vaccine candidate. This is particularly true for RSV vaccine candidates given the history of the 1960's vaccine trial in which enhanced pathology following natural RSV infection of infants that had previously received a formalin-inactivated RSV vaccine (FI-RSV) (Kim H W, Canchola J G, Brandt C D, Pyles G, Chanock R M, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. American journal of epidemiology. 1969; 89(4):422-34. Epub 1969/04/01. PubMed PMID: 4305198). It has been suggested that this vaccine-enhanced disease may have been related to the presence of non-neutralizing antibody, allowing virus replication and simultaneous immune complex deposition in the lung (Polack F P, Teng M N, Collins P L, Prince G A, Exner M, Regele H, et al. A role for immune complexes in enhanced respiratory syncytial virus disease. The Journal of experimental medicine. 2002; 196(6):859-65. PubMed PMID: 12235218; PubMed Central PMCID: PMCPMC2194058). FI-RSV has been shown to generate primarily non-neutralizing antibody in mice, and RSV challenge of mice receiving the FI-RSV vaccine resulted in immune complex mediated pathology (Id.). It is therefore important to demonstrate the induction of long-lasting, virus-specific adaptive immunity by any vaccine candidate, but also to verify the absence of disease-promoting immune responses.
(8) 2.2 HMPV
(9) Human metapneumovirus (hMPV) is a nonsegmented negative strand RNA virus in the Pneumovirinae family that also includes human respiratory syncytial virus (RSV) (Afonso et al., 2016, Arch. Virol. 161: 2351-2360). hMPV was first isolated in the Netherlands in 2001 (van den Hoogen B G, de Jong J C, Groen J, Kuiken T, de Groot R, Fouchier R A, Osterhaus A D. 2001. “A newly discovered human pneumovirus isolated from young children with respiratory tract disease.” Nat Med 7:719-724) and has subsequently been identified worldwide as second to RSV in causing respiratory disease and hospitalization in infants, with also a significant impact in young kids together with RSV and influenza viruses (Esper F, Boucher D, Weibel C, Martinello R A, Kahn J S. 2003. Human metapneumovirus infection in the United States: clinical manifestations associated with a newly emerging respiratory infection in children. Pediatrics 111:1407-1410). In fact, hMPV was found to be a major pathogen associated with hospitalization of children and with the same severity of illness as RSV but in a slightly older population (Akhras N, Weinberg J B, Newton D. 2010. Human metapneumovirus and respiratory syncytial virus: subtle differences but comparable severity. Infect Dis Rep 2:e12). Both RSV and hMPV are an important cause of severe respiratory disease in immunocompromised patients. No vaccines are available at this moment for these two important human respiratory pathogens. Thus, a need exists for a safe and effective vaccine for RSV and hMPV.
(10) 2.3 NDV
(11) Newcastle disease virus (NDV) is a member of the Avulavirus genus in the Paramyxoviridae family, which has been shown to infect a number of avian species (Alexander, DJ (1988). Newcastle disease, Newcastle disease virus—an avian paramyxovirus. Kluwer Academic Publishers: Dordrecht, The Netherlands. pp 1-22). NDV possesses a single-stranded RNA genome in negative sense and does not undergo recombination with the host genome or with other viruses (Alexander, DJ (1988). Newcastle disease, Newcastle disease virus—an avian paramyxovirus. Kluwer Academic Publishers: Dordrecht, The Netherlands. pp 1-22). The genomic RNA contains genes in the order of 3′-NP-P-M-F-HN-L-5′, described in further detail below. Two additional proteins, V and W, are produced by NDV from the P gene by alternative mRNAs that are generated by RNA editing. The genomic RNA also contains a leader sequence at the 3′ end.
(12) The structural elements of the virion include the virus envelope which is a lipid bilayer derived from the cell plasma membrane. The glycoprotein, hemagglutinin-neuraminidase (HN) protrudes from the envelope allowing the virus to contain both hemagglutinin (e.g., receptor binding/fusogenic) and neuraminidase activities. The fusion glycoprotein (F), which also interacts

with the viral membrane, is first produced as an inactive precursor, then cleaved post-translationally to produce two disulfide linked polypeptides. The active F protein is involved in penetration of NDV into host cells by facilitating fusion of the viral envelope with the host cell plasma membrane. The matrix protein (M), is involved with viral assembly, and interacts with both the viral membrane as well as the nucleocapsid proteins.

(13) The main protein subunit of the nucleocapsid is the nucleocapsid protein (NP) which confers helical symmetry on the capsid. In association with the nucleocapsid are the P and L proteins. The phosphoprotein (P), which is subject to phosphorylation, is thought to play a regulatory role in transcription, and may also be involved in methylation, phosphorylation and polyadenylation. The L gene, which encodes an RNA-dependent RNA polymerase, is required for viral RNA synthesis together with the P protein. The L protein, which takes up nearly half of the coding capacity of the viral genome is the largest of the viral proteins, and plays an important role in both transcription and replication. The V protein has been shown to inhibit interferon-alpha and to contribute to the virulence of NDV (Huang et al. (2003). Newcastle disease virus V protein is associated with viral pathogenesis and functions as an Alpha Interferon Antagonist. *Journal of Virology* 77: 8676-8685).

3. SUMMARY

(14) In one aspect, presented herein are recombinant Newcastle disease virus ("NDV") comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a respiratory syncytial virus ("RSV") F protein. The RSV F protein may be an RSV F protein of a human or bovine strain of RSV. In a specific embodiment, the transgene encodes the human RSV F protein comprising the amino acid sequence set forth in SEQ ID NO: 6 or the bovine RSV F protein comprising the amino acid sequence set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, multiple different nucleic acid sequences may encode for the same human RSV F protein or the same bovine RSV F protein. In one embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a human RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:1. In another embodiment described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a human RSV F protein comprising the amino acid sequence set forth in SEQ ID NO:49, 50 or 58. In another embodiment described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a human RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 25, 27 or 29. In another embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a bovine RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:9. In another embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a bovine RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:40 or 42. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding an RSV F protein (e.g., a human or bovine RSV F protein). In a specific embodiment, the RSV F protein is expressed by cells infected with the recombinant NDV.

(15) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding a human RSV F protein. Specific examples of codon optimized nucleic acid sequences encoding a human RSV F protein include SEQ ID NO: 2, 26, 28 or 30. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a human RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:2. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV.

(16) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding a bovine RSV F protein. Specific examples of codon optimized nucleic acid sequences encoding a bovine RSV F protein include SEQ ID NO: 11, 41, or 43. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a bovine RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:11. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV.

(17) In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In other words, the NDV F protein transmembrane and cytoplasmic domains replace the RSV F protein transmembrane and cytoplasmic domains so that the chimeric F protein does not include the RSV F protein transmembrane and cytoplasmic domains. The RSV F protein may be an RSV F protein of a human or bovine strain of RSV. In a specific embodiment, the transgene encodes a chimeric F protein comprising the amino acid sequence set forth in SEQ ID NO: 7 or 33. In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:51. In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 31. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding the RSV F protein ectodomain (e.g., a human or bovine RSV F protein ectodomain). In a specific embodiment, the RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion.

(18) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:4, 44, 45 or 46. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:4. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion.

(19) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein,

wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:14, 38 or 39. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:14. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion.

(20) The recombinant NDV may have the backbone of any NDV type or strain, including, but not limited to, naturally-occurring strains, variants or mutants, mutagenized viruses, reassortants or genetically engineered viruses, or any combination thereof. The NDV that serves as the backbone for genetic engineering of the recombinant NDV may be a lentogenic strain, a mesogenic strain, or a velogenic strain. In a specific embodiment, the recombinant NDV comprises an NDV backbone which is lentogenic. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV LaSota strain. See, .e.g., SEQ ID NO: 47 for a cDNA sequence of the genomic sequence of NDV LaSota strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV Hitchner B1 strain. See, e.g., SEQ ID NO: 48 for a cDNA sequence of the genomic sequence of NDV Hitchner strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of a lentogenic strain other than the NDV Hitchner B1 strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV Fuller strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV Ulster strain.

(21) The transgene encoding a RSV F protein or a chimeric F protein may be incorporated into the genome of any NDV type or strain. In a specific embodiment, the transgene is incorporated into the genome of a lentogenic NDV. In another specific embodiment, the transgene is incorporated in the genome of NDV strain LaSota. See, e.g., SEQ ID NO: 47 for a cDNA sequence of the genomic sequence of NDV LaSota strain. Other examples of NDV strains into which the transgene may be incorporated are the NDV Fuller, the NDV Ulster strain or the NDV Hitchner B1 strain. In a specific embodiment, the transgene may be incorporated into the genomic sequence of NDV Hitchner B1 strain. See, e.g., SEQ ID NO:48 for a cDNA sequence of the genomic sequence of NDV Hitchner B1 strain. In a specific embodiment, the transgene may be incorporated into the genome of a lentogenic strain other than the NDV Hitchner B1 strain. The transgene may be incorporated into the NDV genome between two transcription units (e.g., between NDV P and M genes).

(22) In a specific embodiment, a transgene encoding a human RSV F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). For example, a transgene encoding the human RSV F protein set forth in SEQ ID NO:6 may be incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:1. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same human RSV F protein. In certain embodiments, a transgene encoding the human RSV F protein set forth in SEQ ID NO:49, 50 or 58 may be incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). In some embodiments, a transgene encoding the human RSV F protein comprises the amino acid sequence

encoded by the nucleic acid sequence comprising the sequence of SEQ ID NO:25, 27 or 29. In a specific embodiment, transgene encoding a human RSV F protein is codon optimized. For example, the human RSV F protein is encoded by the codon optimized nucleic acid sequence set forth in SEQ ID NO: 2, 26, 28 or 30. The transgene encoding a human RSV F protein may be incorporated between any two NDV transcription units (e.g., between NDV P and M genes). In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO: 3. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the human RSV F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a human RSV F protein. In certain embodiments, the genome of the recombinant NDV comprises a transgene encoding a human RSV F protein and a transgene encoding an hMPV F protein or a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In such embodiments, the genome of the recombinant NDV may not comprise any additional transgenes.

(23) In a specific embodiment, a transgene encoding a bovine RSV F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). For example, a transgene encoding the bovine RSV F protein comprising the amino acid sequence set forth in SEQ ID NO:10 may be incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:9. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same bovine RSV F protein. In some embodiments, a transgene encoding the bovine RSV F protein comprises the amino acid sequence encoded by the nucleic acid sequence comprising the sequence of SEQ ID NO:40 or 42. In a specific embodiment, transgene encoding a bovine RSV F protein is codon optimized. For example, the bovine RSV F protein is encoded by the codon optimized nucleic acid sequence set forth in SEQ ID NO: 11, 41 or 43. The transgene encoding a bovine RSV F protein may be incorporated between any two NDV transcription units (e.g., between NDV P and M genes). In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome is an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO: 12 or 13. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the bovine RSV F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a bovine RSV F protein.

(24) In a specific embodiment, a transgene encoding a chimeric F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain), wherein the chimeric F protein comprises the ectodomain of an RSV F protein (e.g., a human or bovine RSV F protein) and NDV F protein transmembrane and cytoplasmic domains. For example, a transgene encoding the chimeric F protein comprising the amino acid sequence set forth in SEQ ID NO:7 may be incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO: 51. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same chimeric F protein. In a specific embodiment, the nucleic acid sequence encoding a human RSV F protein ectodomain is codon optimized. For example, the nucleic acid sequence of one or more of the domains of the chimeric F protein may be codon optimized (e.g. the ectodomain of the chimeric F protein may be encoded by a codon optimized nucleic acid sequence, such as set forth in SEQ ID NO: 4, 44, 45, or 46. The transgene encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between NDV P and M genes). In a specific embodiment, a

recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA sequence transcribed from a cDNA sequence comprising the sequence set forth in SEQ ID NO: 5. In certain embodiments, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the chimeric F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a chimeric F protein. In certain embodiments, the genome of the recombinant NDV comprises a transgene encoding a first chimeric F protein and a transgene encoding an hMPV F protein or a second chimeric F protein, wherein the first chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains and the second chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In such embodiments, the genome of the recombinant NDV may not comprise any additional transgenes.

(25) In a specific embodiment, a transgene encoding a chimeric F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain), wherein the chimeric F protein comprises the ectodomain of an RSV F protein (e.g., a human or bovine RSV F protein) and NDV F protein transmembrane and cytoplasmic domains. For example, a transgene encoding the chimeric F protein comprising the amino acid sequence set forth in SEQ ID NO:33 may be incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO: 31. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same chimeric F protein. In a specific embodiment, the nucleic acid sequence encoding a bovine RSV F protein ectodomain is codon optimized. For example, the nucleic acid sequence of one or more of the domains of the chimeric F protein may be codon optimized (e.g. the ectodomain of the chimeric F protein may be encoded by a codon optimized nucleic acid sequence, such as set forth in SEQ ID NO: 14, 38, or 39. The transgene encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between NDV P and M genes). In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the chimeric F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a chimeric F protein. In certain embodiments, the genome of the recombinant NDV comprises a transgene encoding a first chimeric F protein and a transgene encoding an hMPV F protein or a second chimeric F protein, wherein the first chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains and the second chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In such embodiments, the genome of the recombinant NDV may not comprise any additional transgenes.

(26) The recombinant NDV and uses thereof described herein are based, in part, on the robust, long-lived antigen-specific humoral immunity induced by the recombinant NDV and the prevention of RSV infection of the lower airway and the largely eliminated RSV replication in the upper airway in animals. In addition, the recombinant NDV and uses thereof described herein are based, in part, on the demonstration of vaccine efficacy in previously-infected, seropositive animals. Further, the recombinant NDV and uses thereof described herein are based, in part, on the decreased inflammation induced by the recombinant NDV with the NDV LaSota strain backbone and the enhanced RSV F protein expression resulting from the use of a codon optimized nucleic acid sequence encoding RSV F protein or a nucleic acid sequence encoding a chimeric F protein.

(27) In another aspect, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein. In one embodiment, the human RSV F protein comprises the amino acid sequence

set forth in SEQ ID NO: 6, 49, 50 or 58. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same human RSV F protein. For example, the human RSV F protein may be encoded a sequence comprising the amino acid sequence set forth SEQ ID NO:1, 25, 27 or 29. Alternatively, the nucleic acid sequence encoding the human RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 2, 26, 28 or 30. In some embodiments, the human RSV F protein is encoded by a sequence comprising the nucleic acid sequence set forth in SEQ ID NO:1, 2, 25, 26, 27, 28, 29, or 30. In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a human RSV F protein. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human infant six months old or older. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(28) In another aspect, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a bovine RSV F protein. In one embodiment, the bovine RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same bovine RSV F protein. For example, the bovine RSV F protein may be encoded by SEQ ID NO:9. Alternatively, the nucleic acid sequence encoding the bovine RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 11. In some embodiments, the bovine RSV F protein is encoded by a sequence comprising the nucleic acid sequence set forth in SEQ ID NO:9, 11, 40, 41, 42, or 43. In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a bovine RSV F protein. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(29) In another aspect, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO: 7. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:51. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:4, 44, 45, or 46). In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises

a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human infant six months old or older. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(30) In another aspect, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:33. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:31. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:14, 38, or 39). In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(31) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein. In one embodiment, the human RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 6, 49, 50 or 58. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same human RSV F protein. For example, the human RSV F protein may be encoded by SEQ ID NO:1, 25, 27 or 29. Alternatively, the nucleic acid sequence encoding the human RSV F protein may be codon optimized, such as set forth in SEQ ID NO:2, 26, 28, or 30. In some embodiments, the human RSV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO: 1, 2, 25, 26, 27. 28, 29, or 30. In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a human RSV F protein. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human

infant six months old or older. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(32) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a bovine RSV F protein. In one embodiment, the bovine RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same bovine RSV F protein. For example, the bovine RSV F protein may be encoded by SEQ ID NO:9. Alternatively, the nucleic acid sequence encoding the bovine RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 11. In some embodiments, the bovine RSV F protein is encoded by a sequence comprising the nucleic acid sequence set forth in SEQ ID NO:9, 11, 40, 41, 42 or 43. In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a bovine RSV F protein. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(33) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:7. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:51. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:4, 44, 45, or 46). In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human infant six months old or older. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(34) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant

NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:33. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:31. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:14, 38, or 39). In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(35) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein. In one embodiment, the human RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 6, 49, 50 or 58. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same human RSV F protein. For example, the human RSV F protein may be encoded by SEQ ID NO:1, 25, 27 or 29. Alternatively, the nucleic acid sequence encoding the human RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 2, 26, 28 or 30. In some embodiments, the human RSV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO: 1, 2, 25, 26, 27. 28, 29, or 30. In a specific embodiment, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a human RSV F protein. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human infant six months old or older. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(36) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a bovine RSV F protein. In one embodiment, the bovine RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same bovine RSV F protein. For example, the bovine RSV F protein may be encoded by SEQ ID NO:9. Alternatively, the nucleic acid sequence encoding the bovine RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 11. In some embodiments, the bovine RSV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO: 9, 11, 40, 41, 42, or 43. In a specific embodiment, presented herein are

methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a bovine RSV F protein. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(37) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO: 7. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:51. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 4, 44, 45, or 46). In a specific embodiment, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human infant six months old or older. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(38) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:33. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:31. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:14, 38, or 39). In a specific embodiment, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected

with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is seropositive for antibodies to RSV (e.g., the subject is seropositive for antibodies to RSV F protein or RSV G protein).

(39) The recombinant NDV described herein may be administered to a subject in combination with one or more other therapies. The recombinant NDV and one or more other therapies may be administered by the same or different routes of administration to the subject. In a specific embodiment, the recombinant NDV is administered to a subject intranasally. See, e.g., Sections 5.15.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4 for information regarding other therapies, Section 5.4, infra, for information regarding compositions and routes of administration, and Sections 5.5.1 and 66, infra, for information regarding methods of immunizing against RSV.

(40) In another embodiment, presented herein is a recombinant NDV or composition thereof for inducing an immune response to an RSV F protein. In another embodiment, presented herein is a recombinant NDV or composition thereof for immunizing a subject (e.g., a human or bovine subject) against RSV. In another embodiment, presented herein is a recombinant NDV or composition thereof for the prevention of an RSV disease. See, e.g., Sections 5.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4, for information regarding other therapies, Section 5.4, infra, for information regarding compositions and routes of administration, and Sections 5.5.1 and 6, infra, for information regarding methods of immunizing against RSV.

(41) In another aspect, presented herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a human metapneumovirus ("hMPV") F protein. The hMPV F protein may be an hMPV F protein of any strain of hMPV. In a specific embodiment, the transgene encodes the hMPV F protein set forth in SEQ ID NO:17. Due to the degeneracy of the nucleic acid code, multiple different nucleic acid sequences may encode for the same hMPV F protein. In one embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a hMPV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:16. In some embodiments, the hMPV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO:16, 52, 54, or 56. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV.

(42) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding a hMPV F protein. Specific examples of codon optimized nucleic acid sequences encoding a hMPV F protein include those set forth in SEQ ID NO:18, 53, 55, or 57. In a specific embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a human RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:18. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV.

(43) In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In other words, the NDV F protein transmembrane and cytoplasmic domains replace the hMPV F protein transmembrane and cytoplasmic domains so that the chimeric F protein does not include the hMPV F protein transmembrane and cytoplasmic domains. The hMPV F protein may be an hMPV F protein of any of hMPV. In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F

protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:32. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV.

(44) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the hMPV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the hMPV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:19, 34, 35, or 36. In a specific embodiment, described herein is a recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:19. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion.

(45) The recombinant NDV may have the backbone of any NDV type or strain, including, but not limited to, naturally-occurring strains, variants or mutants, mutagenized viruses, reassortants, genetically engineered viruses, or any combination thereof. The NDV that serves as the backbone for genetic engineering of the recombinant NDV may be a lentogenic strain, a mesogenic strain, or a velogenic strain. In a specific embodiment, the recombinant NDV comprises an NDV backbone which is lentogenic. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV LaSota strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV Hitchner B1 strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of a lentogenic strain other than the NDV Hitchner B1 strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV Fuller strain. In another specific embodiment, the recombinant NDV comprises an NDV backbone of the NDV Ulster strain.

(46) The transgene encoding a hMPV F protein or a chimeric F protein may be incorporated into the genome of any NDV type or strain. In a specific embodiment, the transgene is incorporated into the genome of a lentogenic NDV. In another specific embodiment, the transgene is incorporated in the genome of NDV strain LaSota. Other examples of NDV strains into which the transgene may be incorporated are the NDV Fuller, the NDV Ulster strain or the NDV Hitchner B1 strain. The transgene may be incorporated into the NDV genome between two transcription units (e.g., between NDV P and M genes).

(47) In a specific embodiment, a transgene encoding a hMPV F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). For example, a transgene encoding the hMPV F protein comprising the amino acid sequence set forth in SEQ ID NO:17 may be incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:16. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same hMPV F protein. In a specific embodiment, transgene encoding a hMPV F protein is codon optimized. For example, the hMPV F protein is encoded by the codon optimized nucleic acid sequence set forth in

SEQ ID NO: 18. In some embodiments, the hMPV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO: 16, 18, 52, 53, 54, 55, 56, or 57. The transgene encoding a hMPV F protein may be incorporated between any two NDV transcription units (e.g., between NDV P and M genes). In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO: 20 or 21. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the hMPV F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a hMPV F protein.

(48) In a specific embodiment, a transgene encoding a chimeric F protein is incorporated into the genome of any NDV type or strain, wherein the chimeric F protein comprises the ectodomain of an hMPV F protein and NDV F protein transmembrane and cytoplasmic domains. For example, a transgene encoding the chimeric F protein comprising the amino acid sequence set forth in SEQ ID NO:15 may be incorporated into the genome of any NDV type or strain. In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:32. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same chimeric F protein. In a specific embodiment, the nucleic acid sequence encoding the ectodomain of the hMPV F protein is codon optimized. For example, the chimeric F protein may be encoded by the codon optimized nucleic acid sequence, such as set forth in SEQ ID NO: 19, 34, 35, or 36. The nucleotide sequence comprising the nucleic acid sequence encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between NDV P and M genes). In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO:22. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the chimeric F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a chimeric F protein.

(49) In another aspect, presented herein are methods for inducing an immune response to an hMPV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a hMPV F protein. In one embodiment, the hMPV F protein comprises the amino acid sequence set forth in SEQ ID NO: 17. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same hMPV F protein. For example, the hMPV F protein may be encoded by SEQ ID NO:16. Alternatively, the nucleic acid sequence encoding the hMPV F protein may be codon optimized, such as set forth in SEQ ID NO: 18. In some embodiments, the hMPV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO: 16, 18, 52, 53, 54, 55, 56 or 57. In a specific embodiment, presented herein are methods for inducing an immune response to an hMPV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to hMPV.

(50) In another aspect, presented herein are methods for inducing an immune response to an hMPV

F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:15. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:32. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the hMPV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 19, 34, 35 or 36). In a specific embodiment, presented herein are methods for inducing an immune response to an hMPV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise an hMPV RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to hMPV.

(51) In another aspect, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a hMPV F protein. In one embodiment, the hMPV F protein comprises the amino acid sequence set forth in SEQ ID NO: 17. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same hMPV F protein. For example, the hMPV F protein may be encoded by SEQ ID NO:16. Alternatively, the nucleic acid sequence encoding the hMPV F protein may be codon optimized, such as set forth in SEQ ID NO: 18. In some embodiments, the hMPV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO: 16, 18, 52, 53, 54, 55, 56 or 57. In a specific embodiment, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to hMPV.

(52) In another aspect, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:15. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein.

For example, the chimeric F protein may be encoded by SEQ ID NO:32. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the hMPV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 19, 34, 35, or 36). In a specific embodiment, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise an hMPV RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to hMPV.

(53) In another aspect, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a hMPV F protein. In one embodiment, the hMPV F protein comprises the amino acid sequence set forth in SEQ ID NO: 17. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same hMPV F protein. For example, the hMPV F protein may be encoded by SEQ ID NO:16. Alternatively, the nucleic acid sequence encoding the hMPV F protein may be codon optimized, such as set forth in SEQ ID NO: 18. In some embodiments, the hMPV F protein is encoded by a nucleic acid sequence comprising the sequence of SEQ ID NO: 16, 18, 52, 53, 54, 55, 56 or 57. In a specific embodiment, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to hMPV.

(54) In another aspect, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:15. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:32. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the hMPV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 19, 34, 35, or 36). In a specific embodiment, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g.,

a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise an hMPV RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In another specific embodiment, the subject is a human infant. In another specific embodiment, the subject is a human toddler. In another specific embodiment, the subject is a human child. In another specific embodiment, the subject is a human adult. In another specific embodiment, the subject is an elderly human. In another specific embodiment, the subject is seropositive for antibodies to hMPV.

(55) The recombinant NDV described herein may be administered to a subject in combination with one or more other therapies. The recombinant NDV and one or more other therapies may be administered by the same or different routes of administration to the subject. In a specific embodiment, the recombinant NDV is administered to a subject intranasally. See, e.g., Sections 5.15.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4 for information regarding other therapies, Section 5.4, infra, for information regarding compositions and routes of administration, and Sections 5.5.2 5.5.1 and 6, infra, for information regarding methods of immunizing against hMPV.

(56) In another embodiment, presented herein is a recombinant NDV or composition thereof for inducing an immune response to an hMPV F protein. In another embodiment, presented herein is a recombinant NDV or composition thereof for immunizing a subject (e.g., a human subject) against hMPV. In another embodiment, presented herein is a recombinant NDV or composition thereof for the prevention of an hMPV disease. See, e.g., Sections 5.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4 for information regarding other therapies, Section 5.4, infra, for information regarding compositions and routes of administration, and Sections 5.5.2 and 6, infra, for information regarding methods of immunizing against hMPV.

(57) In another aspect, presented herein are pharmaceutical compositions (e.g., immunogenic compositions) comprising a recombinant NDV described herein, in admixture with a pharmaceutically acceptable carrier. In a specific embodiment, a pharmaceutical composition (e.g., an immunogenic composition) comprises a recombinant NDV described herein as the sole active ingredient, in admixture with a pharmaceutically acceptable carrier. In another specific embodiment, a pharmaceutical composition (e.g., an immunogenic composition) comprises two different recombinant NDVs described herein, in admixture with a pharmaceutically acceptable carrier. See, e.g., Section 5.4, infra, for examples of pharmaceutical compositions. The pharmaceutical compositions may be used to induce an immune response to an RSV F protein or hMPV F protein, immunize against RSV or hMPV, or prevent RSV disease or hMPV disease.

(58) 3.1 Terminology

(59) As used herein, the term “about” or “approximately” when used in conjunction with a number refers to any number within 1, 5 or 10% of the referenced number.

(60) As used herein, the terms “antibody” and “antibodies” refer to molecules that contain an antigen binding site, e.g., immunoglobulins. Antibodies include, but are not limited to, monoclonal antibodies, bispecific antibodies, multispecific antibodies, human antibodies, humanized antibodies, synthetic antibodies, chimeric antibodies, polyclonal antibodies, single domain antibodies, camelized antibodies, single-chain Fvs (scFv), single chain antibodies, Fab fragments, F(ab′) fragments, disulfide-linked bispecific Fvs (sdFv), intrabodies, and anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id and anti-anti-Id antibodies to antibodies), and epitope-binding fragments of any of the above. In particular, antibodies include immunoglobulin molecules and

immunologically active fragments of immunoglobulin molecules. Immunoglobulin molecules can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass.

(61) As used herein, the term “heterologous” in the context of NDV refers to an entity not found in nature to be associated with (e.g., encoded by, expressed by the genome of, or both) a naturally occurring NDV. In a specific embodiment, a heterologous sequence encodes a protein that is not found associated with naturally occurring NDV.

(62) As used herein, the term “elderly human” refers to a human 65 years or older.

(63) As used herein, the term “human adult” refers to a human that is 18 years or older.

(64) As used herein, the term “human child” refers to a human that is 1 year to 18 years old.

(65) As used herein, the term “human toddler” refers to a human that is 1 year to 3 years old.

(66) As used herein, the term “human infant” refers to a newborn to 1 year old year human.

(67) “Human Metapneumovirus F protein” and “hMPV F protein” refer to any Human Metapneumovirus F protein known to those of skill in the art. The hMPV F protein is synthesized as a F0 inactive precursor. The F0 inactive precursor requires cleavage during intracellular maturation. The hMPV F is cleaved to form F1 and F2. The hMPV F protein exists in two conformations, prefusion and post-fusion. GenBank™ accession number AY145301.1 and KJ627437.1, provide exemplary nucleic acid sequences encoding hMPV F protein. In a preferred embodiment, an hMPV F protein is encoded by a nucleic acid sequence provided in Section 5.1.4, 5.1.5 or 6, e.g., SEQ ID NOs: 16, 18, 52, 53, 54, 55, 56, or 57. GenBank™ accession numbers AAN52915.1, AHV79975.1, AGJ74035.1, and AGZ48845.1 provide exemplary hMPV F protein amino acid sequences. In a preferred embodiment, an hMPV F protein comprises an amino acid sequence provided in Section 5.1.4 or 6, e.g., SEQ ID NOs: 17. As used herein, the terms “hMPV F protein” and “human metapneumovirus F protein” encompass hMPV F polypeptides that are modified by post-translational processing such as signal peptide cleavage, disulfide bond formation, glycosylation (e.g., N-linked glycosylation), protease cleavage and lipid modification (e.g. S-palmitoylation). In some embodiments, the hMPV F protein includes a signal sequence. In other embodiments, hMPV F protein does not include a signal sequence. The signal sequence can be the naturally occurring signal peptide sequence or a variant thereof. The hMPV F protein signal sequence is typically 18 amino acids in length. See, e.g., SEQ ID NO:24 for an exemplary hMPV protein signal sequence. In some embodiments, the signal peptide is an hMPV F protein signal peptide. In some embodiments, the signal peptide is heterologous to an hMPV F protein signal peptide.

(68) As used herein, the phrases “IFN deficient systems” or “IFN-deficient substrates” refer to systems, e.g., cells, cell lines and animals, such as mice, chickens, turkeys, rabbits, rats, horses etc., which do not produce one, two or more types of IFN, or do not produce any type of IFN, or produce low levels of one, two or more types of IFN, or produce low levels of any IFN (i.e., a reduction in any IFN expression of 5-10%, 10-20%, 20-30%, 30-40%, 40-50%, 50-60%, 60-70%, 70-80%, 80-90% or more when compared to IFN-competent systems under the same conditions), do not respond or respond less efficiently to one, two or more types of IFN, or do not respond to any type of IFN, have a delayed response to one, two or more types of IFN, are deficient in the activity of antiviral genes induced by one, two or more types of IFN, or induced by any type of IFN, or any combination thereof.

(69) As used herein, the phrase “multiplicity of infection” or “MOI” is the average number of virus per infected cell. The MOI is determined by dividing the number of virus added (ml added x Pfu/ml) by the number of cells added (Pfu added/cells).

(70) “RSV F protein” and “respiratory syncytial virus F protein” refer to any respiratory syncytial F protein known to those of skill in the art. The RSV F protein typically exists as a homotrimer. The RSV F protein is synthesized as a F0 inactive precursor which is heavily N-glycosylated. The F0 inactive precursor requires cleavage during intracellular maturation by a furin-like proteases. The

RSV F contains two furin sites, and cleavage by furin-like proteases leads to three polypeptides: F2, p27 and F1, with the latter containing a hydrophobic fusion peptide at its N terminus. The RSV F protein exists in two conformations, prefusion and post-fusion. The RSV F protein may be human RSV F protein or bovine F protein. GenBank™ accession numbers KJ155694.1, KU950686.1, KJ672481.1, KP119747, and AF035006.1 provide exemplary nucleic acid sequences encoding human RSV F protein. In a preferred embodiment, a human RSV F protein may be encoded by the nucleic acid sequence provided in Section 5.1.2, 5.1.3. or 6, e.g., SEQ ID NOs: 1, 2, 25, 26, 27, 28, 29 or 30. GenBank™ accession numbers AHL84194.1, AMT79817.1, AHX57603.1, AIY70220.1 and AAC14902.1 provide exemplary human RSV F protein amino acid sequences. In a preferred embodiment, a human RSV F protein comprises the amino sequence provided in Section 5.1.2 or 6, e.g., SEQ ID NO: 6, 49, 50 or 58. GenBank™ accession numbers AF295543.1, AF092942.1, and Y17970.1 provide exemplary nucleic acid sequences encoding bovine RSV F protein. In a specific embodiment, a bovine RSV F protein is encoded by a nucleic acid sequence comprising the nucleic acid sequence of SEQ ID NO:9, 11, 39, 40, 41, 42 or 43. GenBank™ accession numbers AAL49399.1, NP_048055.1, AAC96308.1, and CAA76980.1 provide exemplary bovine RSV F protein amino acid sequences. In another embodiment, a bovine RSV F protein comprises the amino acid sequence provided in Section 5.1.2 or 6, e.g., SEQ ID NO: 10. As used herein, the terms “RSV F protein” and “respiratory syncytial virus F protein” encompass RSV F polypeptides that are modified by post-translational processing such as signal peptide cleavage, disulfide bond formation, glycosylation (e.g., N-linked glycosylation), protease cleavage and lipid modification (e.g. S-palmitoylation). In some embodiments, the RSV F protein includes a signal sequence. In other embodiments, RSV F protein does not include a signal sequence. The signal sequence can be the naturally occurring signal peptide sequence or a variant thereof. The RSV F protein signal sequence is typically 25 amino acids in length. See, e.g., SEQ ID NO:23 or 60 for an exemplary human RSV F protein signal sequence and bovine RSV F protein signal sequence, respectively. In some embodiments, the signal peptide is an RSV F protein signal peptide. In some embodiments, the signal peptide is heterologous to an RSV F protein signal peptide.

(71) As used herein, the terms “subject” or “patient” are used interchangeably. As used herein, the terms “subject” and “subjects” refers to an animal. In some embodiments, the subject is a mammal including a non-primate (e.g., a camel, donkey, zebra, bovine, horse, horse, cat, dog, rat, and mouse) and a primate (e.g., a monkey, chimpanzee, and a human). In some embodiments, the subject is a non-human mammal. In certain embodiments, the subject is a pet (e.g., dog or cat) or farm animal (e.g., a horse, pig or cow). In specific embodiments, the subject is a human. In other specific embodiments, the subject is a bovine. In certain embodiments, the mammal (e.g., human) is 4 to 6 months old, 6 to 12 months old, 1 to 5 years old, 5 to 10 years old, 10 to 15 years old, 15 to 20 years old, 20 to 25 years old, 25 to 30 years old, 30 to 35 years old, 35 to 40 years old, 40 to 45 years old, 45 to 50 years old, 50 to 55 years old, 55 to 60 years old, 60 to 65 years old, 65 to 70 years old, 70 to 75 years old, 75 to 80 years old, 80 to 85 years old, 85 to 90 years old, 90 to 95 years old or 95 to 100 years old. In specific embodiments, the subject is an animal that is not avian.

(72) As used herein, the term “in combination” in the context of the administration of (a) therapy(ies) to a subject, refers to the use of more than one therapy. The use of the term “in combination” does not restrict the order in which therapies are administered to a subject. A first therapy can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy to a subject. For example, a recombinant NDV described herein may be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours,

72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of another therapy.

(73) As used herein, the terms “therapies” and “therapy” can refer to any protocol(s), method(s), agent(s) or a combination thereof that can be used in the treatment or prevention of RSV disease or hMPV disease, or vaccination. In certain embodiments, the term “therapy” refers to a recombinant NDV described herein. In other embodiments, the term “therapy” refers to an agent that is not a recombinant NDV described herein.

(74) As used herein, the term “wild-type” in the context of nucleotide and amino acid sequences of viruses refers to the nucleotide and amino acid sequences of viral strains found in nature. In particular, the sequences described as wild-type herein are sequences that have been reported in public databases as sequences from natural viral isolates.

Description

4. BRIEF DESCRIPTION OF THE FIGURES

(1) FIGS. **1**A-**1**N. Inflammation following NDV-F vaccination and boost. Cohorts of cotton rats were sacrificed 28 days after the priming intranasal immunization, or 1 month after a second, boosting dose given on day 28. Mock-immunized animals were given allantoic fluid alone, or the NDV vaccine vector. Representative sections from the nasal cavity and lung after a single priming dose (FIGS. **1**A-**1**D, and FIGS. **1**I-**1**K), or after both a priming and a boosting dose (FIGS. **1**E-**1**H and FIGS. **1**L-**1**N), are pictured. A lymphohistiocytic submucosal infiltrate is present in the nasal cavity (FIGS. **1**C and **1**D), and surrounding bronchioles (FIG. **1**K), after priming with NDV-F, with increased cellularity 1 month following the boosting dose (FIGS. **1**G, **3**H, and **3**N). A minimal peribronchiolar infiltrate is detected only after priming and boosting with the NDV vector. Rare eosinophils are indicated (*). Images were captured at 100× or 400× (insets) magnification.

(2) FIGS. **2**A-**2**F. Histology of the nasal cavity and lung following primary RSV challenge. Nasal cavity (FIGS. **2**A-**2**C) and lung (FIGS. **2**D-**2**F) were collected 4 days after primary RSV challenge from animals that had been previously mock-vaccinated, or given a priming and boosting dose of NDV-F. Respiratory mucosa in the noses of infected animals was disrupted by lymphoplasmacytic infiltrates (FIGS. **2**A and **2**B), whereas, the nasal cavities of NDV-F vaccinated animals (FIG. **2**C) were similar to those observed following vaccination alone (FIG. **1**). RSV infection of the lung induced mild peribronchiolar infiltrates of lymphocytes, plasma cells and rare eosinophils and mucus production, with plugging of small airways (FIGS. **2**D and **2**E). RSV challenge of NDV-F vaccinated animals resulted in lymphoplasmacytic peribronchial infiltrates (FIG. **2**F), but without obstruction of small airways by mucus and necrotic cells. Images were taken at 100× (FIGS. **2**D-**2**E), 200× (FIGS. **2**A-**2**C) or 400× (insets) magnification.

(3) FIGS. **3**A-**3**G. Viral burden following primary RSV challenge. Nasal cavity and lung were collected 4 days after primary RSV challenge from controls and animals that had been previously vaccinated. RSV immunohistochemistry revealed marked to complete reduction in antigen-positive cells in nasal cavity (FIGS. **3**A-**3**C) and lung (FIGS. **3**D-**3**F) collected from NDV-F immunized animals compared to controls. Virus was detected by plaque assay (FIG. **3**G) only in samples collected from animals mock-immunized with allantoic fluid or vector alone. Images were taken at 200× (FIGS. **3**A-**3**C), 100× (FIGS. **3**D-**3**F) or 400× (insets) magnification.

(4) FIGS. **4**A-**4**E. Humoral immune responses to vaccination and RSV challenge. Serum, BAL fluid and NW fluid were collected at multiple time points after vaccination and RSV challenge and F-specific IgG levels were determined by ELISA (FIGS. **4**A-**4**C). Virus neutralization assay (FIG.

4D) revealed that F-specific antibodies induced by NDV-F vaccination were neutralizing. Cervical lymph nodes (CLNs) were collected 4 days and 5 months after RSV challenge of vaccinated animals and F-specific IgG secreting cells (ASCs) were enumerated by ELISpot (FIG. **4**E).
(5) FIGS. **5**A-**5**B. BAL fluid cellularity following vaccination and RSV challenge. BAL fluid was collected at multiple time points after vaccination and RSV challenge. Cellularity (FIG. **5**A) of BAL fluid collected from animals in all cohorts increased slightly, but not significantly, in response to primary RSV challenge then decreased gradually over time. Cellularity increased in BAL fluid collected from mock and NDV, but not NDV-F, vaccinated animals in response to secondary RSV challenge. The percentage of eosinophils (FIG. **5**B) in BAL fluid collected from mock and NDV, but not NDV-F vaccinated animals, increased in response to primary and secondary RSV challenge. BAL fluid cellularity and eosinophil percentage were not affected by vaccination alone. * $p<0.05$
(6) FIG. **6**. Immunization of RSV-immune animals. Cotton rats were infected with RSV on day 0. Two months post infection, 20/40 animals were primed with NDV-F, and boosted with a second dose 28 days later. At 4 months and 9 months post infection serum samples were taken from cohorts of immunized and control animals (N=5). At the 9 month time point, all animals were given a second challenge of RSV, and sacrificed day 2 and day 4 post re-infection.
(7) FIGS. **7**A-**7**B. Serum antibody titers following post-infection immunization. Serum was harvested from cotton rats 4 or 9 months following primary RSV infection. (FIG. **7**A) Levels of neutralizing antibody were determined by incubation of a 1/800 dilution of each serum with rgRSV, which was then used to inoculate A549 cells. Percentage of GFP-expressing cells was used to calculate % neutralization. * $p=0.0027$; ** $p<0.0001$. (FIG. **7**B) Levels of RSV F specific antibody in each sample were determined by ELISA. *$p=0.0114$; ** $p=0.0004$. Levels of neutralizing and RSV F specific antibody were significantly higher in the NDV-F vaccinated animals at 4 and 9 months post primary infection as determined by the unpaired t test.
(8) FIG. **8**. Cloning of the chimeric F protein with the ectodomain of the human RSV F and the transmembrane and cytoplasmic domains of the NDV F (not to scale). After rescue all the recombinant NDVs were amplified by inoculation in 8-10 old embryonated chicken eggs and characterized by RT-PCR and immunofluorescence (FIG. **13**).
(9) FIG. **9**. A schematic representation of the different rNDV-F, rNDV-F.sub.opt, rNDV-F.sub.chim are shown.
(10) FIG. **10**. Vero cells were infected with each construct, or the LaSota NDV virus vector for 24 hours, then stained with the Synagis® antibody to detect RSV F expression by flow cytometry. Mean Fluorescence Intensity (MFI) of the positive gated cells is shown.
(11) FIG. **11**. The number of plaque forming units of RSV detected in lung homogenates obtained from cotton rats mock treated or given priming and boosting doses of NDV, rNDV-F, rNDV-F.sub.opt, or rNDV-F.sub.chim following RSV challenge.
(12) FIGS. **12**A-**12**B. FIG. **12**A shows the relationship of serum sampling to immunization and challenge. FIG. **12**B shows antibody titers from individual cotton rats measured with an RSV F protein specific ELISA.
(13) FIG. **13**. Detection of the RSV F protein and NDV HN protein expressed by the different recombinant NDVs by double immunofluorescent microscopy.
(14) FIG. **14**. Detection of virus in cells treated with different concentrations of Synagis® followed by infection with GFP expressing viruses (RSV-GFP and NDV-GFP). Representative microscopic fields were photographed to prepare the figure.
(15) FIG. **15**. Detection of NDV in cells treated with different concentrations of Synagis® followed by infection with NDV, rNDV-F, rNDV-Fopt, or rNDV-Fchim. Representative microscopic fields were photographed to prepare the figure.
(16) FIGS. **16**A-**16**C. An alignment comparing the wild-type nucleic acid sequence encoding human RSV F protein (SEQ ID NO:1) to the codon optimized nucleic acid sequence encoding human RSV F protein (SEQ ID NO:2).

(17) FIGS. **17**A-**17**C. An alignment comparing the wild-type nucleic acid sequence encoding bovine RSV F protein (SEQ ID NO:9) to the codon optimized nucleic acid sequence encoding bovine RSV F protein (SEQ ID NO:11).
(18) FIG. **18**. Detection of NDV in cells treated with different concentrations of Synagis® followed by infection with rNDV-bovine RSV F.sub.opt or rNDV-bovine RSVF.sub.chim. Representative microscopic fields were photographed to prepare the figure.
(19) FIGS. **19**A-**19**C. An alignment comparing the wild-type nucleic acid sequence encoding human metapneumovirus F protein (SEQ ID NO:16) to the codon optimized nucleic acid sequence encoding human metapneumovirus F protein (SEQ ID NO:18).
5. DETAILED DESCRIPTION
(20) In one aspect, described herein are recombinant Newcastle disease viruses ("NDVs") comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a respiratory syncytial virus ("RSV") F protein or human metapneumovirus ('hMPV") F protein. In another aspect, described herein are recombinant NDVs comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises (i) an RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains; or (ii) an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In another aspect, described herein are compositions (e.g., immunogenic compositions) comprising a recombinant NDV described herein. In another aspect, the recombinant NDVs and compositions thereof are useful for inducing an immune response to RSV F protein or hMPV F protein, immunizing against RSV or hMPV, or the prevention of RSV disease or hMPV disease.
(21) 5.1 Recombinant Newcastle Disease Virus
(22) 5.1.1 NDV
(23) Any NDV type or strain may be serve as the "backbone" that is engineered to encode a transgene described herein, including, but not limited to, naturally-occurring strains, variants or mutants, mutagenized viruses, reassortants and/or genetically engineered viruses. In a specific embodiment, the nucleotide sequence is incorporated into the genome of a lentogenic NDV. In another specific embodiment, the nucleotide sequence is incorporated in the genome of NDV strain LaSota. Other examples of NDV strains into which the nucleotide sequence may be incorporated are the NDV Fuller, the NDV Ulster strain or the NDV Hitchner B1 strain. In some embodiments, a lentogenic strain other than NDV Hitchner B1 strain is used as the backbone into which a nucleotide sequence may be incorporated. The nucleotide sequence may be incorporated into the NDV genome between two transcription units (e.g., between the M and P transcription units or between the HN and L transcription units).
(24) In a specific embodiment, the NDV that is engineered to encode a transgene described herein is a naturally-occurring strain. In certain embodiments, the NDV that is engineered to encode a transgene described herein is a lytic strain. In other embodiments, the NDV that is engineered to encode a transgene described herein is a non-lytic strain. In certain embodiments, the NDV that is engineered to encode a transgene described herein is lentogenic strain. In some embodiments, the NDV that is engineered to encode a transgene described herein is a mesogenic strain. In other embodiments, the NDV that is engineered to encode a transgene described herein is a velogenic strain. Specific examples of NDV strains include, but are not limited to, the 73-T strain, NDV HUJ strain, Ulster strain (see, e.g., GenBank No. U25837), Fuller strain, MTH-68 strain, Italien strain (see, e.g., GenBank No. EU293914), Hickman strain (see, e.g., Genbank No. AF309418), PV701 strain, Hitchner B1 strain (see, e.g., GenBank No. AF309418 or NC_002617), La Sota strain (see, e.g., GenBank Nos. AY845400, AF07761.1 and JF950510.1 and GI No. 56799463), YG97 strain (see, e.g., GenBank Nos. AY351959 or AY390310), MET95 strain (see, e.g., GenBank No. AY143159), Roakin strain (see, e.g., GenBank No. AF124443), and F48E9 strain (see, e.g., GenBank Nos. AF163440 and U25837). In a specific embodiment, the NDV that is engineered to

encode a transgene described herein is the Hitchner B1 strain. In another embodiment, the NDV that is engineered to encode a transgene described herein is a B1 strain as identified by GenBank No. AF309418 or NC_002617. In a specific embodiment, the nucleotide sequence of the Hitchner B1 genome comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:48. In another specific embodiment, the NDV that is engineered to encode a transgene described herein is the La Sota strain. In another embodiment, the NDV that is engineered to encode a transgene described herein is a LaSota strain as identified by GenBank Nos. AY845400, AF07761.1 or JF950510.1. In a specific embodiment, the nucleotide sequence of the La Sota genome comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:47. One skilled in the art will understand that the NDV genomic RNA sequence is an RNA sequence corresponding to the negative sense of a cDNA sequence encoding the NDV genome. Thus, any program that converts a nucleotide sequence to its reverse complement sequence may be utilized to convert a cDNA sequence encoding an NDV genome into the genomic RNA sequence (see, e.g., Bioinformatics.org and DNAStar). Accordingly, the nucleotide sequences provided in Tables 1-6, infra, may be readily converted to the negative-sense RNA sequence of the NDV genome by one of skill in the art.

(25) In specific embodiments, the NDV that is engineered to encode a transgene described herein is not pathogenic in birds as assessed by a technique known to one of skill. In certain specific embodiments, the NDV that is engineered to encode a transgene described herein is not pathogenic as assessed by intracranial injection of 1-day-old chicks with the virus, and disease development and death as scored for 8 days. In some embodiments, the NDV that is engineered to encode a transgene described herein has an intracranial pathogenicity index of less than 0.7, less than 0.6, less than 0.5, less than 0.4, less than 0.3, less than 0.2 or less than 0.1. In certain embodiments, the NDV that is engineered to encode a transgene described herein has an intracranial pathogenicity index of zero. See, e.g., OIE Terrestrial Manual 2012, Chapter 2.3.14, entitled “Newcastle Disease (Infection With Newcastle Disease Virus) for a description of this assay, which is incorporated herein by reference in its entirety.

(26) In certain embodiments, the NDV that is engineered to encode a transgene described herein is a mesogenic strain that has been genetically engineered so as not be a considered pathogenic in birds as assessed by techniques known to one skilled in the art. In certain embodiments, the NDV that is engineered to encode a transgene described herein is a velogenic strain that has been genetically engineered so as not be a considered pathogenic in birds as assessed by techniques known to one skilled in the art.

(27) In preferred embodiments, the NDV that is engineered to encode a transgene described herein is non-pathogenic in humans or bovine. In preferred embodiments, the NDV that is engineered to encode a transgene described herein is non-pathogenic in humans, bovines and avians. In certain embodiments, the NDV that is engineered to encode a transgene described herein is attenuated such that the NDV remains, at least partially, infectious and can replicate in vivo, but only generate low titers resulting in subclinical levels of infection that are non-pathogenic (see, e.g., Khattar et al., 2009, J. Virol. 83:7779-7782). Such attenuated NDVs may be especially suited for embodiments wherein the virus is administered to a subject in order to act as an immunogen, e.g., a live vaccine. The viruses may be attenuated by any method known in the art. In a specific embodiment, the NDV genome comprises sequences necessary for infection and replication of the attenuated virus such that progeny is produced and the infection level is subclinical.

(28) 5.1.2 RSV F Protein/Chimeric F Protein with the RSV F Protein Ectodomain

(29) In a specific embodiment, a transgene encoding a human RSV F protein is incorporated into the genome of any NDV type or strain. (e.g., NDV LaSota strain) See, e.g., Section 5.1.1., supra, for types and strains of NDV that may be used. The transgene encoding any RSV F protein may inserted into any NDV type or strain (e.g., NDV LaSota strain). The RSV F protein may be an RSV F protein of a human or bovine strain of RSV. In a specific embodiment, a transgene encoding a

human RSV F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). See, e.g., Section 5.8 3.1 for exemplary sequences for human RSV F protein and exemplary nucleic acid sequences encoding human RSV F protein. One of skill in the art would be able to use such sequence information to produce a transgene for incorporation into the genome of any NDV type or strain. For example, a transgene encoding the human RSV F protein comprising the amino acid sequence set forth in SEQ ID NO:6, 49, 50 or 58 may be incorporated into the genome of any NDV type or strain. In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:1, 25, 27 or 29. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same human RSV F protein. In a specific embodiment, a transgene encoding a human RSV F protein is codon optimized. See, e.g., Section 5.1.6, infra, for a discussion regarding codon optimization. For example, the human RSV F protein may be encoded by a codon optimized nucleic acid sequence, such as set forth in SEQ ID NO: 2, 26, 28 or 30. In some embodiments, the transgene encoding a human RSV F protein comprises the amino acid sequence encoded by the nucleic acid sequence comprising the sequence set forth in SEQ ID NO:1, 2, 25, 26, 27, 28, 29, or 30. The transgene encoding a human RSV F protein may be incorporated between any two NDV transcription units (e.g., between the NDV P and M transcription units, or between the HN and L transcription units).

(30) In a specific embodiment, a transgene encoding a bovine RSV F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). See, e.g., Section 5.8 3.1 for exemplary sequences for bovine RSV F protein and exemplary nucleic acid sequences encoding bovine RSV F protein. One of skill in the art would be able to use such sequence information to produce a transgene for incorporation into the genome of any NDV type or strain. For example, a transgene encoding the bovine RSV F protein comprising the amino acid sequence set forth in SEQ ID NO:10 may be incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). In a specific embodiment, a transgene encoding the bovine RSV F protein comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:9, 40 or 42. However, given the degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same bovine RSV F protein. In a specific embodiment, a transgene encoding a bovine RSV F protein is codon optimized. For example, the bovine RSV F protein may be encoded by the codon optimized nucleic acid sequence set forth in SEQ ID NO: 11, 41 or 43. In some embodiments, the transgene encoding a bovine RSV F protein comprises the amino acid sequence encoded by the nucleic acid sequence comprising the sequence set forth in SEQ ID NO:9, 11, 40, 41, 42, or 43. The transgene encoding a bovine RSV F protein may be incorporated between any two NDV transcription units (e.g., between NDV P and M genes).

(31) In another embodiment, described herein are transgenes encoding a chimeric F protein, wherein the chimeric F protein comprises an RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In other words, the NDV F protein transmembrane and cytoplasmic domains replace the RSV F protein transmembrane and cytoplasmic domains so that the chimeric F protein does not include the RSV F protein transmembrane and cytoplasmic domains. The RSV F protein may be an RSV F protein of a human or bovine strain of RSV. The ectodomain, transmembrane and cytoplasmic domains of the RSV F protein and NDV F protein may be determined using techniques known to one of skill in the art. For example, published information, GenBank or websites such as VIPR virus pathogen website, DTU Bioinformatics domain website or programs available to determine the transmembrane domain may be used to determined the ectodomain, transmembrane and cytoplasmic domains of the RSV F protein and NDV F protein. See, e.g., the tables infra with the transmembrane and cytoplasmic domains indicated. In specific embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein

transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 51. In another embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises the an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 31. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding the RSV F protein ectodomain (e.g., a human or bovine RSV F protein ectodomain). In a specific embodiment, a transgene encoding a chimeric F protein is incorporated into the genome of any NDV type or strain (e.g., NDV LaSota strain). See, e.g., Section 5.1.1, supra, for types and strains of NDV that may be used. The transgene encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between the NDV P and M transcription units, or between the HN and L transcription units).

(32) In a specific embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:4, 44, 45, or 46. In a preferred embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:4. In a specific embodiment, a transgene encoding a chimeric F protein is incorporated into the genome of any NDV type or strain. See, e.g., Section 5.1.1, supra, for types and strains of NDV that may be used. The transgene encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between the NDV P and M transcription units, or between the HN and L transcription units).

(33) In a specific embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:14, 38, or 39. In a preferred embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:14 or 31. In a specific embodiment, a transgene encoding a chimeric F protein is incorporated into the genome of any NDV type or strain. See, e.g., Section 5.1.1, supra, for types and strains of NDV that may be used. The transgene encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between the NDV P and M transcription units, or between the HN and L transcription units).

(34) In a specific embodiments, a transgene encoding a human RSV F protein or a chimeric F protein is encoded by a nucleic acid sequence comprising a nucleic acid sequence set forth in SEQ ID NO:1, 2, 4, 25, 26, 27, 28, 29, 30, 44, 45, 46, or 51, or an RNA sequence corresponding to the negative sense thereof. In specific embodiments, a transgene encoding a bovine RSV F protein or chimeric F protein is encoded by a nucleic acid sequence comprising a nucleic acid sequence set

forth in SEQ ID NO: 9, 11, 14, 31, 38, 39, 40, 41, 42, or 43, or an RNA sequence corresponding to the negative sense thereof. See, e.g., Tables 1 and 3 for nucleic acid and amino acid sequences of RSV F. Also, see, e.g., Section 5.8 for exemplary human or bovine RSV F proteins, or chimeric F proteins.

(35) In a specific embodiment, a transgene encoding an RSV F protein or a chimeric F protein is as described in Section 6, infra.

(36) In certain embodiments, a transgene encoding an RSV F protein or a chimeric F protein comprises NDV regulatory signals (e.g., gene end, intergenic, and gene start sequences) and Kozak sequences. In some embodiments, a transgene encoding an RSV F protein or a chimeric F protein comprises NDV regulatory signals (e.g., gene end, intergenic, and gene start sequences), Kozak sequences and restriction sites to facilitate cloning. See, e.g., FIG. **8**. In certain embodiments, a transgene encoding an RSV F protein or a chimeric F protein comprises NDV regulatory signals (gene end, intergenic and gene start sequences), Kozak sequences, restriction sites to facilitate cloning, and additional nucleotides in the non-coding region to ensure compliance with the rule of six. In a preferred embodiment, the transgene complies with the rule of six.

(37) 5.1.3 Recombinant NDV Encoding an RSV F Protein or a Chimeric F Protein with an RSV Ectodomain

(38) In one aspect, presented herein are recombinant Newcastle disease virus ("NDV") comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a respiratory syncytial virus ("RSV") F protein. The RSV F protein may be an RSV F protein of a human or bovine strain of RSV. See, e.g., Section 5.1.2 and 6 for transgenes encoding a human or bovine RSV F protein which the packaged genome may comprise. In a specific embodiment, the transgene encodes the human RSV F protein comprising the amino sequence set forth in SEQ ID NO: 6, 49, 50 or 58, or the bovine RSV F protein set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, multiple different nucleic acid sequences may encode for the same human RSV F protein or the same bovine RSV F protein. In one embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a human RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:1, 25, 27 or 29. In another embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a bovine RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:9, 40 or 42. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding an RSV F protein (e.g., a human or bovine RSV F protein). In a specific embodiment, the RSV F protein is expressed by cells infected with the recombinant NDV. In some embodiments, RSV F protein is detected in the virion of recombinant NDV.

(39) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding a human RSV F protein. Specific examples of codon optimized nucleic acid sequences encoding a human RSV F protein include those in SEQ ID Nos:2, 26, 28, or 30. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a human RSV F protein, wherein the transgene comprises the an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:2. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV. In some embodiments, RSV F protein is detected in the virion of recombinant NDV.

(40) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding a bovine RSV F protein. Specific examples of codon optimized nucleic acid sequences encoding a bovine RSV F protein include those in SEQ ID Nos: 11, 41, or

43. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a bovine RSV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:11. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV. In some embodiments, RSV F protein is detected in the virion of recombinant NDV.

(41) In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In other words, the NDV F protein transmembrane and cytoplasmic domains replace the RSV F protein transmembrane and cytoplasmic domains so that the chimeric F protein does not include the RSV F protein transmembrane and cytoplasmic domains. In a specific embodiment, the NDV F protein transmembrane and cytoplasmic domains are from the same strain of NDV as the NDV backbone. For example, if the NDV backbone is NDV LaSota, then the transmembrane and cytoplasmic domains of the chimeric F protein are NDV LaSota transmembrane and cytoplasmic domains. The RSV F protein may be an RSV F protein of a human or bovine strain of RSV. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:51. In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:31. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding the RSV F protein ectodomain (e.g., a human or bovine RSV F protein ectodomain). In a specific embodiment, the RSV F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the RSV F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion.

(42) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:4, 44, 45, and 46. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:4. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the virion of the NDV. In another specific embodiment, the RSV F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the NDV virion.

(43) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the RSV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:14, 38, or 39. In a preferred embodiment, described herein is a recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:14. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. In another specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV and the chimeric F protein is incorporated into the virion of the NDV.
(44) In a specific embodiments, a recombinant NDV comprises a packaged genome, wherein the packaged genome comprises a transgene encoding a RSV F protein or a chimeric F protein, wherein the RSV F protein or chimeric F protein is encoded by a nucleic acid sequence comprising a nucleic acid sequence set forth in SEQ ID NO:1, 2, 4, 25, 26, 27, 28, 29, 30, 44, 45, 46, or 51, or an RNA sequence corresponding to the negative sense thereof. In specific embodiments, recombinant NDV comprises a packaged genome, wherein the packaged genome comprises a transgene encoding a RSV F protein or a chimeric F protein, wherein the RSV F protein or chimeric F protein is encoded by a nucleic acid sequence comprising a nucleic acid sequence set forth in SEQ ID NO: 9, 11, 14, 31, 38, 39, 40, 41, 42, or 43, or an RNA sequence corresponding to the negative sense thereof.
(45) In a specific embodiment, a recombinant NDV is as described in Section 6, infra.
(46) In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA transcribed from a cDNA sequence comprising (or consisting of) the sequence set forth in SEQ ID NO: 3. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the human RSV F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a human RSV F protein described herein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a human RSV F protein. In other words, the recombinant NDV encodes for both NDV F protein and the human RSV F protein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV, a transgene encoding a human RSV F protein, and a transgene encoding an hMPV F protein or a chimeric F protein described herein, e.g., in Section 5.1.4, but does not include other transgenes, wherein the chimeric F protein comprises the ectodomain of hMPV F protein and the transmembrane and cytoplasmic domains of NDV F protein. In some embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a human RSV F protein but does not include any other transgenes.
(47) In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA of a cDNA sequence comprising (or consisting of) the sequence set forth in SEQ ID NO: 12 or 13. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the bovine RSV F protein. In some embodiments, the

genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a bovine RSV F protein described herein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a bovine RSV F protein. In other words, the recombinant NDV encodes for both NDV F protein and the bovine RSV F protein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV, a transgene encoding a bovine RSV F protein, and a transgene encoding an hMPV F protein or a chimeric F protein described herein, e.g., in Section 5.1.4, but does not include other transgenes, wherein the chimeric F protein comprises the ectodomain of hMPV F protein and the transmembrane and cytoplasmic domains of NDV F protein. In some embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a bovine RSV F protein but does not include any other transgenes.

(48) In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA sequence of a cDNA sequence comprising (or consisting of) the sequence set forth in SEQ ID NO: 5, 37 or 59. In some embodiments, the packaged genome of NDV encodes a chimeric F protein, wherein the chimeric F protein comprises the human or bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the chimeric F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a chimeric F protein described herein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a chimeric F protein. In other words, the recombinant NDV encodes for both NDV F protein and the chimeric F protein. In some embodiment, the genome of a recombinant NDV described herein comprises a transgene encoding a chimeric F protein and the genes found in NDV except for the gene encoding NDV F protein. In other words, the NDV encodes the chimeric F protein but not the NDV F protein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV, a transgene encoding first chimeric F protein, and a transgene encoding an hMPV F protein or a second chimeric F protein described herein, e.g., in Section 5.1.4, but does not include other transgenes, wherein the first chimeric F protein comprises the ectodomain of human RSV F protein or bovine RSV F protein and the transmembrane and cytoplasmic domains of NDV F protein, and wherein the second chimeric F protein comprises the ectodomain of hMPV F protein and the transmembrane and cytoplasmic domains of NDV F protein. In some embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a chimeric F protein but does not include other transgenes.

(49) 5.1.4 Human Metapneumovirus (hMPV) F Protein

(50) In a specific embodiment, a transgene encoding a hMPV F protein is incorporated into the genome of any NDV type or strain. See, e.g., Section 5.1.1, supra, for types and strains of NDV that may be used. The transgene encoding any hMPV F protein may inserted into any NDV type or strain (e.g., NDV LaSota strain). The hMPV F protein may be an hMPV F protein of any strain of hMPV. See, e.g., Section 5.8 for exemplary sequences for hMPV F protein and exemplary nucleic acid sequences encoding hMPV F protein. One of skill in the art would be able to use such sequence information to produce a transgene for incorporation into the genome of any NDV type or strain. For example, a transgene encoding the hMPV F protein comprising the amino acid sequence set forth in SEQ ID NO:17 may be incorporated into the genome of any NDV type or strain. In a specific embodiment, such a transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:16, 52, 54, or 56. However, given the

degeneracy of the nucleic acid code, there are a number of different nucleic acid sequences that may encode the same hMPV F protein. In a specific embodiment, a transgene encoding an hMPV F protein is codon optimized. See, e.g., Section 5.1.6, infra, for a discussion regarding codon optimization. For example, the hMPV F protein is encoded by the codon optimized nucleic acid sequence, such as set forth in SEQ ID NO: 18, 53, 55, or 57. In some embodiments, the transgene encoding an hMPV F protein comprises the amino acid sequence encoded by the nucleic acid sequence comprising the sequence set forth in SEQ ID NO:16, 18, 52, 53, 54, 55, 56 or 57. In certain embodiments, the hMPV F protein is encoded by a transgene comprising the an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:16, 18, 52, 53, 54, 55, 56 or 57. The transgene encoding a hMPV F protein may be incorporated between any two NDV transcription units (e.g., between the NDV P and M transcription units, or between the HN and L transcription units).

(51) In another embodiment, described herein are transgenes encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In other words, the NDV F protein transmembrane and cytoplasmic domains replace the hMPV F protein transmembrane and cytoplasmic domains so that the chimeric F protein does not include the hMPV F protein transmembrane and cytoplasmic domains. The hMPV F protein may be an hMPV F protein of any strain of hMPV. The ectodomain, transmembrane and cytoplasmic domains of the hMPV F protein and NDV F protein may be determined using techniques known to one of skill in the art. For example, published information, GenBank or websites such as VIPR virus pathogen website, DTU Bioinformatics domain website, or programs available to determine the transmembrane domain may be used to determined the ectodomain, transmembrane and cytoplasmic domains of the hMPV F protein and NDV F protein. See, e.g., the tables below indicating the transmembrane and cytoplasmic domains. In specific embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:32. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding the hMPV F protein ectodomain. In specific embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:19, 34, 35, or 36. In a specific embodiment, a transgene encoding a chimeric F protein is incorporated into the genome of any NDV type or strain. See, e.g., Section 5.1.1, supra, for types and strains of NDV that may be used. The transgene encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between the NDV P and M transcription units, or between the HN and L transcription units).

(52) In a specific embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the hMPV F protein is encoded by a codon optimized nucleic acid sequence. Specific examples of nucleic acid sequences encoding a chimeric F protein, wherein the chimeric F protein comprises a human hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the ectodomain of the hMPV F protein is encoded by a codon optimized nucleic acid sequence, include SEQ ID NO:19, 34, 35, and 36. In a preferred embodiment, described herein is a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:19. In a specific embodiment, a transgene encoding a chimeric F protein is

incorporated into the genome of any NDV type or strain. See, e.g., Section 5.1.1, supra, for types and strains of NDV that may be used. The transgene encoding a chimeric F protein may be incorporated between any two NDV transcription units (e.g., between the NDV P and M transcription units, or between the HN and L transcription units).

(53) In specific embodiments, a transgene encoding an hMPV F protein or a chimeric F protein is encoded by a nucleic acid sequence comprising a nucleic acid sequence set forth in SEQ ID NO:16, 18, 19, 32, 34, 35, 36, 52, 53, 54, 55, 56, or 57, or an RNA sequence corresponding to the negative sense thereof. See, e.g., Section 5.8 for exemplary hMPV F protein or chimeric F proteins.

(54) In a specific embodiment, a transgene encoding an hMPV F protein or a chimeric F protein is as described in Section 6, infra.

(55) In certain embodiments, a transgene encoding an hMPV F protein or a chimeric F protein comprises NDV regulatory signals (e.g., gene end, intergenic, and gene start sequences) and Kozak sequences. In some embodiments, a transgene encoding an hMPV F protein or a chimeric F protein comprises NDV regulatory signals (e.g., gene end, intergenic, and gene start sequences), Kozak sequences and restriction sites to facilitate cloning. In certain embodiments, a transgene encoding an hMPV F protein or a chimeric F protein comprises NDV regulatory signals (gene end, intergenic and gene start sequences), Kozak sequences, restriction sites to facilitate cloning, and additional nucleotides in the non-coding region to ensure compliance with the rule of six. In a preferred embodiment, the transgene complies with the rule of six.

(56) 5.1.5 Recombinant NDV Encoding a hMPV F Protein or a Chimeric F Protein with an hMPV Ectodomain

(57) In one aspect, presented herein are recombinant Newcastle disease virus (“NDV”) comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a human metapneumovirus (“hMPV”) F protein. See, e.g., Section 5.1.4 and 6 for transgenes encoding an hMPV F protein which the packaged genome may comprise. The hMPV F protein may be an hMPV F protein of any strain of hMPV. In a specific embodiment, the transgene encodes the hMPV F protein comprising the sequence set forth in SEQ ID NO: 17. Due to the degeneracy of the nucleic acid code, multiple different nucleic acid sequences may encode for the same hMPV F protein. Specific examples of nucleic acid sequences encoding a hMPV F protein include those set forth in SEQ ID NOs:16, 52, 54 and 56. In one embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a hMPV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:16. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV.

(58) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding a hMPV F protein. Specific examples of codon optimized nucleic acid sequences encoding a hMPV F protein include those set forth in SEQ ID Nos:18, 53, 55 and 57. In a specific embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a hMPV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:18. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV.

(59) In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In other words, the NDV F protein transmembrane and cytoplasmic domains replace the hMPV F protein transmembrane and cytoplasmic domains so that the chimeric F protein does not include the hMPV F protein transmembrane and cytoplasmic

domains. The chimeric hMPV F protein may comprise the amino acid sequence of SEQ ID NO:15. In a specific embodiment, the NDV F protein transmembrane and cytoplasmic domains are from the strain of NDV as the NDV backbone. The hMPV F protein may be an hMPV F protein of any strain of hMPV. See, e.g., Section 5.1.4 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. In another embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:32. In a preferred embodiment, a transgene comprises a codon optimized version of a nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. In some embodiments, hMPV F protein is detected in the NDV virion.

(60) In a specific embodiment, described herein are recombinant NDV comprising a packaged genome, wherein the packaged genome comprises a transgene comprising a codon optimized nucleic acid sequence encoding a hMPV F protein. Specific examples of codon optimized nucleic acid sequences encoding a hMPV F protein include those set forth in SEQ ID NOs: 19, 34, 35 and 36. In a specific embodiment, described herein is a recombinant NDV comprising a packaged genome comprising a transgene encoding a hMPV F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:19. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. In some embodiments, hMPV F protein is detected in the NDV virion.

(61) In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA of the cDNA sequence comprising (or consisting of) the sequence set forth in SEQ ID NO: 20 or 21. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the hMPV F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a hMPV F protein described herein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding an hMPV F protein. In other words, the recombinant NDV encodes for both NDV F protein and the hMPV F protein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV, a transgene encoding an hMPV F protein, and a transgene encoding a human RSV F protein or a second chimeric F protein described herein, e.g., in Section 5.1.2, but does not include other transgenes, wherein the first chimeric F protein comprises the ectodomain of human RSV F protein and the transmembrane and cytoplasmic domains of NDV F protein. In some embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding an hMPV F protein but does not include other transgenes.

(62) In a specific embodiment, a recombinant NDV described herein comprises a packaged genome, wherein the packaged genome corresponds to a negative sense RNA of the cDNA sequence comprising (or consisting of) the sequence set forth in SEQ ID NO: 22. In a specific embodiment, a recombinant NDV is as described in Section 6, infra. In certain embodiment, the genome of the recombinant NDV does not comprise a heterologous sequence encoding a heterologous protein other than the chimeric F protein. In some embodiments, the genome of the recombinant NDV does not comprise a transgene other than a transgene encoding a chimeric F protein described herein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a chimeric F protein. In other words, the recombinant NDV encodes for both NDV F

protein and the chimeric F protein. In some embodiments, the genome of a recombinant NDV described herein comprises a transgene encoding the chimeric F protein and the genes of NDV except the gene encoding NDV F protein. In other words, the recombinant NDV encodes the chimeric F protein but not the NDV F protein. In certain embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV, a transgene encoding a first chimeric F protein, and a transgene encoding a human RSV F protein or a second chimeric F protein described herein, e.g., in Section 5.1.2, but does not include other transgenes, wherein the first chimeric F protein comprises the ectodomain of hMPV F protein and the transmembrane and cytoplasmic domains of NDV F protein, and wherein the second chimeric F protein comprises the ectodomain of human RSV F protein and the transmembrane and cytoplasmic domains of NDV F protein. In some embodiments, a recombinant NDV described herein comprises a packaged genome, wherein the genome comprises the genes found in NDV and a transgene encoding a chimeric F protein but does not include other transgenes.

(63) 5.1.6 Codon Optimization

(64) Any codon optimization technique known to one of skill in the art may be used to codon optimize a nucleic acid sequence encoding an RSV F protein or a domain thereof (e.g., the ectodomain thereof). Similarly, any codon optimization technique may be used to codon optimize a nucleic acid sequence encoding an hMPV F protein or a domain thereof (e.g., the ectodomain thereof). Methods of codon optimization are known in the art, e.g., the OptimumGene™ (GenScript®) protocol and Genewiz® protocol, which are incorporated by reference herein in its entirety. See also U.S. Pat. No. 8,326,547 for methods for codon optimization, which is incorporated herein by reference in its entirety.

(65) As an exemplary method for codon optimization, each codon in the open frame of the nucleic acid sequence encoding an RSV F protein or a domain thereof (e.g., the ectodomain thereof), or an hMPV F protein or a domain thereof (e.g., the ectodomain thereof) is replaced by the codon most frequently used in mammalian proteins. This may be done using a web-based program (Encorbio) that uses the Codon Usage Database, maintained by the Department of Plant Gene Research in Kazusa, Japan. This nucleic acid sequence optimized for mammalian expression may be inspected for: (1) the presence of stretches of 5xA or more that may act as transcription terminators; (2) the presence of restriction sites that may interfere with subcloning; (3) compliance with the rule of six. Following inspection, (1) stretches of 5xA or more that may act as transcription terminators may be replaced by synonymous mutations; (2) restriction sites that may interfere with subcloning may be replaced by synonymous mutations; (3) NDV regulatory signals (gene end, intergenic and gene start sequences), and Kozak sequences for optimal protein expression may be added; and (4) nucleotides may be added in the non-coding region to ensure compliance with the rule of six. Synonymous mutations are typically nucleotide changes that do not change the amino acid encoded. For example, in the case of a stretch of 6 As (AAAAAA), which sequence encodes Lys-Lys, a synonymous sequence would be AAGAAG, which sequence also encodes Lys-Lys.

(66) In a specific embodiment, codon optimization reduces the AU content of the nucleic acid sequences encoding an RSV F protein (e.g., a human or bovine RSV-F protein) or a domain thereof (e.g., the ectodomain thereof), or a human MPV-F or a domain thereof (e.g., the ectodomain thereof). FIGS. **16**A-**16**C is an alignment comparing the wild-type nucleic acid sequence encoding a wild-type human RSV F protein to the codon optimized nucleic acid sequence encoding human RSV F protein. FIGS. **17**A-**17**C is an alignment comparing the wild-type nucleic acid sequence encoding a bovine RSV F protein to the codon optimized nucleic acid sequence encoding bovine RSV F protein. FIGS. **19**A-**19**C is an alignment comparing the wild-type nucleic acid sequence encoding a wild-type hMPV F protein to the codon optimized nucleic acid sequence encoding hMPV F protein.

(67) In a specific embodiment, the codon optimized nucleic acid sequence encoding human RSV F protein has a 10%, 15%, 20%, 25% or more drop in the AU content relative to the wild-type

nucleic acid sequence encoding human RSV F protein. In another specific embodiment, the codon optimized nucleic acid sequence encoding human RSV F protein has a 10% to 25%, 10% to 30%, 15% to 25% 15% to 30%, or 20% to 30% drop in the AU content relative to the wild-type nucleic acid sequence encoding human RSV F protein. The open reading frame of the wild-type nucleic acid sequence encoding human RSV F protein set forth in SEQ ID NO:1 has a 65.16% A+U, whereas the codon optimized nucleic acid sequence set forth in SEQ ID NO:2 has a 39.43% A+U. In a specific embodiment, the codon optimized nucleic acid sequence encoding bovine RSV F protein has a 10%, 15%, 20%, 25% or more drop in the AU content relative to the wild-type nucleic acid sequence encoding bovine RSV F protein. In another specific embodiment, the codon optimized nucleic acid sequence encoding bovine RSV F protein has a 10% to 25%, 10% to 30%, 15% to 25% 15% to 30%, or 20% to 30% drop in the AU content relative to the wild-type nucleic acid sequence encoding bovine RSV F protein. The open reading frame of the wild-type nucleic acid sequence encoding bovine RSV F protein set forth in SEQ ID NO:9 has a 64.4% A+U, whereas the codon optimized nucleic acid sequence set forth in SEQ ID NO:11 has a 39.66% A+U. In a specific embodiment, the codon optimized nucleic acid sequence encoding hMPV F protein has a 10%, 15%, 20%, 25% or more drop in the AU content relative to the wild-type nucleic acid sequence encoding hMPV F protein. In another specific embodiment, the codon optimized nucleic acid sequence encoding hMPV F protein has a 10% to 25%, 10% to 30%, 15% to 25% 15% to 30%, or 20% to 30% drop in the AU content relative to the wild-type nucleic acid sequence encoding hMPV F protein. The open reading frame of the wild-type nucleic acid sequence encoding hMPV F protein set forth in SEQ ID NO:16 has a 56.86% A+U, whereas the codon optimized nucleic acid sequence set forth in SEQ ID NO:18 has a 37.9% A+U.

(68) 5.2 Construction of NDVs

(69) The recombinant NDVs described herein (see, e.g., Sections 5.1 and 6) can be generated using the reverse genetics technique. The reverse genetics technique involves the preparation of synthetic recombinant viral RNAs that contain the non-coding regions of the negative-strand, viral RNA which are essential for the recognition by viral polymerases and for packaging signals necessary to generate a mature virion. The recombinant RNAs are synthesized from a recombinant DNA template and reconstituted in vitro with purified viral polymerase complex to form recombinant ribonucleoproteins (RNPs) which can be used to transfect cells. A more efficient transfection is achieved if the viral polymerase proteins are present during transcription of the synthetic RNAs either in vitro or in vivo. The synthetic recombinant RNPs can be rescued into infectious virus particles. The foregoing techniques are described in U.S. Pat. No. 5,166,057 issued Nov. 24, 1992; in U.S. Pat. No. 5,854,037 issued Dec. 29, 1998; in U.S. Pat. No. 6,146,642 issued Nov. 14, 2000; in European Patent Publication EP 0702085A1, published Feb. 20, 1996; in U.S. patent application Ser. No. 09/152,845; in International Patent Publications PCT WO97/12032 published Apr. 3, 1997; WO96/34625 published Nov. 7, 1996; in European Patent Publication EP A780475; WO 99/02657 published Jan. 21, 1999; WO 98/53078 published Nov. 26, 1998; WO 98/02530 published Jan. 22, 1998; WO 99/15672 published Apr. 1, 1999; WO 98/13501 published Apr. 2, 1998; WO 97/06270 published Feb. 20, 1997; and EPO 780 475A1 published Jun. 25, 1997, each of which is incorporated by reference herein in its entirety.

(70) The helper-free plasmid technology can also be utilized to engineer a NDV described herein. Briefly, a complete cDNA of a NDV (e.g., the Hitchner B1 strain or LaSota strain) is constructed, inserted into a plasmid vector and engineered to contain a unique restriction site between two transcription units (e.g., the NDV P and M genes; or the NDV HN and L genes). A nucleotide sequence encoding a heterologous amino acid sequence (e.g., a transgene or other sequence described herein such as, e.g., a nucleotide sequence encoding an RSV F protein, a chimeric F protein, hMPV F protein) may be inserted into the viral genome at the unique restriction site. Alternatively, a nucleotide sequence encoding a heterologous amino acid sequence (e.g., a transgene or other sequence described herein such as, e.g., a nucleotide sequence encoding an RSV

F protein, a chimeric F protein, hMPV F protein) may be engineered into a NDV transcription unit so long as the insertion does not affect the ability of the virus to infect and replicate. The single segment is positioned between a T7 promoter and the hepatitis delta virus ribozyme to produce an exact negative or positive transcript from the T7 polymerase. The plasmid vector and expression vectors comprising the necessary viral proteins are transfected into cells leading to production of recombinant viral particles (see, e.g., International Publication No. WO 01/04333; U.S. Pat. Nos. 7,442,379, 6,146,642, 6,649,372, 6,544,785 and 7,384,774; Swayne et al. (2003). Avian Dis. 47:1047-1050; and Swayne et al. (2001). J. Virol. 11868-11873, each of which is incorporated by reference in its entirety).

(71) Bicistronic techniques to produce multiple proteins from a single mRNA are known to one of skill in the art. Bicistronic techniques allow the engineering of coding sequences of multiple proteins into a single mRNA through the use of IRES sequences. IRES sequences direct the internal recruitment of ribosomes to the RNA molecule and allow downstream translation in a cap independent manner. Briefly, a coding region of one protein is inserted downstream of the ORF of a second protein. The insertion is flanked by an IRES and any untranslated signal sequences necessary for proper expression and/or function. The insertion must not disrupt the open reading frame, polyadenylation or transcriptional promoters of the second protein (see, e.g., Garcia-Sastre et al., 1994, J. Virol. 68:6254-6261 and Garcia-Sastre et al., 1994 Dev. Biol. Stand. 82:237-246, each of which are incorporated by reference herein in their entirety).

(72) Methods for cloning recombinant NDV to encode a transgene and express a heterologous protein encoded by the transgene (e.g., a transgene encoding an RSV F protein, a chimeric F protein, hMPV F protein) are known to one skilled in the art, such as, e.g., insertion of the transgene into a restriction site that has been engineered into the NDV genome, inclusion an appropriate signals in the transgene for recognition by the NDV RNA-dependent-RNA polymerase (e.g., sequences upstream of the open reading frame of the transgene that allow for the NDV polymerase to recognize the end of the previous gene and the beginning of the transgene, which may be, e.g., spaced by a single nucleotide intergenic sequence), inclusion of a valid Kozak sequence (e.g., to improve eukaryotic ribosomal translation); incorporation of a transgene that satisfies the “rule of six” for NDV cloning; and inclusion of silent mutations to remove extraneous gene end and/or gene start sequences within the transgene. Regarding the rule of six, one skilled in the art will understand that efficient replication of NDV (and more generally, most members of the paramyxoviridae family) is dependent on the genome length being a multiple of six, known as the “rule of six” (see, e.g., Calain, P. & Roux, L. The rule of six, a basic feature of efficient replication of Sendai virus defective interfering RNA. J. Virol. 67, 4822-4830 (1993)). Thus, when constructing a recombinant NDV described herein, care should be taken to satisfy the “Rule of Six” for NDV cloning. Methods known to one skilled in the art to satisfy the Rule of Six for NDV cloning may be used, such as, e.g., addition of nucleotides downstream of the transgene. See, e.g., Ayllon et al., Rescue of Recombinant Newcastle Disease Virus from cDNA. J. Vis. Exp. (80), e50830, doi:10.3791/50830 (2013) for a discussion of methods for cloning and rescuing of NDV (e.g., recombinant NDV), which is incorporated by reference herein in its entirety.

(73) In a specific embodiment, an NDV described herein (see, e.g., Sections 5.1 and 6) may be generated according to a method described in Section 6, infra.

(74) In a specific embodiment, a recombinant NDV comprising a packaged genome comprising a transgene encoding RSV F protein described herein comprises a LaSota strain backbone. In a specific embodiment, the genomic sequence of the La Sota strain backbone (i.e., without the transgene) is as set forth in SEQ ID NO:47.

(75) In a specific embodiment, a recombinant NDV comprising a packaged genome comprising a transgene encoding hMPV F protein described herein comprises a LaSota strain backbone. In a specific embodiment, the genomic sequence of the La Sota strain backbone (i.e., without the transgene) is as set forth in SEQ ID NO:47.

(76) In a specific embodiment, a recombinant NDV comprising a packaged genome comprising a transgene encoding a chimeric F protein described herein comprises a LaSota strain backbone. In a specific embodiment, the genomic sequence of the La Sota strain backbone (i.e., without the transgene) is as set forth in SEQ ID NO:47.

(77) 5.3 Propagation of NDVs

(78) The recombinant NDVs described herein (e.g., Sections 5.1 and 6) can be propagated in any substrate that allows the virus to grow to titers that permit the uses of the viruses described herein. In one embodiment, the substrate allows the recombinant NDVs described herein to grow to titers comparable to those determined for the corresponding wild-type viruses.

(79) The recombinant NDVs described herein (e.g., Sections 5.1 and 6) may be grown in cells (e.g., avian cells, chicken cells, etc.) that are susceptible to infection by the viruses, embryonated eggs (e.g., chicken eggs or quail eggs) or animals (e.g., birds). Such methods are well-known to those skilled in the art. In a specific embodiment, the recombinant NDVs described herein may be propagated in cancer cells, e.g., carcinoma cells (e.g., breast cancer cells and prostate cancer cells), sarcoma cells, leukemia cells, lymphoma cells, and germ cell tumor cells (e.g., testicular cancer cells and ovarian cancer cells). In another specific embodiment, the recombinant NDVs described herein may be propagated in cell lines, e.g., cancer cell lines such as HeLa cells, MCF7 cells, THP-1 cells, U87 cells, DU145 cells, Lncap cells, and T47D cells. In certain embodiments, the cells or cell lines (e.g., cancer cells or cancer cell lines) are obtained, derived, or obtained and derived from a human(s). In another embodiment, the recombinant NDVs described herein are propagated in interferon deficient systems or interferon (IFN) deficient substrates, such as, e.g., IFN deficient cells (e.g., IFN deficient cell lines) or IFN deficient embyronated eggs. In another embodiment, the recombinant NDVs described herein are propagated in chicken cells or embryonated chicken eggs. Representative chicken cells include, but are not limited to, chicken embryo fibroblasts and chicken embryo kidney cells. In a specific embodiment, the recombinant NDVs described herein are propagated in Vero cells. In another specific embodiment, the recombinant NDVs described herein are propagated in chicken eggs or quail eggs. In certain embodiments, a recombinant NDV virus described herein is first propagated in embryonated eggs and then propagated in cells (e.g., a cell line).

(80) The recombinant NDVs described herein may be propagated in embryonated eggs, e.g., from 6 to 14 days old, 6 to 12 days old, 6 to 10 days old, 6 to 9 days old, 6 to 8 days old, 8 to 10 day old, or 10 to 12 days old. In a specific embodiment, 10 day old embryonated chicken eggs are used to propagate the recombinant NDVs described herein. Young or immature embryonated eggs can be used to propagate the recombinant NDVs described herein. Immature embryonated eggs encompass eggs which are less than ten day old eggs, e.g., eggs 6 to 9 days old or 6 to 8 days old that are IFN-deficient. Immature embryonated eggs also encompass eggs which artificially mimic immature eggs up to, but less than ten day old, as a result of alterations to the growth conditions, e.g., changes in incubation temperatures; treating with drugs; or any other alteration which results in an egg with a retarded development, such that the IFN system is not fully developed as compared with ten to twelve day old eggs. The recombinant NDVs described herein can be propagated in different locations of the embryonated egg, e.g., the allantoic cavity. For a detailed discussion on the growth and propagation viruses, see, e.g., U.S. Pat. Nos. 6,852,522 and 7,494,808, both of which are hereby incorporated by reference in their entireties.

(81) For virus isolation, the recombinant NDVs described herein can be removed from embryonated eggs or cell culture and separated from cellular components, typically by well known clarification procedures, e.g., such as centrifugation, depth filtration, and microfiltration, and may be further purified as desired using procedures well known to those skilled in the art, e.g., tangential flow filtration (TFF), density gradient centrifugation, differential extraction, or chromatography.

(82) In a specific embodiment, virus isolation from allantoic fluid of an infected egg (e.g., a

chicken egg) begins with harvesting allantoic fluid, which is clarified using a filtration system to remove cells and other large debris, specifically, comprising a membrane having a net positive charge such that there is a measurable reduction in host cell DNA. The clarified bulk is subsequently processed by tangential flow filtration. The concentrated clarified bulk is then diafiltered against four diavolumes of high salt buffer, followed by four diavolumes of low salt formulation buffer and subsequently concentrated approximately 10-fold. Accordingly, residual egg proteins, e.g., primarily ovalbumin, and residual DNA are reduced to acceptable levels, and the buffer is exchanged to a buffer compatible with formulation of the recombinant NDV for a composition to be administered to a subject. The resulting product is then sterile filtered through a filter, e.g., a 0.2 μm filter, dispensed into appropriate sterile storage containers, frozen, and stored at −70 degrees Celsius.

(83) In a specific embodiment, a recombinant NDV described herein (see, e.g., Sections 5.1 and 6) is propagated, isolated, and/or purified according to a method described in Section 6. In a specific embodiment, a recombinant NDV described herein (see, e.g., Sections 5.1 and 6) is either propagated, isolated, or purified, or any two or all of the foregoing, using a method described in Section 6.

(84) In a specific embodiment, provided herein is a cell (e.g., a cell line) or embryonated egg (e.g., a chicken embryonated egg) comprising a recombinant NDV described herein. In another specific embodiment, provided herein is a method for propagating a recombinant NDV described herein, the method comprising culturing a cell (e.g., a cell line) or embryonated egg (e.g., a chicken embryonated egg) infected with the recombinant NDV. In some embodiments, the method may further comprise isolating or purifying the recombinant NDV from the cell or embryonated egg. In a specific embodiment, provided herein is a method for propagating a recombinant NDV described herein, the method comprising (a) culturing a cell (e.g., a cell line) or embyronated egg infected with a recombinant NDV described herein; and (b) isolating the recombinant NDV from the cell or embyronated egg. The cell or embyronated egg may be one described herein or known to one of skill in the art. In some embodiments, the cell or embyronated egg is IFN deficient.

(85) In a specific embodiment, provided herein is a method for producing a pharmaceutical composition (e.g., an immunogenic composition) comprising a recombinant NDV described herein, the method comprising (a) propagating a recombinant NDV described herein a cell (e.g., a cell line) or embyronated egg; and (b) isolating the recombinant NDV from the cell or embyronated egg. The method may further comprise adding the recombinant NDV to a container along with a pharmaceutically acceptable carrier.

(86) 5.4 Compositions and Routes of Administration

(87) Provided herein are compositions comprising a recombinant NDV described herein (e.g., Section 5.1 or 6). In a specific embodiment, the compositions are pharmaceutical compositions, such as immunogenic compositions (e.g., vaccine compositions). In a specific embodiment, provided herein are immunogenic compositions comprising a recombinant NDV described herein (e.g., Section 5.1 or 6). The compositions may be used in methods of inducing an immune response to RSV F protein or hMPV F protein. The compositions may be used in methods for immunizing against RSV or hMPV. The compositions may be used in methods for preventing an RSV disease or hMPV disease.

(88) In one embodiments, a pharmaceutical composition comprises a recombinant NDV described herein (e.g., Section 5.1 or 6), in an admixture with a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition further comprises one or more additional prophylactic or therapeutic agents, such as described in Section 5.5.4, infra. In a specific embodiment, a pharmaceutical composition comprises an effective amount of a recombinant NDV described herein (e.g., Section 5.1 or 6), and optionally one or more additional prophylactic or therapeutic agents, in a pharmaceutically acceptable carrier. In some embodiments, the recombinant NDV (e.g., Sections 5.1 or 6) is the only active ingredient included in the pharmaceutical

composition. In specific embodiments, two or more recombinant NDV are included in the pharmaceutical composition. In a particular embodiment, the pharmaceutical composition is an immunogenic composition.

(89) In a specific embodiment, a pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, in an admixture with a pharmaceutically acceptable carrier, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes a human RSV F protein, and wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, wherein the second transgene encodes an hMPV F protein. In another specific embodiment, a pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, in an admixture with a pharmaceutically acceptable carrier, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes a human RSV F protein, wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, and wherein the second transgene encodes a chimeric F protein comprising an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In another specific embodiment, a pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, in an admixture with a pharmaceutically acceptable carrier, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes an hMPV F protein, wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, and wherein the second transgene encodes a chimeric F protein comprising a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In another specific embodiment, a pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, in an admixture with a pharmaceutically acceptable carrier, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes a first chimeric F protein comprising an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, and wherein the second transgene encodes a second chimeric F protein comprising a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1 or 6 for nucleic acid sequences encoding such transgenes. In a particular embodiment, the pharmaceutical composition is an immunogenic composition.

(90) In a specific embodiment, the recombinant NDV included in a pharmaceutical composition described herein is a live virus. In particular, embodiment, the recombinant NDV included in a pharmaceutical composition described herein is an attenuated live virus. In some embodiments, the recombinant NDV included in a pharmaceutical composition described herein is inactivated. In particular embodiments, the RSV F protein or hMPV F protein of the inactivated recombinant NDV is in the pre-fusion conformation.

(91) The pharmaceutical compositions provided herein can be in any form that allows for the composition to be administered to a subject. In a specific embodiment, the pharmaceutical compositions are suitable for veterinary administration, human administration, or both. As used herein, the term “pharmaceutically acceptable” means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeiae for use in animals, and more particularly in humans. The term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which the pharmaceutical composition is administered. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. Examples of suitable pharmaceutical carriers are described in “Remington's Pharmaceutical

Sciences" by E. W. Martin. The formulation should suit the mode of administration.
(92) In a specific embodiment, the pharmaceutical compositions are formulated to be suitable for the intended route of administration to a subject. For example, the pharmaceutical composition may be formulated to be suitable for parenteral, intravenous, intraarterial, intrapleural, inhalation, intranasal, intraperitoneal, oral, intradermal, colorectal, intraperitoneal, intracranial, and intratumoral administration. In one embodiment, the pharmaceutical composition may be formulated for intravenous, intraarterial, oral, intraperitoneal, intranasal, intratracheal, intrapleural, intracranial, subcutaneous, intramuscular, topical, pulmonary, or intratumoral administration. In a specific embodiment, the pharmaceutical composition may be formulated for intranasal administration.
(93) In a specific embodiment, the pharmaceutical composition comprising a recombinant NDV described herein (see, e.g., Sections 5.1 or 6) is formulated to be suitable for intranasal administration to the subject (e.g., human subject or bovine subject). In a specific embodiment, the pharmaceutical composition comprising a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding an RSV F protein, is formulated to be suitable for intranasal administration to the subject (e.g., human subject). In another specific embodiment, the pharmaceutical composition comprising a recombinant NDV is formulated to be suitable for intranasal administration to the subject (e.g., human subject), wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, and wherein the chimeric F protein comprises an RSV F protein ectodomain and transmembrane and cytoplasmic domains of an NDV F protein. In a particular embodiment, the pharmaceutical composition is an immunogenic composition.
(94) In a specific embodiment, the pharmaceutical composition comprising a recombinant NDV comprising a packaged genome comprising a transgene encoding an hMPV F protein is formulated to be suitable for intranasal administration to the subject (e.g., human subject). In another specific embodiment, the pharmaceutical composition comprising a recombinant NDV is formulated to be suitable for intranasal administration to the subject (e.g., human subject), wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, and wherein the chimeric F protein comprises an hMPV F protein ectodomain and transmembrane and cytoplasmic domains of an NDV F protein. In a particular embodiment, the pharmaceutical composition is an immunogenic composition.
(95) 5.5 Prophylactic Uses of a Recombinant NDV
(96) 5.5.1 Prevention of RSV Disease
(97) In another aspect, presented herein are methods for inducing an immune response in a subject (e.g., a human subject) comprising administering the subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a human RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In a specific embodiment, the transgene comprises a codon optimized nucleic acid sequence encoding the human RSV F protein. In another aspect, presented herein are methods for inducing an immune response in a subject (e.g., a human subject) comprising administering the subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises the ectodomain of human RSV F protein and the transmembrane and cytoplasmic domains of NDV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In a specific embodiment, the ectodomain of the human RSV F protein is encoded by a codon optimized nucleic acid sequence.
(98) In another aspect, presented herein are methods for inducing an immune response to a RSV F

protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the human RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 6, 49, 50 or 58. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same human RSV F protein. For example, the human RSV F protein may be encoded by SEQ ID NO:1, 25, 27 or 29. Alternatively, the nucleic acid sequence encoding the human RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 2, 26, 28, or 30. Specific examples of transgenes encoding a human RSV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID Nos: 1, 2, 25, 26, 27, 28, 29, and 30. In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a human RSV F protein. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(99) In another aspect, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.2 and 6 for transgenes encoding a human RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:7. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:51. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 4, 44, 45, and 46). In a specific embodiment, the codon optimized sequence comprises the nucleic acid sequence of SEQ ID NO:4. In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(100) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a human RSV F protein which the packaged

genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the human RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 6, 49, 50 or 58. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same human RSV F protein. For example, the human RSV F protein may be encoded by SEQ ID NO:1, 25, 27 or 29. Alternatively, the nucleic acid sequence encoding the human RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 2, 26, 28, or 30. In a specific embodiment, the codon optimized nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO:2. Specific examples of transgenes encoding a human RSV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID Nos: 1, 2, 25, 26, 27, 28, 29, and 30. In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a human RSV F protein. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(101) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO: 7. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:51. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 4, 44, 45, or 46). In a specific embodiment, the codon optimized nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO:4. In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(102) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a human RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the human RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 6, 49, 50 or 58. Due to the degeneracy of the nucleic

acid code, a number of different nucleic acid sequences may encode for the same human RSV F protein. For example, the human RSV F protein may be encoded by SEQ ID NO:1, 25, 27 or 29. Alternatively, the nucleic acid sequence encoding the human RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 2, 26, 28, or 30. Specific examples of transgenes encoding a human RSV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NOs: 1, 2, 25, 26, 27, 28, 29, and 30. In a specific embodiment, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a human RSV F protein. In a specific embodiment, the human RSV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(103) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO: 7. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:51. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 4, 44, 45, or 46). In a specific embodiment, the codon optimized nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO:4. In a specific embodiment, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(104) In another aspect, presented herein are methods for immunizing against RSV in a subject (e.g., a bovine subject) comprising administering the subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a bovine RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a bovine RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In a specific embodiment, the transgene comprises a codon optimized nucleic acid sequence encoding the bovine RSV protein. In another aspect, presented herein are methods for inducing an immune response in a subject (e.g., a bovine subject) comprising administering the subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a

chimeric F protein, wherein the chimeric F protein comprises the ectodomain of bovine RSV F protein and the transmembrane and cytoplasmic domains of NDV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In a specific embodiment, the ectodomain of the bovine RSV F protein is encoded by a codon optimized nucleic acid sequence.

(105) In another aspect, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a bovine RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a bovine RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the bovine RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same bovine RSV F protein. For example, the bovine RSV F protein may be encoded by SEQ ID NO:9. Alternatively, the nucleic acid sequence encoding the bovine RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 11. Specific examples of transgenes encoding a bovine RSV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NOs: 9, 11, 40, 41, 42, and 43. In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a bovine RSV F protein. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(106) In another aspect, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:33. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:33. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:14, 38 or 39). In a specific embodiment, the codon optimized nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO:14. In a specific embodiment, presented herein are methods for inducing an immune response to a RSV F protein comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of

administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(107) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a bovine RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a bovine RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the bovine RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same bovine RSV F protein. For example, the bovine RSV F protein may be encoded by SEQ ID NO:9. Alternatively, the nucleic acid sequence encoding the bovine RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 11. Specific examples of transgenes encoding a bovine RSV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NOs: 9, 11, 40, 41, 42, and 43. In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a bovine RSV F protein. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(108) In another aspect, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:33. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:31. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:14, 38, or 39). In a specific embodiment, the codon optimized nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO:14. In a specific embodiment, presented herein are methods for immunizing against RSV comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(109) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the

recombinant NDV comprises a packaged genome comprising a transgene encoding a bovine RSV F protein. See, e.g., Section 5.1.2 and 6 for transgenes encoding a bovine RSV F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the bovine RSV F protein comprises the amino acid sequence set forth in SEQ ID NO: 10. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same bovine RSV F protein. For example, the bovine RSV F protein may be encoded by SEQ ID NO:9. Alternatively, the nucleic acid sequence encoding the bovine RSV F protein may be codon optimized, such as set forth in SEQ ID NO: 11. Specific examples of transgenes encoding a bovine RSV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NOs: 9, 11, 40, 41, 42, and 43. In a specific embodiment, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding a bovine RSV F protein. In a specific embodiment, the bovine RSV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(110) In another aspect, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.2 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.3 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:33. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:33. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the RSV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO:14, 38 or 39). In a specific embodiment, the codon optimized nucleic acid sequence comprises the nucleic acid sequence of SEQ ID NO:14. In a specific embodiment, presented herein are methods for the prevention of RSV disease comprising administering to a subject (e.g., a bovine subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise a bovine RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(111) In another embodiment, presented herein is a recombinant NDV or composition thereof for inducing an immune response to an RSV F protein. In another embodiment, presented herein is a recombinant NDV or composition thereof for immunizing a subject (e.g., a human or bovine subject) against RSV. In another embodiment, presented herein is a recombinant NDV or composition thereof for the prevention of an RSV disease. See, e.g., Sections 5.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4 for information regarding other therapies, and Section 5.4, infra, for information regarding compositions and routes of administration.

(112) The recombinant NDV described herein may be administered to a subject in combination with one or more other therapies. The recombinant NDV and one or more other therapies may be administered by the same or different routes of administration to the subject. In a specific embodiment, the recombinant NDV is administered to a subject intranasally. See, e.g., Sections 5.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4 for information regarding other therapies, and Section 5.4, infra, for information regarding compositions and routes of administration.
(113) The recombinant NDV and one or more additional therapies may be administered concurrently or sequentially to the subject. In certain embodiments, the recombinant NDV and one or more additional therapies are administered in the same composition. In other embodiments, the recombinant NDV and one or more additional therapies are administered in different compositions. The recombinant NDV and one or more other therapies may be administered by the same or different routes of administration to the subject. Any route known to one of skill in the art or described herein may used to administer the recombinant NDV and one or more other therapies. In a specific embodiment, the recombinant NDV is administered intranasally and the one or more other therapies is administered intravenously.
(114) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a patient to prevent the onset of one, two or more symptoms of an RSV disease (such a patient may be at risk of developing an RSV infection). In a specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents the onset or development of one, two or more symptoms of RSV disease, reduces the severity of one, two or more symptoms of RSV disease, or prevents the onset or development of one, two or more symptoms of RSV disease and reduces the severity of one, two or more symptoms of RSV disease. Symptoms of RSV disease include congested or runny nose, cough, fever, sore throat, headache, wheezing, rapid or shallow breathing or difficulty breathing, bluish color the skin due to lack of oxygen, lack of appetite, lethargy and irritability.
(115) In a specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents the spread of RSV infection. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents hospitalization. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents pneumonia caused by RSV infection. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents otitis media caused by RSV infection. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents bronchiolitis caused by RSV infection. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents recurring RSV infections. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject reduces the likelihood of asthma linked to RSV infection.
(116) In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein induces antibodies to RSV F protein. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein induces both mucosal and systemic antibodies to RSV F protein (e.g., neutralizing antibodies). In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject induces neutralizing antibody to RSV F

protein. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject induces robust, long-lived (e.g., 6 months, 1 year, 2 years, 3 years or more), antigen-specific humoral immunity. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein does not induce a disease-promoting immune response. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof induces no or a low level of inflammation. In a particular embodiment, the administration of a recombinant NDV described herein induces no inflammation in the lung or nasal cavity as assessed by the lack of evidence of inflammatory infiltrates. In another embodiment, the administration of a recombinant NDV described herein induces a small amount of inflammation in the lung or nasal cavity that is not clinically significant. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject induces an IFN response. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents RSV infection of the lower airway and inhibits RSV replication in the upper airway.

(117) In a specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject results one, two, three or more, or all of the effects reported in Section 6 (e.g., Section 6.1, 6.2, or 6.4). In a specific embodiment, a method of preventing RSV disease or immunizing against RSV involves a protocol similar to or the same as that described in Section 6, infra.

(118) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject suffering from an RSV disease. In other embodiments, an NDV (e.g., a recombinant NDV) described herein or a composition thereof, or a combination therapy described herein is administered to a subject predisposed or susceptible to an RSV disease. In some embodiments, an NDV (e.g., a recombinant NDV) or a composition thereof, or a combination therapy described herein is administered to a subject seronegative for RSV antibodies (e.g., antibodies to RSV F protein, RSV G protein, or both). In some embodiments, an NDV (e.g., a recombinant NDV) or a composition thereof, or a combination therapy described herein is administered to a subject seropositive for RSV antibodies (e.g., antibodies to RSV F protein, RSV G protein, or both). In certain embodiments, the subject is assessed for anti-RSV antibodies prior to administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein. In other embodiments, the subject is not assessed for anti-RSV antibodies prior to administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein.

(119) In certain embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human that is 0 to 6 months old, 2 to 4 months old, 4 to 6 months old, 6 to 12 months old, 6 to 18 months old, 18 to 36 months old, 1 to 5 years old, 5 to 10 years old, 10 to 15 years old, 15 to 20 years old, 20 to 25 years old, 25 to 30 years old, 30 to 35 years old, 35 to 40 years old, 40 to 45 years old, 45 to 50 years old, 50 to 55 years old, 55 to 60 years old, 60 to 65 years old, 65 to 70 years old, 70 to 75 years old, 75 to 80 years old, 80 to 85 years old, 85 to 90 years old, 90 to 95 years old or 95 to 100 years old. In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human infant. In another specific embodiment, the subject is a human infant six months old or older. In other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human toddler. In other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human child. In other embodiments, a recombinant NDV described herein or a composition thereof, or a

combination therapy described herein is administered to a human adult. In yet other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to an elderly human.

(120) In a specific embodiment, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) in close contact with an individual with increased risk of an RSV or disease resulting from RSV infection (e.g., immunocompromised or immunosuppressed individuals). In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who is pregnant. In other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who may or will be pregnant during the RSV season (e.g., generally, October to April (with peak RSV in December through February) in the Northern hemisphere). In specific embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who is a woman who has given birth 1, 2, 3, 4, 5, 6, 7, or 8 weeks earlier. In specific embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who is a parent (e.g., a mother or father) of children under the age of 18 years old.

(121) In particular embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) with a condition that increases susceptibility to RSV complications or for which RSV increases complications associated with the condition. Examples of conditions that increase susceptibility to RSV complications or for which RSV increases complications associated with the condition include conditions that affect the lung, such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), emphysema, asthma, or bacterial infections (e.g., infections caused by *Haemophilus influenzae, Streptococcus pneumoniae, Legionella pneumophila*, and *Chlamydia* trachomatus); cardiovascular disease (e.g., congenital heart disease, congestive heart failure, and coronary artery disease); endocrine disorders (e.g., diabetes); and neurological and neuron-developmental conditions (e.g., disorders of the brain, the spinal cord, the peripheral nerve, and muscle (such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (e.g., mental retardation), muscular dystrophy, and spinal cord injury)).

(122) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that resides in a group home, such as a nursing home. In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that works in, or spends a significant amount of time in, a group home, e.g., a nursing home. In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that is a health care worker (e.g., a doctor or nurse). In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that is a smoker.

(123) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to (1) a subject (e.g., a human subject) who can transmit RSV to those at high risk for complications, such as, e.g., members of households with high-risk subjects, including households that include or will include human infants (e.g., infants younger than 6 months), (2) a subject coming into contact with human infants (e.g., infants less than 6 months of age), (3) a subject who is or will come into contact with subjects who live in nursing homes or other long-term care facilities, or (4) a subject who is or will come into contact with subjects with long-term disorders of the lungs, heart, or circulation; (5) subjects with metabolic diseases (e.g., diabetes) or subjects with weakened immune systems (including

immunosuppression caused by medications, malignancies such as cancer, organ transplant, or HIV infection).; or (6) any combination of 1-5

(124) In certain embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a calf. In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a cow. In certain embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a cow undergoing or about to undergo transportation with other cattle.

(125) In certain embodiments a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject in an immunocompromised state or immunosuppressed state or at risk for becoming immunocompromised or immunosuppressed. In certain embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject that has or is at risk of getting RSV disease. For example, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject with COPD, cystic fibrosis or asthma. In some embodiments, a recombinant NDV described herein or a composition thereof is administered to a patient that is a transplant recipient.

(126) 5.5.2 Prevention of Human Metapneumovirus Disease

(127) In another aspect, presented herein are methods for inducing an immune response in a subject (e.g., a human subject) comprising administering the subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a hMPV F protein. See, e.g., Section 5.1.4 and 6 for transgenes encoding an hMPV F protein which the packaged genome may comprise. See also Sections 5.1.5 and 6 for examples of recombinant NDV that may be used in the methods. In a specific embodiment, the transgene comprises a codon optimized nucleic acid sequence encoding the hMPV F protein. In another aspect, presented herein are methods for inducing an immune response in a subject (e.g., a human subject) comprising administering the subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises the ectodomain of hMPV F protein and the transmembrane and cytoplasmic domains of NDV F protein. In a specific embodiment, the ectodomain of the hMPV F protein is encoded by a codon optimized nucleic acid sequence.

(128) In another aspect, presented herein are methods for inducing an immune response to an hMPV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a hMPV F protein. See, e.g., Section 5.1.4 and 6 for transgenes encoding an hMPV F protein which the packaged genome may comprise. See also Sections 5.1.5 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the hMPV F protein comprises the amino acid sequence set forth in SEQ ID NO: 17. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same hMPV F protein. In some embodiments, the hMPV F protein may be encoded by SEQ ID NO:16, 52, 54 or 56. Alternatively, the nucleic acid sequence encoding the hMPV F protein may be codon optimized, such as set forth in SEQ ID NO: 18, 53, 55 or 57. Specific examples of transgenes encoding an hMPV F protein include transgenes comprising RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NOs:16, 18, 52, 53, 54, 55, and 57. In a specific embodiment, presented herein are methods for inducing an immune response to an hMPV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific

embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(129) In another aspect, presented herein are methods for inducing an immune response to an hMPV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.4 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.5 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:15. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:32. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the hMPV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 19, 34, 35, and 36). In a specific embodiment, presented herein are methods for inducing an immune response to an hMPV F protein comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(130) In another aspect, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a hMPV F protein. See, e.g., Section 5.1.4 and 6 for transgenes encoding an hMPV F protein which the packaged genome may comprise. See also Sections 5.1.5 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the hMPV F protein comprises the amino acid sequence set forth in SEQ ID NO: 17. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same hMPV F protein. In some embodiments, the hMPV F protein may be encoded by SEQ ID NO:16, 52, 54 or 56. Alternatively, the nucleic acid sequence encoding the hMPV F protein may be codon optimized, such as set forth in SEQ ID NO: 18, 53, 55, or 57. Specific examples of transgenes encoding an hMPV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NOs:16, 18, 52, 53, 54, 55, and 57. In a specific embodiment, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(131) In another aspect, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein,

wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.4 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.5 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:15. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:32. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the hMPV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 19, 34, 35, and 36). In a specific embodiment, presented herein are methods for immunizing against hMPV comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(132) In another aspect, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a hMPV F protein. See, e.g., Section 5.1.4 and 6 for transgenes encoding an hMPV F protein which the packaged genome may comprise. See also Sections 5.1.5 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the hMPV F protein comprises the amino acid sequence set forth in SEQ ID NO: 17. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for the same hMPV F protein. In some embodiments, the hMPV F protein may be encoded by SEQ ID NO:16, 52, 54 or 56. Alternatively, the nucleic acid sequence encoding the hMPV F protein may be codon optimized, such as set forth in SEQ ID NO: 18, 53, 55 or 57. Specific examples of transgenes encoding an hMPV F protein include transgenes comprising an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NOs:16, 18, 52, 53, 54, 55, and 57. In a specific embodiment, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding an hMPV F protein. In a specific embodiment, the hMPV F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly.

(133) In another aspect, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1.4 and 6 for transgenes encoding a chimeric F protein which the packaged genome may comprise. See also Sections 5.1.5 and 6 for examples of recombinant NDV that may be used in the methods. In one embodiment, the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:15. Due to the degeneracy of the nucleic acid code, a number of different nucleic acid sequences may encode for

the same chimeric F protein. For example, the chimeric F protein may be encoded by SEQ ID NO:32. Alternatively, the nucleic acid sequence encoding one or more domains of the chimeric F protein may be codon optimized (e.g., the nucleic acid sequence encoding the hMPV F protein ectodomain may be codon optimized, such as set forth in SEQ ID NO: 19, 34, 35, and 36). In a specific embodiment, presented herein are methods for the prevention of hMPV disease comprising administering to a subject (e.g., a human subject) a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprise an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the transgene comprises a codon optimized nucleic acid sequence encoding the hMPV F protein ectodomain. In a specific embodiment, the chimeric F protein is expressed by cells infected with the recombinant NDV. The recombinant NDV may be administered to a subject by any route of administration. In another specific embodiment, the recombinant NDV is administered to a subject intranasally. In some embodiments, the recombinant NDV is administered to a subject intramuscularly. In another embodiment, presented herein is a recombinant NDV or composition thereof for inducing an immune response to an hMPV F protein. In another embodiment, presented herein is a recombinant NDV or composition thereof for immunizing a subject (e.g., a human subject) against hMPV. In another embodiment, presented herein is a recombinant NDV or composition thereof for the prevention of an hMPV disease. See, e.g., Sections 5.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4 for information regarding other therapies, and Section 5.4, infra, for information regarding compositions and routes of administration.

(134) The recombinant NDV described herein may be administered to a subject in combination with one or more other therapies. The recombinant NDV and one or more other therapies may be administered by the same or different routes of administration to the subject. In a specific embodiment, the recombinant NDV is administered to a subject intranasally. See, e.g., Sections 5.1, and 6, infra for information regarding recombinant NDV, Section 5.5.4 for information regarding other therapies, and Section 5.4, infra, for information regarding compositions and routes of administration.

(135) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a patient to prevent the onset of one, two or more symptoms of an hMPV disease (e.g., such a patient is at risk of developing an hMPV infection). In a specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents the onset or development of one, two or more symptoms of hMPV disease, reduces the severity of one, two or more symptoms of hMPV disease, or prevents the onset or development of one, two or more symptoms of hMPV disease and reduces the severity of one, two or more symptoms of hMPV disease. Symptoms of hMPV disease include nasal congestion, runny nose, fever, cough, sore throat, wheezing, difficulty breathing, lack of appetite, lethargy and irritability.

(136) In a specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents the spread of hMPV infection. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents hospitalization. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents pneumonia caused by hMPV infection. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject reduces the likelihood of asthma linked to hMPV infection.

(137) In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein induces antibodies to hMPV F protein. In another specific embodiment, the administration of a recombinant NDV described

herein or a composition thereof, or a combination therapy described herein induces both mucosal and systemic antibodies to hMPV F protein (e.g., neutralizing antibodies). In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject induces neutralizing antibody to hMPV F protein. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein does not induce a disease-promoting immune response. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof induces no or a low level of inflammation. In a particular embodiment, the administration of a recombinant NDV described herein induces no inflammation in the lung or nasal cavity as assessed by the lack of evidence of inflammatory infiltrates. In another embodiment, the administration of a recombinant NDV described herein induces a small amount of inflammation in the lung or nasal cavity that is not clinically significant. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject induces robust, long-lived (e.g., 6 months, 1 year, 2 years, 3 years or more), antigen-specific humoral immunity. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject induces an IFN response. In another specific embodiment, the administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein to a subject prevents hMPV infection of the lower airway and inhibits hMPV replication in the upper airway.

(138) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject suffering from an hMPV disease. In other embodiments, an NDV (e.g., a recombinant NDV) described herein or a composition thereof, or a combination therapy described herein is administered to a subject predisposed or susceptible to an hMPV disease. In some embodiments, an NDV (e.g., a recombinant NDV) or a composition thereof, or a combination therapy described herein is administered to a subject seronegative for hMPV antibodies (e.g., antibodies to hMPV F protein, hMPV G protein or both). In some embodiments, an NDV (e.g., a recombinant NDV) or a composition thereof, or a combination therapy described herein is administered to a subject seropositive for hMPV antibodies (e.g., antibodies to hMPV F protein, hMPV G protein, both). In certain embodiments, the subject is assessed for anti-hMPV antibodies prior to administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein. In other embodiments, the subject is not assessed for anti-hMPV antibodies prior to administration of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein.

(139) In certain embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human that is 0 to 6 months old, 2 to 4 months old, 4 to 6 months old, 6 to 12 months old, 6 to 18 months old, 18 to 36 months old, 1 to 5 years old, 5 to 10 years old, 10 to 15 years old, 15 to 20 years old, 20 to 25 years old, 25 to 30 years old, 30 to 35 years old, 35 to 40 years old, 40 to 45 years old, 45 to 50 years old, 50 to 55 years old, 55 to 60 years old, 60 to 65 years old, 65 to 70 years old, 70 to 75 years old, 75 to 80 years old, 80 to 85 years old, 85 to 90 years old, 90 to 95 years old or 95 to 100 years old. In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human infant. In another specific embodiment, the subject is a human infant six months old or older. In other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human toddler. In other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a human child. In other embodiments, a recombinant NDV described herein or a composition thereof, or a

combination therapy described herein is administered to a human adult. In yet other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to an elderly human.

(140) In a specific embodiment, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) in close contact with an individual with increased risk of an hMPV infection or disease resulting from hMPV infection (e.g., immunocompromised or immunosuppressed individuals). In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who is pregnant. In other embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who may or will be pregnant during the hMPV season (e.g., generally, November to July in the Northern hemisphere). In specific embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who is a woman who has given birth 1, 2, 3, 4, 5, 6, 7, or 8 weeks earlier. In specific embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) who is a parent (e.g., a mother or father) of children under the age of 18 years old.

(141) In particular embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) with a condition that increases susceptibility to hMPV complications or for which hMPV increases complications associated with the condition. Examples of conditions that increase susceptibility to hMPV complications or for which hMPV increases complications associated with the condition include conditions that affect the lung, such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), emphysema, asthma, or bacterial infections (e.g., infections caused by *Haemophilus influenzae, Streptococcus pneumoniae, Legionella pneumophila*, and *Chlamydia* trachomatus); cardiovascular disease (e.g., congenital heart disease, congestive heart failure, and coronary artery disease); endocrine disorders (e.g., diabetes); and neurological and neuron-developmental conditions (e.g., disorders of the brain, the spinal cord, the peripheral nerve, and muscle (such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (e.g., mental retardation), muscular dystrophy, and spinal cord injury)).

(142) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that resides in a group home, such as a nursing home. In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that works in, or spends a significant amount of time in, a group home, e.g., a nursing home. In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that is a health care worker (e.g., a doctor or nurse). In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered a subject (e.g., a human subject) that is a smoker.

(143) In some embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to (1) a subject (e.g., a human subject) who can transmit hMPV to those at high risk for complications, such as, e.g., members of households with high-risk subjects, including households that include or will include human infants (e.g., infants younger than 6 months), (2) a subject coming into contact with human infants (e.g., infants less than 6 months of age), (3) a subject who is or will come into contact with subjects who live in nursing homes or other long-term care facilities, (4) a subject who is or will come into contact with subjects with long-term disorders of the lungs, heart, or circulation; (5) subjects with metabolic diseases (e.g., diabetes) or subjects with weakened immune systems (including immunosuppression

caused by medications, malignancies such as cancer, organ transplant, or HIV infection); or (6) any combination of 1-5.

(144) In certain embodiments a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject in an immunocompromised state or immunosuppressed state or at risk for becoming immunocompromised or immunosuppressed. In certain embodiments, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject that has or is at risk of getting hMPV disease. For example, a recombinant NDV described herein or a composition thereof, or a combination therapy described herein is administered to a subject with COPD, cystic fibrosis or asthma. In some embodiments, a recombinant NDV described herein or a composition thereof is administered to a patient that is a transplant recipient.

(145) 5.5.3 Dosage and Frequency

(146) The amount of a recombinant NDV or a composition thereof, which will be effective in the prevention of RSV disease or hMPV disease, or immunization against RSV or hMPV will depend on the route of administration, the general health of the subject, etc. Standard clinical techniques, such as in vitro assays, may optionally be employed to help identify dosage ranges. However, suitable dosage ranges of a recombinant NDV for administration are generally about 10.sup.4 to about 10.sup.12, and can be administered to a subject once, twice, three, four or more times with intervals as often as needed. In certain embodiments, dosages similar to those currently being used in clinical trials for NDV are administered to a subject.

(147) In certain embodiments, a recombinant NDV or a composition thereof is administered to a subject as a single dose followed by a second dose 1 to 6 weeks, 1 to 5 weeks, 1 to 4 weeks, 1 to 3 weeks, 1 to 2 weeks, 6 to 12 weeks, 3 to 6 months, 6 to 9 months, 6 to 12 months, or 6 to 9 months later. In accordance with these embodiments, booster inoculations may be administered to the subject at 3 to 6 month or 6 to 12 month intervals following the second inoculation.

(148) In certain embodiments, administration of the same recombinant NDV or a composition thereof may be repeated and the administrations may be separated by at least 1 day, 2 days, 3 days, 5 days, 6 says, 7 days, 10 days, 14 days, 15 days, 21 days, 28 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months. In other embodiments, administration of the same recombinant NDV or a composition thereof may be repeated and the administrations may be separated by 1 to 14 days, 1 to 7 days, 7 to 14 days, 1 to 30 days, 15 to 30 days, 15 to 45 days, 15 to 75 days, 15 to 90 days, 1 to 3 months, 3 to 6 months, 3 to 12 months, or 6 to 12 months. In some embodiments, a first recombinant NDV or a composition thereof is administered to a subject followed by the administration of a second recombinant NDV or a composition thereof. In some embodiments, the first and second recombinant NDV are different from each other. For example, the first recombinant NDV may comprise a packaged genome comprising a transgene encoding an RSV F protein, and the second recombinant NDV may comprise a package genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In another example, the first recombinant NDV may comprise a packaged genome comprising a transgene encoding an hMPV F protein, and the second recombinant NDV may comprise a package genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In certain embodiments, the first and second recombinant NDVs or compositions thereof may be separated by at least 1 day, 2 days, 3 days, 5 days, 6 days, 7 days, 10 days, 14 days, 15 days, 21 days, 28 days, 30 days, 45 days, 2 months, 75 days, 3 months, or at least 6 months. In other embodiments, the first and second recombinant NDVs or compositions thereof may be separated by 1 to 14 days, 1 to 7 days, 7 to 14 days, 1 to 30 days, 15 to 30 days, 15 to 45 days, 15 to 75 days, 15 to 90 days, 1 to 3 months, 3 to 6 months, 3 to 12 months, or 6 to 12 months.

(149) In certain embodiments, a recombinant NDV or composition thereof is administered to a

subject in combination with one or more additional therapies, such as a therapy described in Section 5.5.4, infra. The dosage of the other one or more additional therapies will depend upon various factors including, e.g., the therapy, the route of administration, the general health of the subject, etc. and should be decided according to the judgment of a medical practitioner. In specific embodiments, the dose of the other therapy is the dose and/or frequency of administration of the therapy recommended for the therapy for use as a single agent is used in accordance with the methods disclosed herein. Recommended doses for approved therapies can be found in the Physician's Desk Reference.

(150) In certain embodiments, an recombinant NDV or composition thereof is administered to a subject concurrently with the administration of one or more additional therapies. In a specific embodiment, a first pharmaceutical composition comprising a first recombinant NDV is administered to a subject in combination with a second pharmaceutical composition comprising a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes a human RSV F protein, and wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, wherein the second transgene encodes an hMPV F protein. In another specific embodiment, a first pharmaceutical composition comprising a first recombinant NDV is administered to a subject in combination with a second pharmaceutical composition comprising a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes a human RSV F protein, wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, and wherein the second transgene encodes a chimeric F protein comprising an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In another specific embodiment, a first pharmaceutical composition comprising a first recombinant NDV is administered to a subject in combination with a second pharmaceutical composition comprising a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes an hMPV F protein, wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, and wherein the second transgene encodes a chimeric F protein comprising a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In another specific embodiment, a first pharmaceutical composition comprising a first recombinant NDV is administered to a subject in combination with a second pharmaceutical composition comprising a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a first transgene, wherein the first transgene encodes a first chimeric F protein comprising an hMPV RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, wherein the second recombinant NDV comprises a packaged genome comprising a second transgene, and wherein the second transgene encodes a second chimeric F protein comprising a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. See, e.g., Section 5.1 or 6 for nucleic acid sequences encoding such transgenes. In certain embodiments, the first and second pharmaceutical compositions are administered concurrently to the subject, or within 1 minute, 2 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, 30 minutes, 45 minutes, 60 minutes, 1.5 hours, 2 hours, 3 hours, 4 hours, 5 hours, or 6 hours of each other. In certain embodiments, the first and second pharmaceutical compositions are administered to the subject within 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks or 12 weeks of each other. In certain embodiments, the first and second pharmaceutical compositions are administered to the subject within 3-6 months, 6-9 months, 6-12 months, or 3 months, 4 months, 6 months, 9 months, or 12 months of each other.

(151) In certain embodiments, a first pharmaceutical composition is administered to a subject as a priming dose and after a certain period (e.g., 1 month, 2 months, 3 months, 4 months, 5 months, 6

months, or 1-6 months) a booster dose of a second pharmaceutical composition is administered. In some embodiments, the first pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein, and the second recombinant NDV comprises a package genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In certain embodiments, the first pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a transgene encoding an hMPV F protein, and the second recombinant NDV comprises a package genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In some embodiments, the first pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a transgene encoding a human RSV F protein, and the second recombinant NDV comprises a package genome comprising a transgene encoding an hMPV F protein. In certain embodiments, the first pharmaceutical composition comprises a first recombinant NDV and a second recombinant NDV, wherein the first recombinant NDV comprises a packaged genome comprising a transgene encoding a first chimeric F protein, and the second recombinant NDV comprises a package genome comprising a transgene encoding a second chimeric F protein, wherein the first chimeric F protein comprises a human RSV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains, and wherein the second chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. In some embodiments, the second pharmaceutical composition comprises the same recombinant NDV as the first pharmaceutical composition. In another embodiments, the second pharmaceutical composition comprises the same recombinant NDV as the first pharmaceutical composition with the exception that the strain of NDV used as the backbone of the virus is different.

(152) 5.5.4 Additional Therapies

(153) Additional therapies that can be used in a combination with a recombinant NDV described herein or a composition thereof include, but are not limited to, acetaminophen, ibuprofen, throat lozenges, cough suppressants, inhalers, antibiotics and oxygen. In a specific embodiment, the additional therapy is a second recombinant NDV described herein.

(154) 5.6 Biological Assays

(155) In a specific embodiment, one, two or more of the assays described in Section 6 may be used to characterize a recombinant NDV described herein, or an F protein or a chimeric F protein.

(156) 5.6.1 In Vitro Viral Assays

(157) Viral assays include those that indirectly measure viral replication (as determined, e.g., by plaque formation) or the production of viral proteins (as determined, e.g., by western blot analysis) or viral RNAs (as determined, e.g., by RT-PCR or northern blot analysis) in cultured cells in vitro using methods which are well known in the art.

(158) Growth of the recombinant NDVs described herein can be assessed by any method known in the art or described herein (e.g., in cell culture (e.g., cultures of chicken embryonic kidney cells or cultures of chicken embryonic fibroblasts (CEF)) (see, e.g., Section 6). Viral titer may be determined by inoculating serial dilutions of a recombinant NDV described herein into cell cultures (e.g., CEF, MDCK, EFK-2 cells, Vero cells, primary human umbilical vein endothelial cells (HUVEC), H292 human epithelial cell line or HeLa cells), chick embryos, or live animals (e.g., avians). After incubation of the virus for a specified time, the virus is isolated using standard methods. Physical quantitation of the virus titer can be performed using PCR applied to viral supernatants (Quinn & Trevor, 1997; Morgan et al., 1990), hemagglutination assays, tissue culture infectious doses (TCID50) or egg infectious doses (EID50). An exemplary method of assessing

viral titer is described in Section 6, below.
(159) Incorporation of nucleotide sequences encoding a heterologous peptide or protein (e.g., a transgene into the genome of a recombinant NDV described herein can be assessed by any method known in the art or described herein (e.g., in cell culture, an animal model or viral culture in embryonated eggs)). For example, viral particles from cell culture of the allantoic fluid of embryonated eggs can be purified by centrifugation through a sucrose cushion and subsequently analyzed for protein expression by Western blotting using methods well known in the art. In a specific embodiment, a method described in Section 6, infra, is used to assess the incorporation of a transgene into the genome of a recombinant NDV.
(160) Immunofluorescence-based approaches may also be used to detect virus and assess viral growth. Such approaches are well known to those of skill in the art, e.g., fluorescence microscopy and flow cytometry (see, e.g., Section 6, infra). Methods for flow cytometry, including fluorescence activated cell sorting (FACS), are available (see, e.g., Owens, et al. (1994) *Flow Cytometry Principles for Clinical Laboratory Practice*, John Wiley and Sons, Hoboken, NJ; Givan (2001) *Flow Cytometry*, 2.sup.nd ed.; Wiley-Liss, Hoboken, NJ; Shapiro (2003) *Practical Flow Cytometry*, John Wiley and Sons, Hoboken, NJ). Fluorescent reagents suitable for modifying nucleic acids, including nucleic acid primers and probes, polypeptides, and antibodies, for use, e.g., as diagnostic reagents, are available (Molecular Probesy (2003) *Catalogue*, Molecular Probes, Inc., Eugene, OR; Sigma-Aldrich (2003) *Catalogue*, St. Louis, MO). See, e.g., the assays described in Section 6, infra.
(161) Standard methods of histology of the immune system are described (see, e.g., Muller-Harmelink (ed.) (1986) *Human Thymus: Histopathology and Pathology*, Springer Verlag, New York, NY; Hiatt, et al. (2000) *Color Atlas of Histology*, Lippincott, Williams, and Wilkins, Phila, PA; Louis, et al. (2002) *Basic Histology: Text and Atlas*, McGraw-Hill, New York, NY). See also Section 6, infra, for histology and immunohistochemistry assays that may be used.
(162) 5.6.2 Interferon Assays
(163) IFN induction and release by a recombinant NDV described herein may be determined using techniques known to one of skill in the art. For example, the amount of IFN induced in cells following infection with a recombinant NDV described herein may be determined using an immunoassay (e.g., an ELISA or Western blot assay) to measure IFN expression or to measure the expression of a protein whose expression is induced by IFN. Alternatively, the amount of IFN induced may be measured at the RNA level by assays, such as Northern blots and quantitative RT-PCR, known to one of skill in the art. In specific embodiments, the amount of IFN released may be measured using an ELISPOT assay. Further, the induction and release of cytokines and/or interferon-stimulated genes may be determined by, e.g., an immunoassay or ELISPOT assay at the protein level and/or quantitative RT-PCR or northern blots at the RNA level.
(164) 5.6.3 Activation Marker Assays and Immune Cell Infiltration Assay
(165) Techniques for assessing the expression of T cell marker, B cell marker, activation marker, co-stimulatory molecule, ligand, or inhibitory molecule by immune cells are known to one of skill in the art. For example, the expression of T cell marker, B cell marker, an activation marker, co-stimulatory molecule, ligand, or inhibitory molecule by an immune cell can be assessed by flow cytometry. In a specific embodiment, an assay described in Section 6, infra, is used to assess infiltration of a type(s) of immune cell.
(166) 5.6.4 Toxicity Studies
(167) In some embodiments, the recombinant NDVs described herein or compositions thereof, or combination therapies described herein are tested for cytotoxicity in mammalian, preferably human, cell lines. In certain embodiments, cytotoxicity is assessed in one or more of the following non-limiting examples of cell lines: U937, a human monocyte cell line; primary peripheral blood mononuclear cells (PBMC); Huh7, a human hepatoblastoma cell line; HL60 cells, HT1080, HEK 293T and 293H, MLPC cells, human embryonic kidney cell lines; human melanoma cell lines,

such as SkMel2, SkMel-119 and SkMel-197; THP-1, monocytic cells; a HeLa cell line; and neuroblastoma cells lines, such as MC-IXC, SK-N-MC, SK-N-MC, SK-N-DZ, SH-SY5Y, and BE(2)-C. In some embodiments, the ToxLite assay is used to assess cytotoxicity.

(168) Many assays well-known in the art can be used to assess viability of cells or cell lines following infection with a recombinant NDV described herein or composition thereof, and, thus, determine the cytotoxicity of the recombinant NDV or composition thereof. For example, cell proliferation can be assayed by measuring Bromodeoxyuridine (BrdU) incorporation, (.sup.3H) thymidine incorporation, by direct cell count, or by detecting changes in transcription, translation or activity of known genes such as proto-oncogenes (e.g., fos, myc) or cell cycle markers (Rb, cdc2, cyclin A, D1, D2, D3, E, etc.). The levels of such protein and mRNA and activity can be determined by any method well known in the art. For example, protein can be quantitated by known immunodiagnostic methods such as ELISA, Western blotting or immunoprecipitation using antibodies, including commercially available antibodies. mRNA can be quantitated using methods that are well known and routine in the art, for example, using northern analysis, RNase protection, or polymerase chain reaction in connection with reverse transcription. Cell viability can be assessed by using trypan-blue staining or other cell death or viability markers known in the art. In a specific embodiment, the level of cellular ATP is measured to determined cell viability. In preferred embodiments, a recombinant NDV described herein or composition thereof does not kill healthy (i.e., non-cancerous) cells.

(169) In specific embodiments, cell viability may be measured in three-day and seven-day periods using an assay standard in the art, such as the CellTiter-Glo Assay Kit (Promega) which measures levels of intracellular ATP. A reduction in cellular ATP is indicative of a cytotoxic effect. In another specific embodiment, cell viability can be measured in the neutral red uptake assay. In other embodiments, visual observation for morphological changes may include enlargement, granularity, cells with ragged edges, a filmy appearance, rounding, detachment from the surface of the well, or other changes.

(170) The recombinant NDVs described herein or compositions thereof, or combination therapies can be tested for in vivo toxicity in animal models. For example, animal models, known in the art to test the effects of compounds on RSV infection or hMPV infection can also be used to determine the in vivo toxicity of the recombinant NDVs described herein or compositions thereof, or combination therapies. For example, animals are administered a range of pfu of a recombinant NDV described herein, and subsequently, the animals are monitored over time for various parameters, such as one, two or more of the following: lethality, weight loss or failure to gain weight, and levels of serum markers that may be indicative of tissue damage (e.g., creatine phosphokinase level as an indicator of general tissue damage, level of glutamic oxalic acid transaminase or pyruvic acid transaminase as indicators for possible liver damage). These in vivo assays may also be adapted to test the toxicity of various administration mode and regimen in addition to dosages.

(171) The toxicity, efficacy or both of a recombinant NDV described herein or a composition thereof, or a combination therapy described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Therapies that exhibit large therapeutic indices are preferred.

(172) The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage of the therapies for use in subjects. The dosage of such agents lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any therapy described herein, the therapeutically effective dose can be estimated initially from cell culture assays.

(173) 5.6.5 Biological Activity Assays
(174) The recombinant NDVs described herein or compositions thereof, or combination therapies described herein can be tested for biological activity using animal models for inhibiting RSV disease, hMPV disease, antibody response to the recombinant NDVs, etc. (see, e.g., Section 6). Such animal model systems include, but are not limited to, rats, mice, hamsters, cotton rats, chicken, cows, monkeys (e.g., African green monkey), pigs, dogs, rabbits, etc.
(175) In a specific embodiment, the recombinant NDVs described herein or compositions thereof, or combination therapies described herein may be tested using animal models for the ability to induce a certain geometric mean titer of antibody(ies) that binds to the RSV F protein (e.g., human RSV F protein or bovine F protein) or hMPV F protein. In another specific embodiment, the recombinant NDVs described herein or compositions thereof, or combination therapies described herein may be tested using animal models for the ability to induce antibodies that have neutralizing activity against RSV F protein (e.g., human RSV F protein or bovine F protein) or hMPV F protein in a microneutralization assay. For example, the microneutralization assay described in Section 6, infra, may be used to assess neutralizing activity. In some embodiments, the recombinant NDVs described herein or compositions thereof, or combination therapies described herein may be tested using animal models for the ability to induce a certain geometric mean titer of antibody(ies) that binds to the RSV F protein (e.g., human RSV F protein or bovine F protein) or hMPV F protein and neutralizes RSV F protein (e.g., human RSV F protein or bovine F protein) or hMPV F protein in a microneutralizsation assay. In a specific embodiment, the recombinant NDVs described herein or compositions thereof, or combination therapies described herein may be tested using animal models for the ability to induce a certain fold increase in levels of antibody(ies) that binds to RSV F protein (e.g., human RSV F protein or bovine F protein) or hMPV F protein post-immunization with a recombinant NDV described herein or a composition thereof relative to the levels of such antibody pre-immunization. For example, a 3 fold, 4 fold, 5 fold, 6 fold, 7 fold, 8 fold or greater increase in levels of antibody(ies) that binds to RSV F protein (e.g., human RSV F protein or bovine F protein) or hMPV F protein post-immunization with a recombinant NDV described herein or a composition thereof relative to the levels of such antibody(ies) pre-immunization.
(176) 5.6.6 Expression of Transgene
(177) Assays for testing the expression of RSV F protein, chimeric F protein, or hMPV F protein in cells infected with a recombinant NDV comprising a packaged genome comprising a transgene encoding RSV F protein, chimeric F protein, or hMPV F protein, respectively may be conducted using any assay known in the art, such as, e.g., western blot, immunofluorescence, and ELISA, or any assay described herein (see, e.g., Section 6).
(178) In a specific aspect, ELISA is utilized to detect expression of RSV F protein, chimeric F protein, or hMPV F protein in cells infected with a recombinant NDV comprising a packaged genome comprising a transgene encoding of RSV F protein, chimeric F protein, or hMPV F protein. In a specific embodiment, RSV F protein is quantified using an ELISA such as described in Section 6, infra.
(179) In one embodiment, RSV F protein or chimeric F protein encoded by a packaged genome of a recombinant NDV described herein is assayed for proper folding by testing its ability to bind specifically to an anti-RSV F protein antibody (e.g., Synagis®) using any assay for antibody-antigen interaction known in the art. In another embodiment, hMPV F protein or chimeric F protein encoded by a packaged genome of a recombinant NDV described herein is assayed for proper folding by testing its ability to bind specifically to an anti-hMPV F protein antibody using any assay for antibody-antigen interaction known in the art. In another embodiment, an RSV F protein, a chimeric F protein, or an hMPV F protein encoded by a packaged genome of a recombinant NDV described herein is assayed for proper folding by determination of the structure or conformation of the RSV F protein, chimeric F protein, or hMPV F protein, respectively using any method known in the art such as, e.g., NMR, X-ray crystallographic methods, or secondary structure prediction

methods, e.g., circular dichroism. Additional assays assessing the conformation and antigenicity of RSV F protein, chimeric F protein, or hMPV F protein may include, e.g., immunofluorescence microscopy, flow cytometry, western blot, and ELISA may be used. In vivo immunization in animal models, such as cotton rats or mice, may also be used to assess the antigenicity of RSV F protein, chimeric F protein, or hMPV F protein.

(180) Assays for testing the functionality of RSV F protein, chimeric F protein, or hMPV F protein in cells infected with a recombinant NDV comprising a packaged genome comprising a transgene encoding RSV F protein, chimeric F protein, or hMPV F protein, respectively, may be conducted using any assay known in the art. However, it is not necessary that the RSV F protein, chimeric F protein, or hMPV F protein of a recombinant NDV described herein maintain the ability of the F protein to fuse the virus envelope with the cell membrane.

(181) 5.7 Kits

(182) In one aspect, provided herein is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of a composition (e.g., a pharmaceutical compositions) described herein. In a specific embodiment, provided herein is a pharmaceutical pack or kit comprising a container, wherein the container comprises a recombinant NDV comprising a packaged genome comprising a transgene encoding an RSV F protein (e.g., a human or bovine RSV F protein), or a pharmaceutical composition comprising the recombinant NDV. In another specific embodiment, provided herein is a pharmaceutical pack or kit comprising a container, wherein the container comprises a recombinant NDV comprising a packaged genome comprising a transgene encoding chimeric F protein, or a pharmaceutical composition comprising the recombinant NDV, wherein the chimeric F protein comprises an RSV F protein (e.g., a human or bovine RSV F protein) ectodomain and NDV F protein transmembrane and cytoplasmic domains. In a specific embodiment, provided herein is a pharmaceutical pack or kit comprising a container, wherein the container comprises a recombinant NDV comprising a packaged genome comprising a transgene encoding an hMPV F protein, or a pharmaceutical composition comprising the recombinant NDV. In another specific embodiment, provided herein is a pharmaceutical pack or kit comprising a container, wherein the container comprises a recombinant NDV comprising a packaged genome comprising a transgene encoding chimeric F protein, or a pharmaceutical composition comprising the recombinant NDV, wherein the chimeric F protein comprises an hMPV F protein ectodomain and NDV F protein transmembrane and cytoplasmic domains. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

(183) 5.8 Sequences

(184) The sequences disclosed in this section may be used to produce the recombinant NDV described herein.

(185) TABLE-US-00001 TABLE 1 Human RSV F Sequences SEQ ID Description Sequence NO. Wild-type atggagttgctaatcctcaaagcaaatgcaattaccacaatcctcactgcag 1 nucleic acid tcacattttgttttgcttctggtcaaaacatcactgaagaattttatcaatc sequence aacatgcagtgcagttagcaaaggctatcttagtgctctgagaactggttgg encoding human tataccagtgttataactatagaattaagtaatatcaaggaaaataagtgta RSV-F of A2 atggaacagatgctaaggtaaaattgataaaacaagaattagataaatataa strain aaatgctgtaacagaattgcagttgctcatgcaaagcacaccagcaacaaac aatcgagccagaagagaactaccaaggtttatgaattatacactcaacaatg ccaaaaaaaccaatgtaacattaagcaagaaaaggaaaagaagatttcttgg ttttttgttaggtgttggatctgcaatcgccagtggcgttgctgtatctaag gtcctgcacctagaaggggaagtgaacaagatcaaaagtgctctactatcca caaacaaggctgtagtcagcttatcaaatggagttagtgtcttaaccagcaa agtgttagacctcaaaaactatatagataaacaattgttacctattgtgaac

aagcaaagctgcagcatatcaaatatagcaactgtgatagagttccaacaaa
agaacaacagactactagagattaccagggaatttagtgttaatgcaggtgt
aactacacctgtaagcacttacatgttaactaatagtgaattattgtcatta
atcaatgatatgcctataacaaatgatcagaaaaagttaatgtccaacaatg
ttcaaatagttagacagcaaagttactctatcatgtccataataaaagagga
agtcttagcatatgtagtacaattaccactatatggtgttatagatacaccc
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ccaacatctgtttaacaagaactgacagaggatggtactgtgacaatgcagg
atcagtatctttcttcccacaagctgaaacatgtaaagttcaatcaaatcga
gtattttgtgacacaatgaacagtttaacattaccaagtgaagtaaatctct
gcaatgttgacatattcaaccccaaatatgattgtaaaattatgacttcaaa
aacagatgtaagcagctccgttatcacatctctaggagccattgtgtcatgc
tatggcaaaactaaatgtacagcatccaataaaaatcgtggaatcataaaga
cattttctaacgggtgcgattatgtatcaaataaaggggtggacactgtgtc
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atgaatttgatgcatcaatatctcaagtcaacgagaagattaaccagagcct
agcatttattcgtaaatccgatgaattattacataatgtaaatgctggtaaa
tccaccataaatatcatgataactactataattatagtgattatagtaatat
tgttatcattaattgctgttggactgctcttatactgtaaggccagaagcac
accagtcacactaagcaaagatcaactgagtggtataaataatattgcattt agtaactaa Codon-
ATGGAGCTGCTGATCCTGAAGGCCAACGCCATCACCAC 2 optimized
CATCCTGACCGCCGTGACCTTCTGCTTCGCCAGCGGCCA nucleic acid
GAACATCACCGAGGAGTTCTACCAGAGCACCTGCAGCG sequence
CCGTGAGCAAGGGCTACCTGAGCGCCCTGCGCACCGGC encoding human
TGGTACACCAGCGTGATCACCATCGAGCTGAGCAACAT RSV F of A2
CAAGGAGAACAAGTGCAACGGCACCGACGCCAAGGTG strain (codon
AAGCTGATCAAGCAGGAGCTGGACAAGTACAAGAACG optimized
CCGTGACCGAGCTGCAGCTGCTGATGCAGAGCACCCCC version of SEQ
GCCACCAACAACCGCGCCCGCCGCGAGCTGCCCCGCTT ID NO:1)
CATGAACTACACCCTGAACAACGCCAAGAAGACCAACG
TGACCCTGAGCAAGAAGCGCAAGCGCCGCTTCCTGGGC
TTCCTGCTGGGCGTGGGCAGCGCCATCGCCAGCGGCGT
GGCCGTGAGCAAGGTGCTGCACCTGGAGGGCGAGGTGA
ACAAGATCAAGAGCGCCCTGCTGAGCACCAACAAGGCC
GTGGTGAGCCTGAGCAACGGCGTGAGCGTGCTGACCAG
CAAGGTGCTGGACCTGAAGAACTACATCGACAAGCAGC
TGCTGCCCATCGTGAACAAGCAGAGCTGCAGCATCAGC
AACATCGCCACCGTGATCGAGTTCCAGCAGAAGAACAA
CCGCCTGCTGGAGATCACCCGCGAGTTCAGCGTGAACG
CCGGCGTGACCACCCCCGTGAGCACCTACATGCTGACC
AACAGCGAGCTGCTGAGCCTGATCAACGACATGCCCAT
CACCAACGACCAGAAGAAGCTGATGAGCAACAACGTG
CAGATCGTGCGCCAGCAGAGCTACAGCATCATGAGCAT
CATCAAGGAGGAGGTGCTGGCCTACGTGGTGCAGCTGC
CCCTGTACGGCGTGATCGACACCCCCTGCTGGAAGCTG
CACACCAGCCCCCTGTGCACCACCAACACCAAGGAGGG
CAGCAACATCTGCCTGACCCGCACCGACAGGGGCTGGT
ACTGCGACAACGCCGGCAGCGTGAGCTTCTTCCCCCAG
GCCGAGACCTGCAAGGTGCAGAGCAACCGCGTGTTCTG

CGACACCATGAACAGCCTGACCCTGCCCAGCGAGGTGA
ACCTGTGCAACGTGGACATCTTCAACCCCAAGTACGAC
TGCAAGATCATGACCAGCAAGACCGACGTGAGCAGCAG
CGTGATCACCAGCCTGGGCGCCATCGTGAGCTGCTACG
GCAAGACCAAGTGCACCGCCAGCAACAAGAACAGGGG
CATCATCAAGACCTTCAGCAACGGCTGCGACTACGTGA
GCAACAAGGGCGTGGACACCGTGAGCGTGGGCAACAC
CCTGTACTACGTGAACAAGCAGGAGGGCAAGAGCCTGT
ACGTGAAGGGCGAGCCCATCATCAACTTCTACGACCCC
CTGGTGTTCCCCAGCGACGAGTTCGACGCCAGCATCAG
CCAGGTGAACGAGAAGATCAACCAGAGCCTGGCCTTCA
TCCGCAAGAGCGACGAGCTGCTGCACAACGTGAACGCC
GGCAAGAGCACCATCAACATCATGATCACCACCATCAT
CATCGTGATCATCGTGATCCTGCTGAGCCTGATCGCCGT
GGGCCTGCTGCTGTACTGCAAGGCCCGCAGCACCCCCG
TGACCCTGAGCAAGGACCAGCTGAGCGGCATCAACAAC ATCGCCTTCAGCAACTAA

cDNA of the full accaaacagagaatccgtgagttacgataaaaggcgaaggagcaattg 3 genome of NDV
aagtcgcacgggtagaaggtgtgaatctcgagtgcgagcccgaagcac strain LaSota
aaactcgagaaagccttctgccaacatgtcttccgtatttgatgagta with the
cgaacagctcctcgcggctcagactcgccccaatggagctcatggagg transgene
gggagaaaaagggagtaccttaaaagtagacgtcccggtattcactct comprising the
taacagtgatgacccagaagatagatggagctttgtggtattctgcct codon-
ccggattgctgttagcgaagatgccaacaaaccactcaggcaaggtgc optimized
tctcatatctcttttatgctcccactcacaggtaatgaggaaccatgt nucleic acid
tgccCttgcagggaaacagaatgaagccacattggccgtgcttgagat sequence (SEQ
tgatggctttgccaacggcacgccccagttcaacaataggagtggagt ID NO: 2)
gtctgaagagagagcacagagatttgcgatgatagcaggatctctccc encoding human
tcgggcatgcagcaacggaaccccgttcgtcacagccggggcCgaaga RSV F protein
tgatgcaccagaagacatcaccgataccctggagaggatcctctctat of A2 strain
ccaggctcaagtatgggtcacagtagcaaaagccatgactgcgtatga inserted between
gactgcagatgagtcggaaacaaggcgaatcaataagtatatgcagca the NDV P and
aggcagggtccaaaagaaatacatcctctaccccgtatgcaggagcac M genes (The
aatccaactcacgatcagacagtctcttgcagtccgcatctttttggt Sac II
tagcgagctcaagagaggccgcaacacggcaggtggtacctctactta (CCGCGG)
ttataacctggtaggggacgtagactcatacatcaggaataccgggct restriction sites
tactgcattcttcttgacactcaagtacggaatcaacaccaagacatc used to insert the
agcccttgcacttagtagcctctcaggcgacatccagaagatgaagca codon optimized
gctcatgcgtttgtatcggatgaaaggagataatgcgccgtacatgac human RSV F
attacttggtgatagtgaccagatgagctttgcgcctgccgagtatgc protein open
acaactttactcctttgccatgggtatggcatcagtcctagataaagg reading frame
tactgggaaataccaatttgccagggactttatgagcacatcattctg into the genomic
gagacttggagtagagtacgctcaggctcagggaagtagcattaacga sequence are
ggatatggctgccgagctaaagctaaccccagcagcaaGgaGgggcct double
ggcagctgctgcccaacgggtctccgaGgaGaccagcagcataGacat underlined. The
gcctactcaacaagtcggagtcctcactgggcttagcgaggggggtc initiation and
ccaagctctacaaggcggatcgaatagatcgcaagggcaaccagaagc stop codons of
cggggatggggagacccaattcctggatctgatgagagcggtagcaaa the codon
tagcatgagggaggcgccaaactctgcacagggcactccccaatcggg optimized human
gcctcccccaactcctgggccatcccaagataacgacaccgactgggg RSV F open
gtattgatggacaaaacccagcctgcttccacaaaaacatcccaatgc reading frame

cctcacccgtagtcgacccctcgatttgcggctctatatgaccacacc are underlined.
ctcaaacaaacatccccctctttcctccctcccctgctgtacaactA The open reading
cgTacgccctagataccacaggcacaatgcggctcactaacaatcaaa from of the
acagagccgagggaattagaaaaaagtacgggtagaagagggatattc codon optimized
agagatcagggcaagtctcccgagtctctgctctctcctctacctgat human RSV F is
agaccaggacaaacatggccacctttacagatgcagagatcgacgagc in bold.
tatttgagacaagtggaactgtcattgacaacataattacagcccagg
gtaaaccagcagagactgttggaaggagtgcaatcccacaaggcaaga
ccaaggtgctgagcgcagcatgggagaagcatgggagcatccagccac
cggccagtcaagacaaccccgatcgacaggacagatctgacaaacaac
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CAGAAGAAGCTGATGAGCAACAACGTGCAGATCGTGCGCCAGCAGAGC
TACAGCATCATGAGCATCATCAAGGAGGAGGTGCTGGCCTACGTGGTG
CAGCTGCCCCTGTACGGCGTGATCGACACCCCCTGCTGGAAGCTGCAC

ACCAGCCCCCTGTGCACCACCAACACCAAGGAGGGCAGCAACATCTGC
CTGACCCGCACCGACaGgGGCTGGTACTGCGACAACGCCGGCAGCGTG
AGCTTCTTCCCCCAGGCCGAGACCTGCAAGGTGCAGAGCAACCGCGTG
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CAGGTGAACGAGAAGATCAACCAGAGCCTGGCCTTCATCCGCAAGAGC
GACGAGCTGCTGCACAACGTGAACGCCGGCAAGAGCACCATCAACATC
ATGATCACCACCATCATCATCGTGATCATCGTGATCCTGCTGAGCCTG
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ACCCTGAGCAAGGACCAGCTGAGCGGCATCAACAACATCGCCTTCAGC
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cacctatggattcatctttcaagttgggaatgaagaagccacCgtcgg
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ctgcctaggaagcgtcccaaataccggagaccttattgagctggcaag
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ITSLGAIVSCYGKTKCTASNKNRGIIKTFSNGCDYVSNKGV amino acid
DTVSVGNTLYYVNKQEGKSLYVKGEPIINFYDPLVFPSDEF sequence of the
DASISQVNEKINQSLAFIRKSDELLHNVNAGKSTINIMITTII RSV F protein
IVIIVILLSLIAVGLLLYCKARSTPVTLSKDQLSGINNIAFSN encoded by the wild-type
nucleic acid sequence for the human RSV F protein (SEQ ID NO: 1) is identical
to the amino acid sequence of the human RSV F protein encoded by the codon-
optimized nucleic acid sequence for human RSV F protein. (SEQ ID NO: 2))
Amino acid MELLILKANAITTILTAVTFCFASGQNITEEFYQSTCSAVSK 7 sequence of
GYLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQEL chimeric F
DKYKNAVTELQLLMQSTPATNNRARRELPRFMNYTLNNA protein encoded
KKTNVTLSKKRKRRFLGFLLGVGSAIASGVAVSKVLHLEG by SEQ ID NO:
EVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ 4 (The
LLPIVNKQSCSISNIATVIEFQQKNNRLLEITREFSVNAGVT transmembrane
TPVSTYMLTNSELLSLINDMPITNDQKKLMSNNVQIVRQQ and cytoplasmic
SYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTN domains are

TKEGSNICLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRV underlined.)
FCDTMNSLTLPSEVNLCNVDIFNPKYDCKIMTSKTDVSSSV
ITSLGAIVSCYGKTKCTASNKNRGIIKTFSNGCDYVSNKGV
DTVSVGNTLYYVNKQEGKSLYVKGEPIINFYDPLVFPSDEF
DASISQVNEKINQSLAFIRKSDELLHNVNAGKSTINVNLITY
IVLTIISLVFGILSLILACYLMYKQKAQQKTLLWLGNNTLD QMRATTKM Wild-type
ATGGAGTTGCCAATCCTCAAAACAAATGCTATTACCAC 25 nucleic acid
AATCCTTGCTGCAGTCACACTCTGTTTTGCTTCCAGTCA sequence
AAACATCACTGAAGAATTTTATCAATCAACATGCAGTG encoding human
CAGTTAGCAAAGGCTATCTTAGTGCTCTAAGAACTGGTT RSV F protein
GGTATACTAGTGTTATAACTATAGAATTAAGTAATATCA from strain
AGGAAAATAAGTGTAATGGTACAGACGCTAAGGTAAA RSVA/Homo
ATTAATAAAACAAGAATTAGATAAATATAAAAATGCTG sapiens/USA/T
TAACAGAATTGCAGTTGCTCATGCAAAGCACACCAGCA H_10656/2014
GCCAACAGTCGAGCCAGAAGAGAACTACCAAGATTTAT (transmembrane
GAATTATACACTCAACAATACCAAAAACACCAATGTAA and cytoplasmic
CATTAAGTAAGAAAAGGAAAAGAAGATTTCTTGGATTT domains are
TTGTTAGGTGTTGGATCTGCAATCGCCAGTGGCATTGCC underlined)
GTATCCAAGGTCCTGCACCTAGAAGGGGAAGTGAACAA
AATCAAAAGTGCTCTACTATCCACAAACAAGGCTGTAG
TCAGCTTATCTAATGGAGTCAGTGTCTTAACCAGCAAG
GTGTTAGACCTCAAAAACTATATAGATAAACAGTTGTT
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ATGGAGCTGCCCATCCTGAAGACCAACGCCATCACCAC 26 optimized
CATCCTGGCCGCCGTGACCCTGTGCTTCGCCAGCAGCCA nucleic acid
GAACATCACCGAGGAGTTCTACCAGAGCACCTGCAGCG sequence
CCGTGAGCAAGGGCTACCTGAGCGCCCTGAGAACCGGC encoding human
TGGTACACCAGCGTGATCACCATCGAGCTGAGCAACAT RSV F protein
CAAGGAGAACAAGTGCAACGGCACCGACGCCAAGGTG from strain
AAGCTGATCAAGCAGGAGCTGGACAAGTACAAGAACG RSVA/Homo
CCGTGACCGAGCTGCAGCTGCTGATGCAGAGCACCCCC sapiens/USA/T
GCCGCCAACAGCAGAGCCAGAAGAGAGCTGCCCAGATT H_10656/2014
CATGAACTACACCCTGAACAACACCAAGAACACCAACG
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ACGTGAAGGGCGAGCCCATCATCAACTTCTACGACCCC
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TCAGAAAGAGCGACGAGCTGCTGCACAACGTGAACGCC
GGCAAGAGCACCACCAACATCATGATCACCACCATCAT
CATCGTGATCATCGTGATCCTGCTGGCCCTGATCGCCGT
GGGCCTGCTGCTGTACTGCAAGGCCAGAAGCACCCCCG
TGACCCTGAGCAAGGACCAGCTGAGCGGCATCAACAAC ATCGCCTTCAGCAAC
Amino acid MELPILKTNAITTILAAVTLCFASSQNITEEFYQSTCSAVSK 50 sequence of
GYLSALRTGWYTSVITIELSNIKENKCNGTDAKVKLIKQEL human RSV F
DKYKNAVTELQLLMQSTPAANSRARRELPRFMNYTLNNT protein from the
KNTNVTLSKKRKRRFLGFLLGVGSAIASGIAVSKVLHLEG strain

EVNKIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQ RSVA/Homo
LLPIVNKQSCSISNIETVIEFQQKNNRLLEITREFSVNAGVTT sapiens/USA/T
PVSTYMLTNSELLSLINDMPITNDQKKLMSSNVQIVRQQS H_10656/2014
YSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNT
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CDTMNSLTLPSEVNLCNIDIFNPKYDCKIMTSKTDVSSSVIT
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TVSVGNTLYYVNKQEGKSLYVKGEPIINFYDPLVFPSDEFD
ASISQVNEKINQSLAFIRKSDELLHNVNAGKSTTNIMITTIII
VIIVILLALIAVGLLLYCKARSTPVTLSKDQLSGINNIAFSN Wild-type
ATGGAGTTGCTGATCCATAGATCAAGTGTAATCTTCCTA 27 nucleic acid
ACTCTTGCTATTAACGCATTGTACCTCACCTCAAGTCAG sequence
AACATAACTGAGGAGTTTTACCAATCGACATGTAGTGC encoding human
AGTTAGCAGAGGTTACTTTAGTGCTTTAAGAACAGGTT RSV F protein
GGTATACTAGTGTCATAACAATAGAATTAAGTAATATA from strain
AAAGAAACCAAATGCAATGGAACTGACACTAAAGTAA RSVB/Homo
AACTTATAAAACAAGAATTAGATAAGTATAAGAATGCA sapiens/USA/L
GTAACAGAATTACAGTTACTTATGCAAAACATACCAGC A2_82/2013
TGCCAACAACCGAGCCAGAAGAGAAGCACCACAGTAT (transmembrane
ATGAACTACACAATCAATACCACTAAAAACCTAAATGT and cytoplasmic
ATCAATAAGCAAGAAGAGGAAACGAAGATTTCTGGGCT domains are
TCTTGTTAGGTGTAGGATCTGCAATAGCAAGTGGCATA underlined)
GCTGTATCCAAAGTTCTACACCTTGAAGGAGAAGTGAA
CAAGATCAAAAATGCTTTGCTGTCTACAAACAAAGCTG
TAGTCAGTCTATCAAATGGGGTCAGTGTTTTAACCAGCA
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ATGGAGCTGCTGATCCACAGAAGCAGCGTGATCTTCCT 28 optimized
GACCCTGGCCATCAACGCCCTGTACCTGACCAGCAGCC nucleic acid
AGAACATCACCGAGGAGTTCTACCAGAGCACCTGCAGC sequence
GCCGTGAGCAGAGGCTACTTCAGCGCCCTGAGAACCGG encoding human
CTGGTACACCAGCGTGATCACCATCGAGCTGAGCAACA RSV F protein
TCAAGGAGACCAAGTGCAACGGCACCGACACCAAGGT from strain
GAAGCTGATCAAGCAGGAGCTGGACAAGTACAAGAAC RSVB/Homo
GCCGTGACCGAGCTGCAGCTGCTGATGCAGAACATCCC sapiens/USA/L
CGCCGCCAACAACAGAGCCAGAAGAGAGGCCCCCCAG A2_82/2013
TACATGAACTACACCATCAACACCACCAAGAACCTGAA
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ACCGGCAAGAGCACCACCAACATCATGATCACCGTGAT
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CATCGGCCTGCTGCTGTACTGCAAGGCCAAGAACACCC
CCGTGACCCTGAGCAAGGACCAGCTGAGCGGCATCAAC AACATCGCCTTCAGCAAG

Amino acid MELLIHRSSVIFLTLAINALYLTSSQNITEEFYQSTCSAVSR 58 sequence of
RSV GYFSALRTGWYTSVITIELSNIKETKCNGTDTKVKLIKQEL F protein from
DKYKNAVTELQLLMQNIPAANNRARREAPQYMNYTINTT strain
KNLNVSISKKRKRRFLGFLLGVGSAIASGIAVSKVLHLEGE RSVB/Homo
VNKIKNALLSTNKAVVSLSNGVSVLTSKVLDLKNYINNQL sapiens/USA/L
LPIVNQQSCRISNIETVIEFQQKNSRLLEITREFSVNAGVTTP A2_82/2013
LSTYMLTNSELLSLINDMPITNDQKKLMSSNVQIVRQQSYS
IMSIIKEEVLAYVVQLPIYGVIDTPCWKLHTSPLCTTNIKEG
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MNSLTLPSEVSLCNTDIFNSKYDCKIMTSKTDISSSVITSLG
AIVSCYGKTKCTASNKNRGIIKTFSNGCDYVSNKGVDTVS
VGNTLYYVNKLEGKNLYVKGEPIINYYDPLVFPSDEFDASI
SQVNEKINQSLAFIRRSDELLHNVNTGKSTTNIMITVIIIVII
VVLLSLIAIGLLLYCKAKNTPVTLSKDQLSGINNIAFSK Wild-type
ATGGAGTTGCCAATCCTCAAAGCAAATGCTATTACCAC 29 nucleic acid
AATCCTTGCTGCAGTCACACTCTGTTTTGCTTCCAGTCA sequence
AAACATCACTGAAGAATTTTATCAATCAACATGCAGTG encoding human
CAGTTAGCAAAGGCTATCTTAGTGCTCTAAGAACTGGTT RSV F protein
GGTATACTAGTGTTATAACTATAGAATTAAGTAATATCA from strain
AGGAAAATAAGTGTAATGGAACAGATGCTAAGGTAAA HRSV-A-GZ08-
ATTGATAAAACAAGAATTAGATAAATACAAAAATGCTG 18
TAACAGAATTGCAGTTGCTCATGCAAAGCACACCAGCA (transmembrane
GCCAACAATCGAGCCAGAAGGGAATTACCAAGATTTAT and cytoplasmic
GAATTATACACTCAACAATACTGAAAACACCAATGTAA domains are
CATTAAGCAAGAAAAGGAAAAGAAGATTTCTTGGCTTT underlined)
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TAATATTGTTATCATTAATTGTAGTTGGACTGCTTCTAT
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GATCAACTGAGTGGTATAAATAATATTGCATTTAGTAG CTGA Codon
ATGGAGCTGCCCATCCTGAAGGCCAACGCCATCACCAC 30 optimized
CATCCTGGCCGCCGTGACCCTGTGCTTCGCCAGCAGCCA nucleic acid
GAACATCACCGAGGAGTTCTACCAGAGCACCTGCAGCG sequence
CCGTGAGCAAGGGCTACCTGAGCGCCCTGAGAACCGGC encoding human
TGGTACACCAGCGTGATCACCATCGAGCTGAGCAACAT RSV F protein
CAAGGAGAACAAGTGCAACGGCACCGACGCCAAGGTG from RSV strain
AAGCTGATCAAGCAGGAGCTGGACAAGTACAAGAACG HRSV-A-GZ08-
CCGTGACCGAGCTGCAGCTGCTGATGCAGAGCACCCCC 18
GCCGCCAACAACAGAGCCAGAAGAGAGCTGCCCAGATT
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Amino acid
MELPILKANAITTILAAVTLCFASSQNITEEFYQSTCSAVSKGYLSALRTGWYTSVI 49
sequence of
TIELSNIKENKCNGTDAKVKLIKQELDKYKNAVTELQLLMQSTPAANNRARREL human
RSV F PRFMNYTLNNTENTNVTLSKKRKRRFLGFLLGVGSAIASGIAVSKVLHLEGEVN
protein from
KIKSALLSTNKAVVSLSNGVSVLTSKVLDLKNYIDKQLLPIVNKQSCSISNIETVIEF strain
HRSV-A- QQKNNRLLEITREFSVNAGVTTPVSTYMLTNSELLSLINDMPITNDQKKLMSN
GZ08-18 NVQIVRQQSYSIMSIIKEEVLAYVVQLPLYGVIDTPCWKLHTSPLCTTNTKEGSNI
CLTRTDRGWYCDNAGSVSFFPQAETCKVQSNRVFCDTMNSLTLPSEVSLCNV
DIFNPKYDCKIMTSKTDVSSSVITSLGAIVSCYGKTKCTASNKNRGIIKTFSNGCD
YVSNKGVDTVSVGNTLYYVNKQEGKNLYVKGEPIINFYDPLVFPSDEFDASISQV
NEKINQSLAFIRKSDELLHNVNAVKSTTNIMITTIIIVIIVILLSLIVVGLLLYCKARST
PVTLSKDQLSGINNIAFSS Nucleic acid
ATGGAGCTGCCCATCCTGAAGACCAACGCCATCACCACCATCCTGGCCGCC 44 sequence
GTGACCCTGTGCTTCGCCAGCAGCCAGAACATCACCGAGGAGTTCTACCAG encoding
AGCACCTGCAGCGCCGTGAGCAAGGGCTACCTGAGCGCCCTGAGAACCGG chimeric F
CTGGTACACCAGCGTGATCACCATCGAGCTGAGCAACATCAAGGAGAACAA protein,
wherein GTGCAACGGCACCGACGCCAAGGTGAAGCTGATCAAGCAGGAGCTGGACA
the nucleic acid
AGTACAAGAACGCCGTGACCGAGCTGCAGCTGCTGATGCAGAGCACCCCC sequence
GCCGCCAACAGCAGAGCCAGAAGAGAGCTGCCCAGATTCATGAACTACAC comprises
a CCTGAACAACACCAAGAACACCAACGTGACCCTGAGCAAGAAGAGAAAGA codon
optimized GAAGATTCCTGGGCTTCCTGCTGGGCGTGGGCAGCGCCATCGCCAGCGGC
nucleic acid
ATCGCCGTGAGCAAGGTGCTGCACCTGGAGGGCGAGGTGAACAAGATCAA sequence
GAGCGCCCTGCTGAGCACCAACAAGGCCGTGGTGAGCCTGAGCAACGGCG encoding
the TGAGCGTGCTGACCAGCAAGGTGCTGGACCTGAAGAACTACATCGACAAG human
RSV F CAGCTGCTGCCCATCGTGAACAAGCAGAGCTGCAGCATCAGCAACATCGAG
protein ACCGTGATCGAGTTCCAGCAGAAGAACAACAGACTGCTGGAGATCACCAG
ectodomain of
AGAGTTCAGCGTGAACGCCGGCGTGACCACCCCCGTGAGCACCTACATGCT strain
GACCAACAGCGAGCTGCTGAGCCTGATCAACGACATGCCCATCACCAACGA
RSVA/Homo
CCAGAAGAAGCTGATGAGCAGCAACGTGCAGATCGTGAGACAGCAGAGCT
sapiens/USA/TH_
ACAGCATCATGAGCATCATCAAGGAGGAGGTGCTGGCCTACGTGGTGCAG
10656/2014 and
CTGCCCCTGTACGGCGTGATCGACACCCCCTGCTGGAAGCTGCACACCAGC a
nucleic acid
CCCCTGTGCACCACCAACACCAAGGAGGGCAGCAACATCTGCCTGACCAGA sequence
ACCGACAGAGGCTGGTACTGCGACAACGCCGGCAGCGTGAGCTTCTTCCCC encoding
the CAGGCCGAGACCTGCAAGGTGCAGAGCAACAGAGTGTTCTGCGACACCAT
transmembrane
GAACAGCCTGACCCTGCCCAGCGAGGTGAACCTGTGCAACATCGACATCTT and
cytoplasmic CAACCCCAAGTACGACTGCAAGATCATGACCAGCAAGACCGACGTGAGCA

domains of F
GCAGCGTGATCACCAGCCTGGGCGCCATCGTGAGCTGCTACGGCAAGACC protein
from AAGTGCACCGCCAGCAACAAGAACAGAGGCATCATCAAGACCTTCAGCAAC
NDV strain GGCTGCGACTACGTGAGCAACAAGGGCGTGGACACCGTGAGCGTGGGCA
LaSota ACACCCTGTACTACGTGAACAAGCAGGAGGGCAAGAGCCTGTACGTGAAG
(transmembrane
GGCGAGCCCATCATCAACTTCTACGACCCCCTGGTGTTCCCCAGCGACGAG and
cytoplasmic TTCGACGCCAGCATCAGCCAGGTGAACGAGAAGATCAACCAGAGCCTGGC
domains of NDV
CTTCATCAGAAAGAGCGACGAGCTGCTGCACAACGTGAACGCCGGCAAGA F are
underlined) GCACCACCAACATCATGgttaacCTCATTACCTATATCGTTTTGACTATCATAT
CTCTTGTTTTTGGTATACTTAGCCTGATTCTAGCATGCTACCTAATGTACAAG
CAAAAGGCGCAACAAAAGACCTTATTATGGCTTGGGAATAATACCCTAGAT
CAGATGAGAGCCACTACAAAAATGTGAccgcgg Nucleic acid
ATGGAGCTGCTGATCCACAGAAGCAGCGTGATCTTCCTGACCCTGGCCATC 45 sequence
AACGCCCTGTACCTGACCAGCAGCCAGAACATCACCGAGGAGTTCTACCAG encoding
AGCACCTGCAGCGCCGTGAGCAGAGGCTACTTCAGCGCCCTGAGAACCGG chimeric F
CTGGTACACCAGCGTGATCACCATCGAGCTGAGCAACATCAAGGAGACCAA protein,
wherein GTGCAACGGCACCGACACCAAGGTGAAGCTGATCAAGCAGGAGCTGGACA
the nucleic acid
AGTACAAGAACGCCGTGACCGAGCTGCAGCTGCTGATGCAGAACATCCCCG sequence
CCGCCAACAACAGAGCCAGAAGAGAGGCCCCCCAGTACATGAACTACACC comprises
a ATCAACACCACCAAGAACCTGAACGTGAGCATCAGCAAGAAGAGAAAGAG codon
optimized AAGATTCCTGGGCTTCCTGCTGGGCGTGGGCAGCGCCATCGCCAGCGGCAT
nucleic acid
CGCCGTGAGCAAGGTGCTGCACCTGGAGGGCGAGGTGAACAAGATCAAGA sequence
ACGCCCTGCTGAGCACCAACAAGGCCGTGGTGAGCCTGAGCAACGGCGTG encoding
the AGCGTGCTGACCAGCAAGGTGCTGGACCTGAAGAACTACATCAACAACCA human
RSV F GCTGCTGCCCATCGTGAACCAGCAGAGCTGCAGAATCAGCAACATCGAGAC
protein CGTGATCGAGTTCCAGCAGAAGAACAGCAGACTGCTGGAGATCACCAGAG
ectodomain of
AGTTCAGCGTGAACGCCGGCGTGACCACCCCCCTGAGCACCTACATGCTGA strain
CCAACAGCGAGCTGCTGAGCCTGATCAACGACATGCCCATCACCAACGACC
RSVB/Homo
AGAAGAAGCTGATGAGCAGCAACGTGCAGATCGTGAGACAGCAGAGCTAC
sapiens/USA/LA2_
AGCATCATGAGCATCATCAAGGAGGAGGTGCTGGCCTACGTGGTGCAGCT 82/2013
and a GCCCATCTACGGCGTGATCGACACCCCCTGCTGGAAGCTGCACACCAGCCC
nucleic acid
CCTGTGCACCACCAACATCAAGGAGGGCAGCAACATCTGCCTGACCAGAAC sequence
CGACAGAGGCTGGTACTGCGACAACGCCGGCAGCGTGAGCTTCTTCCCCCA encoding
the GGCCGACACCTGCAAGGTGCAGAGCAACAGAGTGTTCTGCGACACCATGA
transmembrane
ACAGCCTGACCCTGCCCAGCGAGGTGAGCCTGTGCAACACCGACATCTTCA and
cytoplasmic ACAGCAAGTACGACTGCAAGATCATGACCAGCAAGACCGACATCAGCAGC
domains of F
AGCGTGATCACCAGCCTGGGCGCCATCGTGAGCTGCTACGGCAAGACCAA protein
from GTGCACCGCCAGCAACAAGAACAGAGGCATCATCAAGACCTTCAGCAACG
NDV strain
GCTGCGACTACGTGAGCAACAAGGGCGTGGACACCGTGAGCGTGGGCAAC LaSota

ACCCTGTACTACGTGAACAAGCTGGAGGGCAAGAACCTGTACGTGAAGGG (transmembrane
CGAGCCCATCATCAACTACTACGACCCCCTGGTGTTCCCCAGCGACGAGTTC and cytoplasmic GACGCCAGCATCAGCCAGGTGAACGAGAAGATCAACCAGAGCCTGGCCTT domains of NDV
CATCAGAAGAAGCGACGAGCTGCTGCACAACGTGAACACCGGCAAGAGCA F are underlined) CCACCAACATCATGgttaacCTCATTACCTATATCGTTTTGACTATCATATCTCT
TGTTTTTGGTATACTTAGCCTGATTCTAGCATGCTACCTAATGTACAAGCAA
AAGGCGCAACAAAAGACCTTATTATGGCTTGGGAATAATACCCTAGATCAG
ATGAGAGCCACTACAAAAATGTGAccgcgg Nucleic acid
ATGGAGCTGCCCATCCTGAAGGCCAACGCCATCACCACCATCCTGGCCGCC 46 sequence
GTGACCCTGTGCTTCGCCAGCAGCCAGAACATCACCGAGGAGTTCTACCAG encoding
AGCACCTGCAGCGCCGTGAGCAAGGGCTACCTGAGCGCCCTGAGAACCGG chimeric F
CTGGTACACCAGCGTGATCACCATCGAGCTGAGCAACATCAAGGAGAACAA protein, wherein GTGCAACGGCACCGACGCCAAGGTGAAGCTGATCAAGCAGGAGCTGGACA the nucleic acid
AGTACAAGAACGCCGTGACCGAGCTGCAGCTGCTGATGCAGAGCACCCCC sequence
GCCGCCAACAACAGAGCCAGAAGAGAGCTGCCCAGATTCATGAACTACACC comprises a
CTGAACAACACCGAGAACACCAACGTGACCCTGAGCAAGAAGAGAAAGAG codon optimized AAGATTCCTGGGCTTCCTGCTGGGCGTGGGCAGCGCCATCGCCAGCGGCAT nucleic acid
CGCCGTGAGCAAGGTGCTGCACCTGGAGGGCGAGGTGAACAAGATCAAGA sequence
GCGCCCTGCTGAGCACCAACAAGGCCGTGGTGAGCCTGAGCAACGGCGTG encoding
the AGCGTGCTGACCAGCAAGGTGCTGGACCTGAAGAACTACATCGACAAGCA human
RSV F GCTGCTGCCCATCGTGAACAAGCAGAGCTGCAGCATCAGCAACATCGAGAC protein CGTGATCGAGTTCCAGCAGAAGAACAACAGACTGCTGGAGATCACCAGAG ectodomain of
AGTTCAGCGTGAACGCCGGCGTGACCACCCCCGTGAGCACCTACATGCTGA strain
HRSV-A- CCAACAGCGAGCTGCTGAGCCTGATCAACGACATGCCCATCACCAACGACC GZ08-18 and a
AGAAGAAGCTGATGAGCAACAACGTGCAGATCGTGAGACAGCAGAGCTAC nucleic acid AGCATCATGAGCATCATCAAGGAGGAGGTGCTGGCCTACGTGGTGCAGCT sequence
GCCCCTGTACGGCGTGATCGACACCCCCTGCTGGAAGCTGCACACCAGCCC encoding
the CCTGTGCACCACCAACACCAAGGAGGGCAGCAACATCTGCCTGACCAGAAC transmembrane
CGACAGAGGCTGGTACTGCGACAACGCCGGCAGCGTGAGCTTCTTCCCCCA and cytoplasmic GGCCGAGACCTGCAAGGTGCAGAGCAACAGAGTGTTCTGCGACACCATGA domains of F
ACAGCCTGACCCTGCCCAGCGAGGTGAGCCTGTGCAACGTGGACATCTTCA protein from ACCCCAAGTACGACTGCAAGATCATGACCAGCAAGACCGACGTGAGCAGC NDV strain AGCGTGATCACCAGCCTGGGCGCCATCGTGAGCTGCTACGGCAAGACCAA LaSota GTGCACCGCCAGCAACAAGAACAGAGGCATCATCAAGACCTTCAGCAACG (transmembrane
GCTGCGACTACGTGAGCAACAAGGGCGTGGACACCGTGAGCGTGGGCAAC and cytoplasmic ACCCTGTACTACGTGAACAAGCAGGAGGGCAAGAACCTGTACGTGAAGGG domains of NDV
CGAGCCCATCATCAACTTCTACGACCCCCTGGTGTTCCCCAGCGACGAGTTC F are underlined) GACGCCAGCATCAGCCAGGTGAACGAGAAGATCAACCAGAGCCTGGCCTT CATCAGAAAGAGCGACGAGCTGCTGCACAACGTGAACGCCGTGAAGAGCA

CCACCAACATCATGgttaacCTCATTACCTATATCGTTTTGACTATCATATCTCT
TGTTTTTGGTATACTTAGCCTGATTCTAGCATGCTACCTAATGTACAAGCAA
AAGGCGCAACAAAAGACCTTATTATGGCTTGGGAATAATACCCTAGATCAG
ATGAGAGCCACTACAAAAATGTGAccgcgg Nucleic acid
atggagttgctaatcctcaaagcaaatgcaattaccacaatcctcactgcagtcacattttgttttgct 51 sequence
tctggtcaaaacatcactgaagaatttttatcaatcaacatgcagtgcagttagcaaaggctatctta encoding a
gtgctctgagaactggttggtataccagtgttataactatagaattaagtaatatcaaggaaaataa chimeric F
gtgtaatggaacagatgctaaggtaaaattgataaaacaagaattagataaatataaaaatgctgt protein, wherein
aacagaattgcagttgctcatgcaaagcacaccagcaacaaacaatcgagccagaagagaacta the chimeric F
ccaaggtttatgaattatacactcaacaatgccaaaaaaaccaatgtaacattaagcaagaaaag protein
gaaaagaagatttcttggtttttgttaggtgttggatctgcaatcgccagtggcgttgctgtatctaa comprises the
ggtcctgcacctagaaggggaagtgaacaagatcaaaagtgctctactatccacaaacaaggctg human RSV F
tagtcagcttatcaaatggagttagtgtcttaaccagcaaagtgttagacctcaaaaactatataga protein
taaacaattgttacctattgtgaacaagcaaagctgcagcatatcaaatatagcaactgtgataga ectodomain of
gttccaacaaaagaacaacagactactagagattaccagggaatttagtgttaatgcaggtgtaac RSV A2 strain
tacacctgtaagcacttacatgttaactaatagtgaattattgtcattaatcaatgatatgcctataac and the
aaatgatcagaaaaagttaatgtccaacaatgttcaaatagttagacagcaaagttactctatcatg transmembrane
tccataataaaagaggaagtcttagcatatgtagtacaattaccactatatggtgttatagatacac and cytoplasmic
cctgttggaaactacacacatcccctctatgtacaaccaacacaaaagaagggtccaacatctgttt domains of
aacaagaactgacagaggatggtactgtgacaatgcaggatcagtatctttcttcccacaagctga NDV F protein
aacatgtaaagttcaatcaaatcgagtattttgtgacacaatgaacagtttaacattaccaagtgaa of NDV LaSota
gtaaatctctgcaatgttgacatattcaaccccaaatatgattgtaaaattatgacttcaaaaacag strain
atgtaagcagctccgttatcacatctctaggagccattgtgtcatgctatggcaaaactaaatgtac
agcatccaataaaaatcgtggaatcataaagacattttctaacgggtgcgattatgtatcaaataaa
ggggtggacactgtgtctgtaggtaacacattatattatgtaaataagcaagaaggtaaaagtctct
atgtaaaaggtgaaccaataataaatttctatgacccattagtattcccctctgatgaatttgatgca
tcaatatctcaagtcaacgagaagattaaccagagcctagcatttattcgtaaatccgatgaattatt
acataatgtaaatgctggtaaatccaccataaatgttaacCTCATTACCTATATCGTTTTGA
CTATCATATCTCTTGTTTTTGGTATACTTAGCCTGATTCTAGCATGCTACCTA
ATGTACAAGCAAAAGGCGCAACAAAAGACCTTATTATGGCTTGGGAATAAT
ACCCTAGATCAGATGAGAGCCACTACAAAAATGTGA
(186) TABLE-US-00002 TABLE 2 NDV LaSota F protein Amino acid
MGSRPSTKNPAPMTLTIRVALVLSCICPANSIDGRPLAAAG 8 sequence of F
IVVTGDKAVNIYTSSQTGSIIVKLLPNLPKDKEACAKAPLD protein of NDV
AYNRTLTTLLTPLGDSIRRIQESVTTSGGGRQGRLIGAIIGG strain LaSota
VALGVATAAQITAAAALIQAKQNAANILRLKESIAATNEA (transmembrane
VHEVTDGLSQLAVAVGKMQQFVNDQFNKTAQELDCIKIA domain is
QQVGVELNLYLTELTTVFGPQITSPALNKLTIQALYNLAG underlined and
GNMDYLLTKLGVGNNQLSSLIGSGLITGNPILYDSQTQLLG cytoplasmic
IQVTLPSVGNLNNMRATYLETLSVSTTRGFASALVPKVVT domain is in
QVGSVIEELDTSYCIETDLDLYCTRIVTFPMSPGIYSCLSGN bold)
TSACMYSKTEGALTTPYMTIKGSVIANCKMTTCRCVNPPG
IISQNYGEAVSLIDKQSCNVLSLGGITLRLSGEFDVTYQKNI
SIQDSQVIITGNLDISTELGNVNNSISNALNKLEESNRKLDK
VNVKLTSTSALITYIVLTIISLVFGILSLILACYL**MYKQKAQ**
QKTLLWLGNNTLDQMRATTKM
(187) TABLE-US-00003 TABLE 3 Bovine RSV F Sequences Wild-type
ATGGCGACAACAGCCATGAGGATGATCATCAGCATTATCTTCATCTCT 9 Nucleic acid
ACCTATGTGACACATATCACTTTATGCCAAAACATAACAGAAGAATTT sequence
TATCAATCAACATGCAGTGCAGTTAGTAGAGGTTACCTTAGTGCATTA encoding bovine

AGAACTGGATGGTATACAAGTGTGGTAACAATAGAGTTGAGCAAAATA RSV F protein
CAAAAAAATGTGTGTAATAGTACTGATTCAAAAGTGAAATTAATAAAG of bovine RSV
CAAGAACTAGAAAGATACAACAATGCAGTAGTGGAATTGCAGTCACTT strain
ATGCAAAATGAACCGGCCTCCTTCAGTAGAGCAAAAAGAGGGATACCA ATCC51908
GAGTTGATACATTATACAAGAAACTCTACAAAAAAGTTTTATGGGCTA (transmembrane
ATGGGCAAGAAGAGAAAAAGGAGATTTTTAGGATTCTTGCTAGGTATT and cytoplasmic
GGATCTGCTATTGCAAGTGGTGTAGCAGTGTCCAAAGTACTACACCTG domains
GAGGGAGAGGTGAATAAAATTAAAAATGCACTGCTATCCACAAATAAA underlined)
GCAGTAGTTAGTCTATCCAATGGAGTTAGTGTCCTTACTAGCAAAGTA
CTTGATCTAAAGAACTATATAGACAAAGAGCTTCTACCTAAAGTTAAC
AATCATGATTGTAGGATATCCAAAATAGAAACTGTGATAGAATTCCAA
CAAAAAAACAATAGATTGTTAGAAATTGCTAGGGAATTTAGTGTAAAT
GCTGGTATTACCACACCTCTCAGTACATACATGTTGACCAATAGTGAA
TTACTATCACTAATTAATGATATGCCTATAACGAATGACCAAAAAAAG
CTAATGTCAAGTAATGTTCAAATAGTCAGGCAACAGAGTTATTCCATT
ATGTCAGTGGTCAAAGAAGAAGTCATAGCTTATGTTGTACAATTGCCT
ATTTATGGAGTTATAGACACCCCCTGTTGGAAACTACACACCTCTCCG
TTATGCACCACTGATAATAAAGAAGGGTCAAACATCTGCTTAACTAGG
ACAGATCGTGGGTGGTATTGTGACAATGCAGGCTCTGTGTCTTTTTTC
CCACAGACAGAGACATGTAAGGTACAATCAAATAGAGTGTTCTGTGAC
ACAATGAACAGTTTAACTCTGCCTACTGACGTTAACTTATGCAACACT
GACATATTCAATACAAAGTATGACTGTAAAATAATGACATCTAAAACT
GACATAAGTAGCTCTGTGATAACTTCAATTGGAGCTATTGTATCATGC
TATGGGAAGACAAAATGTACAGCTTCTAATAAAAATCGTGGAATCATA
AAGACTTTTTCCAATGGGTGTGATTATGTATCAAACAAAGGAGTAGAT
ACTGTATCTGTTGGTAACACACTATATTATGTAAATAAGCTAGAGGGG
AAAGCACTCTATATAAAGGGTGAACCAATTATTAATTACTATGATCCA
CTAGTGTTTCCTTCTGATGAGTTTGATGCATCAATTGCCCAAGTAAAC
GCAAAAATAAACCAAAGCCTGGCCTTCATACGTCGATCTGATGAGTTA
CTTCACAGTGTAGATGTAGGAAAATCCACCACAAATGTAGTAATTACT
ACTATTATCATAGTGATAGTTGTAGTGATATTAATGTTAATAGCTGTA
GGATTACTGTTTTACTGTAAGACCAAGAGTACTCCTATCATGTTAGGG
AAGGATCAGCTCAGTGGTATCAACAATCTTTCCTTTAGTAAATGA Amino acid
MATTAMRMIISIIFISTYVTHITLCQNITEEFYQSTCSAVSRGY 10 sequence of
LSALRTGWYTSVVTIELSKIQKNVCNSTDSKVKLIKQELERYNN bovine RSV F
AVVELQSLMQNEPASFSRAKRGIPELIHYTRNSTKKFYGLMGKK protein of
RKRRFLGFLLGIGSAIASGVAVSKVLHLEGEVNKIKNALLSTNK bovine RSV
AVVSLSNGVSVLTSKVLDLKNYIDKELLPKVNNHDCRISKIETV strain
IEFQQKNNRLLEIAREFSVNAGITTPLSTYMLTNSELLSLINDM ATCC51908
PITNDQKKLMSSNVQIVRQQSYSIMSVVKEEVIAYVVQLPIYGV (transmembrane
IDTPCWKLHTSPLCTTDNKEGSNICLTRTDRGWYCDNAGSVSFF and cytoplasmic
PQTETCKVQSNRVFCDTMNSLTLPTDVNLCNTDIFNTKYDCKIM domains
TSKTDISSSVITSIGAIVSCYGKTKCTASNKNRGIIKTESNGCD underlined. The
YVSNKGVDTVSVGNTLYYVNKLEGKALYIKGEPIINYYDPLVFP amino acid
SDEFDASIAQVNAKINQSLAFIRRSDELLHSVDVGKSTTNVVIT sequence
TIIIVIVVVILMLIAVGLLFYCKTKSTPIMLGKDQLSGINNLSF encoded by SEQ SK ID
NO: 9) Codon ATGGCCACCACCGCCATGCGCATGATCATCAGCATCATCTTCAT 11
optimized CAGCACCTACGTGACCCACATCACCCTGTGCCAGAACATCACCG nucleic acid
AGGAGTTCTACCAGAGCACCTGCAGCGCCGTGAGTCGCGGCTAC sequence
CTGAGCGCCCTGCGCACCGGCTGGTACACCAGCGTGGTGACCAT encoding bovine

CGAGCTGAGCAAGATCCAGAAGAACGTGTGCAACAGCACCGACA RSV F protein
GCAAGGTGAAGCTGATCAAGCAGGAGCTGGAGCGCTACAACAAC of bovine RSV
GCCGTGGTGGAGCTGCAGAGCCTGATGCAGAACGAGCCCGCCAG strain
CTTCAGCCGCGCCAAGCGCGGCATCCCCGAGCTGATCCACTACA ATCC51908
CCCGCAACAGCACCAAGAAGTTCTACGGCCTGATGGGCAAGAAG
CGCAAGCGCCGCTTCCTGGGCTTCCTGCTGGGCATCGGCAGCGC
CATCGCCAGCGGCGTGGCCGTGAGCAAGGTGCTGCACCTGGAGG
GCGAGGTGAACAAGATCAAGAACGCCCTGCTGAGCACCAACAAG
GCCGTGGTGAGCCTGAGCAACGGCGTGAGCGTGCTGACCAGCAA
GGTGCTGGACCTGAAGAACTACATCGACAAGGAGCTGCTGCCCA
AGGTGAACAACCACGACTGCCGCATCAGCAAGATCGAGACCGTG
ATCGAGTTCCAGCAGAAGAACAACCGCCTGCTGGAGATCGCCCG
CGAGTTCAGCGTGAACGCCGGCATCACCACCCCCCTGAGCACCT
ACATGCTGACCAACAGCGAGCTGCTGAGCCTGATCAACGACATG
CCCATCACCAACGACCAGAAGAAGCTGATGAGCAGCAACGTGCA
GATCGTGCGCCAGCAGAGCTACAGCATCATGAGCGTGGTGAAGG
AGGAGGTGATCGCCTACGTGGTGCAGCTGCCCATCTACGGCGTG
ATCGACACCCCCTGCTGGAAGCTGCACACCAGCCCCCTGTGCAC
CACCGACAACAAGGAGGGCAGCAACATCTGCCTGACCCGCACCG
ATCGCGGCTGGTACTGCGACAACGCCGGCAGCGTGAGCTTCTTC 12
CCCCAGACCGAGACCTGCAAGGTGCAGAGCAACCGCGTGTTCTG
CGACACCATGAACAGCCTGACCCTGCCCACCGACGTGAACCTGT
GCAACACCGACATCTTCAACACCAAGTACGACTGCAAGATCATG
ACCAGCAAGACCGACATCAGCAGCAGCGTGATCACCAGCATCGG
CGCCATCGTGAGCTGCTACGGCAAGACCAAGTGCACCGCCAGCA
ACAAGAATCGCGGCATCATCAAGACCTTCAGCAACGGCTGCGAC
TACGTGAGCAACAAGGGCGTGGACACCGTGAGCGTGGGCAACAC
CCTGTACTACGTGAACAAGCTGGAGGGCAAGGCCCTGTACATCA
AGGGCGAGCCCATCATCAACTACTACGACCCCCTGGTGTTCCCC
AGCGACGAGTTCGACGCCAGCATCGCCCAGGTGAACGCCAAGAT
CAACCAGAGCCTGGCCTTCATCCGCCGCAGCGACGAGCTGCTGC
ACAGCGTGGACGTGGGCAAGAGCACCACCAACGTGGTGATCACC
ACCATCATCATCGTGATCGTGGTGGTGATCCTGATGCTGATCGC
CGTGGGCCTGCTGTTCTACTGCAAGACCAAGAGCACCCCCATCA
TGCTGGGCAAGGACCAGCTGAGCGGCATCAACAACCTGAGCTTC AGCAAGTAA
cDNA of accaaacagagaatccgtgagttacgataaaaggcgaaggagcaattg genomic
aagtcgcacgggtagaaggtgtgaatctcgagtgcgagcccgaagcac sequence of
aaactcgagaaagccttctgccaacatgtcttccgtatttgatgagta NDV of LaSota
cgaacagctcctcgcggctcagactcgccccaatggagctcatggagg strain with the
gggagaaaaagggagtaccttaaaagtagacgtcccggtattcactct nucleic acid
taacagtgatgacccagaagatagatggagctttgtggtattctgcct encoding bovine
ccggattgctgttagcgaagatgccaacaaaccactcaggcaaggtgc RSV F protein
tctcatatctcttttatgctcccactcacaggtaatgaggaaccatgt of strain
tgccCttgcagggaaacagaatgaagccacattggccgtgcttgagat ATCC51908
tgatggctttgccaacggcacgccccagttcaacaataggagtggagt (nucleic acid
gtctgaagagagagcacagagatttgcgatgatagcaggatctctccc sequence
tcgggcatgcagcaacggaaccccgttcgtcacagccggggcCgaaga encoding bovine
tgatgcaccagaagacatcaccgataccctggagaggatcctctctat RSV F protein is
ccaggctcaagtatgggtcacagtagcaaaagccatgactgcgtatga underlined)
gactgcagatgagtcggaaacaaggcgaatcaataagtatatgcagca

aggcagggtccaaaagaaatacatcctctaccccgtatgcaggagcac
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tactgggaaataccaatttgccagggactttatgagcacatcattctg
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cggccagtcaagacaaccccgatcgacaggacagatctgacaaacaac
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ccgccgaccagccccccacccaggccacagacgaagccgtcgacacac
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gtcgcggaaacagtcaggaaagaccgcagaaccaagtcaaggccgccc
ctggaaaccagggcacagacgtgaacacagcatatcatggacaatggg
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ggcagagccaagacaatacccttgtatctgcggatcatgtccagccac
ctgtagactttgtgcaagcgatgatgtctatgatggaggcgatatcac agagagtaagtaaggttgactatcagctagatcttgtcttgaaacaga
catcctccatccctatgatgcggtccgaaatccaacagctgaaaacat
ctgttgcagtcatggaagccaacttgggaatgatgaagattctggatc ccggttgtgccaacatttcatctctgagtgatctacgggcagttgccc
gatctcacccggttttagtttcaggccctggagacccctctccctatg
tgacacaaggaggcgaaatggcacttaataaactttcgcaaccagtgc
cacatccatctgaattgattaaacccgccactgcatgcgggcctgata
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tgcacccgagttcttcagccaagctcctaagcaagttagatgcagccg
ggtcgatcgaggaaatcaggaaaatcaagcgccttgctctaaatggct
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TTCATCTCTACCTATGTGACACATATCACTTTATGCCAAAACATAACA
GAAGAATTTTATCAATCAACATGCAGTGCAGTTAGTAGAGGTTACCTT

AGTGCATTAAGAACTGGATGGTATACAAGTGTGGTAACAATAGAGTTG
AGCAAAATACAAAAAAATGTGTGTAATAGTACTGATTCAAAAGTGAAA
TTAATAAAGCAAGAACTAGAAAGATACAACAATGCAGTAGTGGAATTG
CAGTCACTTATGCAAAATGAACCGGCCTCCTTCAGTAGAGCAAAAAGA
GGGATACCAGAGTTGATACATTATACAAGAAACTCTACAAAAAAGTTT
TATGGGCTAATGGGCAAGAAGAGAAAAAGGAGATTTTTAGGATTCTTG
CTAGGTATTGGATCTGCTATTGCAAGTGGTGTAGCAGTGTCCAAAGTA
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AGCAAAGTACTTGATCTAAAGAACTATATAGACAAAGAGCTTCTACCT
AAAGTTAACAATCATGATTGTAGGATATCCAAAATAGAAACTGTGATA
GAATTCCAACAAAAAAACAATAGATTGTTAGAAATTGCTAGGGAATTT
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CAATTGCCTATTTATGGAGTTATAGACACCCCCTGTTGGAAACTACAC
ACCTCTCCGTTATGCACCACTGATAATAAAGAAGGGTCAAACATCTGC
TTAACTAGGACAGATCGTGGGTGGTATTGTGACAATGCAGGCTCTGTG
TCTTTTTTCCCACAGACAGAGACATGTAAGGTACAATCAAATAGAGTG
TTCTGTGACACAATGAACAGTTTAACTCTGCCTACTGACGTTAACTTA
TGCAACACTGACATATTCAATACAAAGTATGACTGTAAAATAATGACA
TCTAAAACTGACATAAGTAGCTCTGTGATAACTTCAATTGGAGCTATT
GTATCATGCTATGGGAAGACAAAATGTACAGCTTCTAATAAAAATCGT
GGAATCATAAAGACTTTTTCCAATGGGTGTGATTATGTATCAAACAAA
GGAGTAGATACTGTATCTGTTGGTAACACACTATATTATGTAAATAAG
CTAGAGGGGAAAGCACTCTATATAAAGGGTGAACCAATTATTAATTAC
TATGATCCACTAGTGTTTCCTTCTGATGAGTTTGATGCATCAATTGCC
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GATGAGTTACTTCACAGTGTAGATGTAGGAAAATCCACCACAAATGTA
GTAATTACTACTATTATCATAGTGATAGTTGTAGTGATATTAATGTTA
ATAGCTGTAGGATTACTGTTTTACTGTAAGACCAAGAGTACTCCTATC
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ATGGCGACAACAGCCATGAGGATGATCATCAGCATTATCTTCATCTCTACCT 31 sequence
ATGTGACACATATCACTTTATGCCAAAACATAACAGAAGAATTTTATCAATC encoding a
AACATGCAGTGCAGTTAGTAGAGGTTACCTTAGTGCATTAAGAACTGGATG chimeric F
GTATACAAGTGTGGTAACAATAGAGTTGAGCAAAATACAAAAAAATGTGTG protein
TAATAGTACTGATTCAAAAGTGAAATTAATAAAGCAAGAACTAGAAAGATA comprising
CAACAATGCAGTAGTGGAATTGCAGTCACTTATGCAAAATGAACCGGCCTC bovine
RSV F CTTCAGTAGAGCAAAAAGAGGGATACCAGAGTTGATACATTATACAAGAAA
protein CTCTACAAAAAAGTITTATGGGCTAATGGGCAAGAAGAGAAAAAGGAGAT
ectodomain of
TTTTAGGATTCTTGCTAGGTATTGGATCTGCTATTGCAAGTGGTGTAGCAGT bovine RSV
GTCCAAAGTACTACACCTGGAGGGAGAGGTGAATAAAATTAAAAATGCACT strain
GCTATCCACAAATAAAGCAGTAGTTAGTCTATCCAATGGAGTTAGTGTCCTT
ATCC51908 and

ACTAGCAAAGTACTTGATCTAAAGAACTATATAGACAAAGAGCTTCTACCTA NDV F
protein AAGTTAACAATCATGATTGTAGGATATCCAAAATAGAAACTGTGATAGAAT
transmembrane
TCCAACAAAAAAACAATAGATTGTTAGAAATTGCTAGGGAATTTAGTGTAA and
cytoplasmic ATGCTGGTATTACCACACCTCTCAGTACATACATGTTGACCAATAGTGAATT
domains of the
ACTATCACTAATTAATGATATGCCTATAACGAATGACCAAAAAAAGCTAATG NDV
LaSota TCAAGTAATGTTCAAATAGTCAGGCAACAGAGTTATTCCATTATGTCAGTGG
strain TCAAAGAAGAAGTCATAGCTTATGTTGTACAATTGCCTATTTATGGAGTTAT
(transmembrane
AGACACCCCCTGTTGGAAACTACACACCTCTCCGTTATGCACCACTGATAAT and
cytoplasmic AAAGAAGGGTCAAACATCTGCTTAACTAGGACAGATCGTGGGTGGTATTGT
domains of NDV
GACAATGCAGGCTCTGTGTCTTTTTTCCCACAGACAGAGACATGTAAGGTA F protein
are CAATCAAATAGAGTGTTCTGTGACACAATGAACAGTTTAACTCTGCCTACTG
underlined) ACGTTAACTTATGCAACACTGACATATTCAATACAAAGTATGACTGTAAAAT
AATGACATCTAAAACTGACATAAGTAGCTCTGTGATAACTTCAATTGGAGCT
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(188) TABLE-US-00004 Nucleic acid
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ACGTGACCCACATCACCCTGTGCCAGAACATCACCGAGGAGTTCTACCAGA encoding
GCACCTGCAGCGCCGTGAGCAGAGGCTACCTGAGCGCCCTGAGAACCGGC chimeric F
TGGTACACCAGCGTGGTGACCATCGAGCTGAGCAAGATCCAGAAGAACGT protein,
wherein GTGCAAGAGCACCGACAGCAAGGTGAAGCTGATCAAGCAGGAGCTGGAG
the nucleic acid
AGATACAACAACGCCGTGGTGGAGCTGCAGAGCCTGATGCAGAACGAGCC sequence
CGCCAGCTTCAGCAGAGCCAAGAGAGGCATCCCCGAGCTGATCCACTACAC
comprises a
CAGAAACAGCACCAAGAAGTTCTACGGCCTGATGGGCAAGAAGAGAAAGA codon
optimized GAAGATTCCTGGGCTTCCTGCTGGGCATCGGCAGCGCCGTGGCCAGCGGC
nucleic acid GTGGCCGTGAGCAAGGTGCTGCACCTGGAGGGCGAGGTGAACAAGATCA
sequence AGAACGCCCTGCTGAGCACCAACAAGGCCGTGGTGAGCCTGAGCAACGGC
encoding the
GTGAGCGTGCTGACCAGCAAGGTGCTGGACCTGAAGAACTACATCGACAA bovine
RSV F GGAGCTGCTGCCCCAGGTGAACAACCACGACTGCAGAATCAGCAACATCG
protein AGACCGTGATCGAGTTCCAGCAGAAGAACAACAGACTGCTGGAGATCGCC
ectodomain of
AGAGAGTTCAGCGTGAACGCCGGCATCACCACCCCCCTGAGCACCTACATG strain
CTGACCAACAGCGAGCTGCTGAGCCTGATCAACGACATGCCCATCACCAAC
ATue51908 and
GACCAGAAGAAGCTGATGAGCAGCAACGTGCAGATCGTGAGACAGCAGA a nucleic

acid GCTACAGCATCATGAGCGTGGTGAAGGAGGAGGTGATCGCCTACGTGGTG sequence
CAGCTGCCCATCTACGGCGTGATCGACACCCCCTGCTGGAAGCTGCACACC encoding
the AGCCCCCTGTGCACCACCGACAACAAGGAGGGCAGCAACATCTGCCTGACC
transmembrane
AGAACCGACAGAGGCTGGTACTGCGACAACGCCGGCAGCGTGAGCTTCTT and
cytoplasmic CCCCCAGACCGAGACCTGCAAGGTGCAGAGCAACAGAGTGTTCTGCGACA
domains of F
CCATGAACAGCCTGACCCTGCCCACCGACGTGAACCTGTGCAACACCGACA protein
from TCTTCAACACCAAGTACGACTGCAAGATCATGACCAGCAAGACCGACATCA
NDV strain GCAGCAGCGTGATCACCAGCATCGGCGCCATCGTGAGCTGCTACGGCAAG
LaSota ACCAAGTGCACCGCCAGCAACAAGAACAGAGGCATCATCAAGACCTTCAGC
(transmembrane
AACGGCTGCGACTACGTGAGCAACAAGGGCGTGGACACCGTGAGCGTGG and
cytoplasmic GCAACACCCTGTACTACGTGAACAAGCTGGAGGGCAAGGCCCTGTACATCA
domains of NDV
AGGGCGAGCCCATCATCAACTACTACGACCCCCTGGTGTTCCCCAGCGACG F are
underlined) AGTTCGACGCCAGCATCGCCCAGGTGAACGCCAAGATCAACCAGAGCCTG
GCCTTCATCAGAAGAAGCGACGAGCTGCTGCACAGCGTGGACGTGGGCAA
GAGCACCACCAACGTGgttaacCTCATTACCTATATCGTTTTGACTATCATATC
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AAAAGGCGCAACAAAAGACCTTATTATGGCTTGGGAATAATACCCTAGATC
AGATGAGAGCCACTACAAAAATGTGAccgcgg Nucleic acid
ATGGCCACCACCGCCATGACCATGATCATCAGCATCATCTTCATCAGCACCT 39 sequence
ACGTGACCCACATCACCCTGTGCCAGAACATCACCGAGGAGTTCTACCAGA encoding
GCACCTGCAGCGCCGTGAGCAGAGGCTACCTGAGCGCCCTGAGAACCGGC chimeric F
TGGTACACCAGCGTGGTGACCATCGAGCTGAGCAAGATCCAGAAGAACGT protein,
wherein GTGCAAGAGCACCGACAGCAAGGTGAAGCTGATCAAGCAGGAGCTGGAG
the nucleic acid
AGATACAACAACGCCGTGGTGGAGCTGCAGAGCCTGATGCAGAACGAGCC sequence
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comprises a
CAGAAACAGCACCAAGAAGTTCTACGGCCTGATGGGCAAGAAGAGAAAGA codon
optimized GAAGATTCCTGGGCTTCCTGCTGGGCATCGGCAGCGCCATCGCCAGCGGCG
nucleic acid TGGCCGTGAGCAAGGTGCTGCACCTGGAGGGCGAGGTGAACAAGATCAA
sequence GAACGCCCTGCTGAGCACCAACAAGGCCGTGGTGAGCCTGAGCAACGGCG
encoding the
TGAGCGTGCTGACCAGCAAGGTGCTGGACCTGAAGAACTACATCGACAAG bovine
RSV F GAGCTGCTGCCCAAGGTGAACAACCACGACTGCAGAATCAGCAACATCGCC
protein ACCGTGATCGAGTTCCAGCAGAAGAACAACAGACTGCTGGAGATCGCCAG
ectodomain of
AGAGTTCAGCGTGAACGCCGGCATCACCACCCCCCTGAGCACCTACATGCT strain
snook and GACCAACAGCGAGCTGCTGAGCCTGATCAACGACATGCCCATCACCAACGA
a nucleic acid
CCAGAAGAAGCTGATGAGCAGCAACGTGCAGATCGTGAGACAGCAGAGCT sequence
ACAGCATCATGAGCGTGGTGAAGGAGGAGGTGATCGCCTACGTGGTGCAG encoding
the CTGCCCATCTACGGCGTGATCGACACCCCCTGCTGGAAGCTGCACACCAGC
transmembrane
CCCCTGTGCACCACCGACAACAAGGAGGGCAGCAACATCTGCCTGACCAGA and
cytoplasmic ACCGACAGAGGCTGGTACTGCGACAACGCCGGCAGCGTGAGCTTCTTCCCC
domains of F

CAGGCCGAGACCTGCAAGGTGCAGAGCAACAGAGTGTTCTGCGACACCAT protein
from GAACAGCCTGACCCTGCCCACCGACGTGAACCTGTGCAACACCGACATCTT
NDV strain
CAACACCAAGTACGACTGCAAGATCATGACCAGCAAGACCGACATCAGCAG LaSota
CAGCGTGATCACCAGCATCGGCGCCATCGTGAGCTGCTACGGCAAGACCAA
(transmembrane
GTGCACCGCCAGCAACAAGAACAGAGGCATCATCAAGACCTTCAGCAACG and
cytoplasmic GCTGCGACTACGTGAGCAACAAGGGCGTGGACACCGTGAGCGTGGGCAAC
domains of NDV
ACCCTGTACTACGTGAACAAGCTGGAGGGCAAGGCCCTGTACATCAAGGG F are
underlined) CGAGCCCATCATCAACTACTACGACCCCCTGGTGTTCCCCAGCGACGAGTTC
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ATGGCGACAACAGCCATGAGGATGATCATCAGCATTAT 40 Nucleic acid
CTTCATCTCTACCTATGTGACACATATCACTTTATGCCA encoding bovine
AAACATAACAGAAGAATTTTATCAATCAACATGCAGTG RSV F protein
CAGTTAGTAGAGGTTACCTTAGTGCATTAAGAACTGGA of strain
TGGTATACAAGTGTGGTAACAATAGAGTTGAGCAAAAT ATue51908 (the
ACAAAAAAATGTGTGTAAAAGTACTGATTCAAAAGTGA transmembrane
AATTAATAAAGCAAGAACTAGAAAGATACAACAATGC and cytoplasmic
AGTAGTGGAATTGCAGTCACTTATGCAAAATGAACCGG domains are
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TGGTACACCAGCGTGGTGACCATCGAGCTGAGCAAGAT RSV F protein
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CAGTTAGTAGAGGTTACCTTAGTGCATTAAGAACTGGA RSV F protein
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CCGTGAGCAGAGGCTACCTGAGCGCCCTGAGAACCGGC encoding bovine
TGGTACACCAGCGTGGTGACCATCGAGCTGAGCAAGAT RSV F protein
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Amino acid MATTAMRMIISIIFISTYVTHITLCQNITEEFYQSTCSAVSRG 33 sequence
YLSALRTGWYTSVVTIELSKIQKNVCNSTDSKVKLIKQELE encoding
RYNNAVVELQSLMQNEPASFSRAKRGIPELIHYTRNSTKK chimeric F

FYGLMGKKRKRRFLGFLLGIGSAIASGVAVSKVLHLEGEV protein
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PKVNNHDCRISKIETVIEFQQKNNRLLEIAREFSVNAGITTP ectodomain of
LSTYMLTNSELLSLINDMPITNDQKKLMSSNVQIVRQQSYS bovine RSV F
IMSVVKEEVIAYVVQLPIYGVIDTPCWKLHTSPLCTTDNKE protein of bovine
GSNICLTRTDRGWYCDNAGSVSFFPQTETCKVQSNRVFCD RSV strain
TMNSLTLPTDVNLCNTDIFNTKYDCKIMTSKTDISSSVITSI ATCC51908 and
GAIVSCYGKTKCTASNKNRGIIKTFSNGCDYVSNKGVDTV the
SVGNTLYYVNKLEGKALYIKGEPIINYYDPLVFPSDEFDAS transmembrane
IAQVNAKINQSLAFIRRSDELLHSVDVGKSTTNVNLITYIVL and cytoplasmic
TIISLVFGILSLILACYLMYKQKAQQKTLLWLGNNTLDQM domains of NDV RATTKM
F protein of NDV LaSota strain (transmembrane and cytoplasmic domains of NDV F
protein are underlined) Genome of
accaaacagagaatccgtgagttacgataaaaggcgaaggagcaattgaagtcgcacggg 37 NDV LaSota
tagaaggtgtgaatctcgagtgcgagcccgaagcacaaactcgagaaagccttctgccaac with a chimeric
atgtcttccgtatttgatgagtacgaacagctcctcgcggctcagactcgccccaatggagct F protein
catggaggggagaaaaagggagtaccttaaaagtagacgtcccggtattcactcttaaca (underlined).
gtgatgacccagaagatagatggagctttgtggtattctgcctccggattgctgttagcgaag Ectodomain is
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tccgcatctttttggttagcgagctcaagagaggccgcaacacggcaggtggtacctctactt protein of NDV
attataacctggtaggggacgtagactcatacatcaggaataccgggcttactgcattcttctt strain LaSota
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(189) TABLE-US-00005 TABLE 4 hMPV F Sequences Wild-type
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ACATTAGAGGTGGGTGATGTAGAAAACCTTACATGTTCTGATGGACCT protein of
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or 18 LSSAEKGNTGFIIVIILIAVLGSSMILVSIFIIIKKTKKPTGAPPELS encode this
GVTNNGFIPHS amino acid sequence) Codon
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NPRQSRFVLGAIALGVATAAAVTAGVAIAKTIRLESEVTAIKNALKTT protein
NEAVSTLGNGVRVLATAVRELKDFVSKNLTRAINKNKCDIDDLKMAVS comprising the
FSQFNRRFLNVVRQFSDNAGITPAISLDLMTDAELARAVSNMPTSAGQ ectodomain of
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CGTGGCCGAGCAGAGCAGAGAGTGCAACATCAACATCA and cytoplasmic
GCACCACCAACTACCCCTGCAAGGTGAGCACCGGCAGA domains of NDV
CACCCCATCAGCATGGTGGCCCTGAGCCCCCTGGGCGC F are underlined)
CCTGGTGGCCTGCTACAAGGGCGTGAGCTGCAGCATCG
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AAAAGGCGCAACAAAAGACCTTATTATGGCTTGGGAAT
AATACCCTAGATCAGATGAGAGCCACTACAAAAATGTG Accgcgg Nucleic acid
ATGAGCTGGAAGGTGGTGATCATCTTCAGCCTGCTGATCACCCCCCAGCAC 36 sequence
GGCCTGAAGGAGAGCTACCTGGAGGAGAGCTGCAGCACCATCACCGAGGG encoding
CTACCTGAGCGTGCTGAGAACCGGCTGGTACACCAACGTGTTCACCCTGGA chimeric F
GGTGGGCGACGTGGAGAACCTGACCTGCAGCGACGGCCCCAGCCTGATCA protein,
wherein AGACCGAGCTGGACCTGACCAAGAGCGCCCTGAGAGAGCTGAAGACCGTG
the nucleic acid
AGCGCCGACCAGCTGGCCAGAGAGGAGCAGATCGAGAACCCCAGACAGA sequence
GCAGATTCGTGCTGGGCGCCATCGCCCTGGGCGTGGCCACCGCCGCCGCC comprises a
GTGACCGCCGGCGTGGCCATCGCCAAGACCATCAGACTGGAGAGCGAGGT codon
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encoding the
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ectodomain of
CACCAGCGCCGGCCAGATCAAGCTGATGCTGGAGAACAGAGCCATGGTGA strain
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HMPV/ARG/10
TACATGGTGCAGCTGCCCATCTTCGGCGTGATCGACACCCCCTGCTGGATC 7/2002/A
and a GTGAAGGCCGCCCCCAGCTGCAGCGAGAAGAAGGGCAACTACGCCTGCCT
nucleic acid
GCTGAGAGAGGACCAGGGCTGGTACTGCCAGAACGCCGGCAGCACCGTGT sequence
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the GACACCGCCGCCGGCATCAACGTGGCCGAGCAGAGCAAGGAGTGCAACAT
transmembrane
CAACATCAGCACCACCAACTACCCCTGCAAGGTGAGCACCGGCAGACACCC and
cytoplasmic CATCAGCATGGTGGCCCTGAGCCCCCTGGGCGCCCTGGTGGCCTGCTACAA
domains of F
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NDV strain
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(transmembrane
GACCAGTTCAACGTGGCCCTGGACCAGGTGTTCGAGAACATCGAGAACAG and
cytoplasmic CCAGGCCCTGGTGGACCAGAGCAACAGAATCCTGAGCAGCGCCGAGAAGG
domains of NDV

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(191) TABLE-US-00007 TABLE 5 Signal Sequences Human RSV F MELLILKANAITTILTAVTFCFASG 23 signal sequence of the F protein of RSV strain A2 (first 25 amino acids of SEQ ID NO: 6) hMPV F signal MSWKVVIIFSLLITPQHG 24 sequence of the F protein of hMPV strains CAN00-16 (SEQ ID NO: 16), HMPV/*Homo sapiens*/PER/FPP 00726/2011/A (SEQ ID NO: 52) and HMPV/ARG/10 7/2002/A (SEQ ID NO: 56) Bovine RSV F MATTAMRMIISIIFISTYVTHITLC 60 signal sequence of the F protein of ATCC51908 strain (SEQ ID NO: 33)

(192) TABLE-US-00008 TABLE 6 cDNA of genome of NDV Strains cDNA of genomic sequence of NDV strain LaSota

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6. EXAMPLES

6.1 Example 1: Viral Vectored RSV Vaccine Induces Long-Lived Humoral Immunity in Cotton Rats

(193) This example demonstrates that vaccination with a recombinant Newcastle disease virus-vectored vaccine that expresses the F glycoprotein of RSV (rNDV-F) protects cotton rats from RSV challenge and induces long-lived neutralizing antibody production, even in RSV immune animals. In addition, this example demonstrates that the pulmonary eosinophilia induced by RSV infection of unvaccinated cotton rats is prevented by rNDV-F vaccination. Overall, these example demonstrates enhanced protective immunity to RSV F when this protein is presented in the context of an abortive NDV infection.

(194) 6.1.1 Materials & Methods

(195) 6.1.1.1 Animals

(196) 6-10 week old female cotton rats (*Sigmodon hispidus*) were used in this study (Sigmovir Biosystems, Inc., Bethesda, MD, USA). Animals were housed in groups of 3 in a BSL 2 facility and were offered a commercial pelleted rat chow and water ad libitum. Animals were acclimated for 7 to 10 days prior to vaccination or viral challenge. All procedures used here were conducted humanely. Data were collected from 3-5 cotton rats per cohort per time point, unless otherwise specified. All cotton rat studies were approved by the Institutional Animal Care and Use Committees of New York University School of Medicine (protocol 100504-02) and Rutgers-New Jersey Medical School.

(197) 6.1.1.2 Generation rNDV-F Construct

(198) rNDV-F was constructed as previously described [6]. Briefly, the sequence coding for the F protein of RSV (strain Long; SEQ ID NO:1) was inserted in the cDNA of the full length genome of NDV strain Hitchner B1 (a non-virulent vaccine strain of NDV), between the P and M genes. The inserted sequence contained NDV gene end and gene start sequences to make it a functional transcription unit, and a Kozak sequence for efficient translation. The cDNA sequence of the full length genome of NDV strain Hitchner B1 with the nucleic acid sequence encoding the RSV F protein inserted.

(199) 6.1.1.3 Vaccination

(200) rNDV-F was constructed as previously described [6] then amplified in 10-day-old embryonated chicken eggs. While under isoflurane anesthesia, cotton rats were intranasally (i.n.)

vaccinated with 1×10.sup.6 pfu rNDV-F, 1×10.sup.6 pfu NDV vector alone, or allantoic fluid as a mock control in a 100 μl total volume divided equally between nares. Twenty-eight days after the priming vaccination, cotton rats were boosted in the same manner.

(201) 6.1.1.4 RSV Challenge

(202) Human RSV strain A2, originally obtained from ATCC (VR-1540), was passaged on murine STAT1.sup.−/− fibroblast monolayers as previously described [12]. The challenge dose of 1×10.sup.6 pfu RSV was instilled into the nasal cavities of cotton rats under isoflurane anesthesia in a 50 μl total volume, divided equally between nares. The inoculum was delivered slowly, over approximately 15 seconds, to restrict initial virus infection to the upper airway.

(203) 6.1.1.5 Plaque Assay

(204) Cotton rats were euthanized by CO.sub.2 asphyxiation, and nasal wash fluids and lungs were collected immediately after euthanasia and stored at −80° C. until use in viral plaque assay. Viral plaque assay was performed on murine STAT1−/− fibroblast monolayers as previously described [13].

(205) 6.1.1.6 Histology and Immunohistochemistry

(206) Nasal cavities and lung were collected immediately following CO.sub.2 asphyxiation. Nasal cavities were fixed in neutral buffered formalin then decalcified with 0.35M EDTA in 0.1M Tris (pH 6.95). The lung and decalcified nasal cavities were processed routinely, paraffin-embedded and sectioned at 5 μm. Tissues sections were stained with hematoxylin and eosin (H&E) or were left unstained for immunohistochemistry (IHC). For IHC, tissue sections were incubated with goat polyclonal RSV antiserum (Biodesign, Saco, Maine, USA) diluted 1:500 followed by incubation with biotinylated rabbit anti-goat IgG antibody then HRP (ScyTek, Logan, UT, USA). Virus detection was accomplished with the streptavidin link and AEC chromagen (Scytek, Logan, UT, USA). IHC-labeled tissue sections were counterstained with hematoxylin.

(207) 6.1.1.7 RSV F-Specific ELISA

(208) Purified RSV F glycoprotein, whose transmembrane anchor was replaced with a 6His tag (SEQ ID NO:61), was produced by transfection of HEK293F cells and purified as described [14]. For RSV F-specific ELISA, Nunc maxisorb immunoplates (ThermoScientific, Waltham, MA, USA) were coated overnight at 4° C. with 0.3 μg purified F protein diluted in 0.1M sodium carbonate buffer. Plates were washed with PBS containing 0.05% Tween 20 (PBS-T) then blocked with PBS containing 10% fetal calf serum (PBS-F). Plates were washed with PBS-T then samples, serially diluted in PBS-F, were added followed by incubation at 25° C. for 60 minutes. Wells were washed with PBS-T and secondary antibody diluted in PBS-F was added (chicken anti-cotton rat IgG, Immunology Consultants Laboratory, Inc., Portland, OR, USA). Plates were incubated at 25° C. for 60 minutes. After washing with PBS-T, tertiary antibody diluted in PBS-F was added (goat anti-chicken IgG conjugated to HRP, Southern Biotech, Birmingham, AL, USA). Following a second incubation at 25° C. for 60 minutes, plates were again washed with PBS-T followed by the addition of tetramethylbenzidine peroxidase substrate (ScyTek, Logan, UT, USA). After incubation at 25° C. for 30 minutes, the reaction was stopped by addition of 2N H.sub.2SO.sub.4. Absorbance at 450 nm (A.sub.450) was determined using an Epoch Microplate Spectrophotomer (BioTek, Winooki, VT, USA). Titers were defined as the highest dilution of the sample resulting in A.sub.450 four-fold greater than background (PBS-F alone).

(209) 6.1.1.8 Serum Neutralization Assay

(210) Two different methods were used for detection of RSV neutralizing antibody. Data shown in FIG. **4**D were collected using a standard plaque reduction assay. Serum dilutions pre-incubated with 200 pfu RSV were used as the inoculum for plaque assay on murine STAT1.sup.−/− fibroblast monolayers as previously described [13].

(211) For a more quantitative approach to determining neutralizing antibody titer, a flow cytometric assay was devised. For data shown in FIG. **7**A, serum samples at a 1/800 dilution were incubated with rg-RSV [8] at a concentration of 3×10.sup.5 pfu/ml. in DMEM+5% fetal calf serum for 1 hour

at 37° C. The serum-virus mixture was then used to inoculate, in duplicate, monolayers of Vero cells (10.sup.5 cells plated in 2 cm.sup.2 wells). After a 20 hour incubation, cells were resuspended and analyzed by flow cytometry. Only infected cells will express gfp. Percent neutralization was calculated as 100 (1−f.sub.s/f.sub.0) where f.sub.s=fraction of gfp+ cells in the sample, and f.sub.0=the fraction of gfp+ cells in the no-serum control.

(212) 6.1.1.9 Enumeration of RSV F-Specific B Cells

(213) For T cell depletion, mouse anti-cotton rat CD8 and mouse anti-cotton rat CD4 monoclonal antibodies (r&d systems) were labeled with DSB-X according to the manufacturer's protocol (Dynabeads FlowComp Flexi, Invitrogen Life Technologies, Grand Island, NY, USA). Single cell suspensions of cervical lymph nodes, pooled by cohort, were incubated with 0.5 μg each of CD8 and CD4 DSB-X labeled antibody per sample, then T cells were depleted according to the manufacturer's protocol (Dynabeads FlowComp Flexi, Invitrogen Life Technologies, Grand Island, NY, USA). Cervical lymph node single cell suspensions, depleted of T cells and pooled by cohort, were used in ELISpot assays.

(214) For F-specific ELISpot, multiscreen HTS HA plates (Millipore, Jaffrey, NH, USA) were coated overnight at 4° C. with 0.3 μg purified F protein diluted in 0.1M sodium carbonate buffer. Plates were washed with RPMI supplemented with 10% fetal calf serum (cRPMI) and then were blocked with cRPMI for 1 hr at 37° C. in a 5% C02 incubator. Plates were washed with RPMI then cervical lymph node single cell suspensions were added in duplicate. Plates were incubated 4-6 hrs at 37° C. in 5% C02. Plates were then washed with PBS containing 0.05% Tween-20 (PBS-T). Secondary antibody diluted in PBS-T (chicken anti-cotton rat IgG, Immunology Consultants Laboratory, Inc., Portland, OR, USA) was added and plates were incubated overnight at 4° C. Plates were washed with PBS-T. Tertiary antibody diluted in PBS-T was added (goat anti-chicken AP, Southern Biotech, Birmingham, AL, USA) and plates were incubated at 25° C. for 60 minutes. Plates were again washed with PBS-T. NBT/BCIP substrate (Millipore, Jaffrey, NH, USA) was added and plates were incubated in the dark for 30 minutes at 25° C. Plates were washed with tap water. Spots were counted visually.

(215) 6.1.1.10 BAL Fluid Analysis

(216) BAL fluids were collected from cotton rats immediately after C02 asphyxiation by washing the lung with 2 ml of sterile saline. BAL fluid cell counts were determined by hemocytometer and BAL differentials were determined on Wright-Giemsa stained CytoSpin preparations (ThermoScientific, Waltham, MA, USA). For the 1 month time point, BAL fluid data was available for only 2 NDV vaccinated animals as BAL fluid collected from one NDV vaccinated animals was of poor quality and thus excluded. For the 2 month time point, BAL fluid data was available for only 2 mock vaccinated animals because one of the mock vaccinated animals died prior to sampling. For the 4 days after secondary RSV infection time point, BAL fluid data was available for only 2 mock vaccinated animals as necropsy of a third mock-vaccinated animal revealed pyometra, an abdominal mass and fibrinous pericarditis. BAL fluid analysis was not performed on that animal.

(217) 6.1.1.11 Statistical Analysis

(218) SigmaPlot 12.0 (Systat Software, Inc., San Jose, CA, USA) and GraphPad (GraphPad Software, Inc., La Jolla, CA USA) were used to perform ANOVA and t-test where appropriate. A p-value<0.05 was considered statistically significant.

(219) 6.1.2 Results

(220) 6.1.2.1 rNDV-F Vaccination Induces a Mild Inflammatory Response

(221) The immunization regimen involved intranasal delivery of 10.sup.6 pfu of rNDV-F into the nasal cavity of cotton rats. To determine the effect of inoculation, the nasal cavity and lung tissues were examined following each of the two i.n. vaccine doses. Histologic sections from the upper airway taken 24 hours, 48 hours, 72 hours and 7 days following intranasal instillation of 10.sup.6 pfu of rNDV-F showed minimal signs of inflammation, indistinguishable from similar sections

taken from untreated cotton rats (Data not shown).
(222) The nasal cavities of inoculated animals were also examined 28 days following priming, and 28 days following boost, for any evidence of disease secondary to immunization alone. No histologic changes were observed at this time point following delivery of allantoic fluid (FIGS. **3**A and **3**B) or the NDV vector alone (FIGS. **3**E and **3**F), but nasal cavity tissues collected from rNDV-F vaccinated animals showed submucosal lymphoplasmacytic infiltrates (FIGS. **1**C and **1**D), indicative of an acquired immune response. A more pronounced infiltrate was observed following rNDV-F boosting (FIGS. **1**G and **1**H).
(223) No histologic changes were observed in the lung following delivery of allantoic fluid or a priming dose of NDV vector alone (FIGS. **1**I, **1**L, and **1**J). However, in response to rNDV-F priming, submucosal lymphoplasmacytic infiltrates similar to those observed in the nasal cavity mucosa, were observed surrounding bronchioles (FIG. **1**K), with an increased number of lymphocytes and plasma cells surrounding bronchioles following rNDV-F boosting (FIG. **1**N). Similar peribronchiolar infiltrates were observed in response to a boosting dose of NDV vector alone (FIG. **1**M), but these were less cellular than those that accompanied rNDV-F vaccination. Additionally, following a second dose with NDV vector alone, or either dose of rNDV-F, rare eosinophils were observed intermixed with the lymphocytic and plasma cell infiltrates surrounding bronchioles (FIGS. **1**K, **1**M and **1**N). Based on these studies it appears that intranasal immunization with rNDV-F causes no acute injury to the upper or lower airway, but does induce a mucosal lymphocytic response. The basis for the enhanced, though still mild, inflammatory response to rNDV-F when compared with the NDV vector alone is not clear, but is consistent with the ability to boost immunity with a second, boosting vaccine dose.
(224) 6.1.2.2 rNDV-F Vaccination Protects Against RSV Infection and Reinfection
(225) Tissues were harvested 4 days after RSV challenge of animals that had been immunized with two i.n. doses of allantoic fluid, NDV vector alone, or rNDV-F. In the nasal cavity and lung tissue of animals receiving allantoic fluid or NDV vector alone prior to RSV challenge, primary RSV infection was associated with mucosal and submucosal inflammatory infiltrates composed primarily of lymphocytes (FIGS. **2**A and **2**B). The lungs from these mock-immunized cotton rats had sparse peribronchiolar lymphohistiocytic infiltrates, with mucus and inflammatory cells in small airways (FIGS. **2**D and **2**E). In contrast, both lung and nasal cavity tissues collected from RSV-challenged, rNDV-F vaccinated cotton rats exhibited changes similar to those observed in response to vaccination alone (FIGS. **2**C and **2**F), with a more pronounced lymphocytic infiltrate, but lacking the mucus production and mixed inflammatory infiltrate.
(226) Viral load following challenge was assayed by immunohistochemistry (IHC) and by plaque assay. IHC staining with a polyclonal antiviral serum revealed diffuse RSV antigen staining in the nasal cavities and small foci of infected cells in the lower airways of mock and NDV vaccinated animals. In contrast, only rare RSV antigen positive cells were detected in the nasal cavities of the rNDV-F vaccinated cotton rats, and none in the lower airways of the immunized animals (FIGS. **3**A-**3**F). In support of IHC findings, viable virions were not detected by plaque assay of nasal mucosa and lung collected from animals that had received rNDV-F vaccination prior to RSV challenge (FIG. **3**G).
(227) Following a second RSV challenge delivered 6 months after the first RSV challenge of mock-vaccinated or rNDV-F vaccinated animals, lung and nasal tissues were collected. IHC of nasal cavity and lung collected 4 days after secondary RSV challenge revealed rare, scattered antigen-positive cells in the nasal mucosa of cohorts primed with allantoic fluid or NDV vector only. No RSV antigen was detected in the lungs or nasal cavities of rNDV-F vaccinated animals. Plaque assay of nasal cavity mucosa and lung tissues collected after secondary RSV challenge was negative in all animals (not shown).
(228) 6.1.2.3 rNDV-F Vaccination Induces a Long-Lived Mucosal Antibody Response
(229) Serum, bronchoalveolar lavage (BAL) fluid and nasal wash (NW) fluid were collected at

multiple time points after vaccination and RSV challenge for determination of RSV F-specific IgG levels by ELISA (FIG. **4**). rNDV-F vaccination induced robust, F-specific IgG responses that were boosted following RSV challenge and then maintained at high levels. While serum antibody levels were similar amongst cohorts 1-2 months after RSV challenge, mucosal F-specific antibody responses remained significantly elevated in BAL and NW fluid samples collected from rNDV-F vaccinated animals compared to controls up to 6 months after RSV infection, the latest time point examined. Serum neutralization, assayed by plaque reduction, demonstrated that antibodies produced in response to rNDV-F vaccination were neutralizing (FIG. **4**D).

(230) Cervical lymph nodes were collected 4 days or 5 months after RSV challenge of mock and rNDV-F primed and boosted animals, and RSV F-specific IgG antibody secreting cells (ASCs) were enumerated by ELISpot (FIG. **4**E). While a response was not detected, or was minimal, by cells harvested from cervical lymph nodes of mock or NDV vaccinated animals, robust F-specific ASC responses were observed in cervical lymph nodes collected from rNDV-F vaccinated animals at both the 4 day and 5 month time points. This is a significant finding given the short-lived mucosal protection that follows natural infection, and the importance of augmenting this protection by any RSV vaccine candidate [5]. Reagents to assay IgA in the cotton rat model are not yet available.

(231) 6.1.2.4 rNDV-F Vaccination Prevents Eosinophilic Lung Inflammation

(232) The cellularity of BAL fluid collected at multiple time points after vaccination and RSV challenge was determined by cell counts, and evaluated for cell type by examination of Wright-Giemsa stained cytospin preparations (FIGS. **5**A and **5**B). While vaccination alone did not increase total BAL fluid cellularity, a small, but not statistically significant, increase in total BAL fluid cellularity was detected in all cohorts after primary RSV challenge. After secondary RSV infection this increase in cellularity was again detected in BAL fluid collected from animals that had been vaccinated with allantoic fluid or NDV vector alone, but not present in BAL fluids collected from rNDV-F vaccinated animals.

(233) As previously described [7], eosinophils are present in the lungs of naïve cotton rats, in the absence of pulmonary pathology, and the composition of the BAL fluid was not altered by vaccination alone. Consistent with these prior observations, eosinophils were significantly increased one month after primary RSV challenge of control animals [7], but this increase did not occur in animals vaccinated with rNDV-F (FIG. **5**). The number of pulmonary eosinophils decreased nearly to baseline 2 months after primary RSV infection, but rose again in response to secondary RSV challenge of control animals that had received only allantoic fluid or NDV vector. This increase in BAL eosinophils following secondary RSV infection, while striking, did not reach statistical significance ($p=0.06$). Thus, in the cotton rat model, rNDV-F vaccination confers long-lasting protection, but also inhibits eosinophilic inflammation in response to RSV infection and reinfection.

(234) 6.1.2.5 Immunization of RSV-Immune Animals

(235) Based on the vaccination strategy wherein the RSV F protein is expressed only in rNDV-F infected cells, it was hypothesized that it might be possible to immunize animals previously exposed to RSV. To test this possibility, 20 cotton rats were infected with RSV, and half of these were immunized with 10.sup.6 pfu of rNDV-F administered i.n. at 2 months, and again at 3 months, after primary RSV infection (FIG. **6**). The 2 month time point for vaccination was chosen to ensure that RSV F protein specific antibodies would be present in serum and at the mucosal surface of the respiratory tree (see FIG. **4**). Serum antibody titers were determined at 4 months, and again at 9 months after primary RSV infection as outlined in FIG. **6**. All remaining animals were re-challenged with RSV at the 9 month time point, and no virus was detected in the lungs or noses of animals in either cohort at 2 or 4 days post virus instillation.

(236) RSV F-specific IgG levels in all animals were measured by an F-protein specific ELISA assay which demonstrated an approximately 3-fold increase in animals that had received rNDV-F

(1/2500 versus 1/7500), a level maintained for 6 months after the boosting dose of vaccine was administered (FIG. **7**B). Neutralizing antibody was assessed by incubating serum samples with rg-RSV, a recombinant virus expressing eGFP [8], and determining % of Vero cell infection by flow cytometry. The result of this assay is shown in FIG. **7**A, demonstrating an enhancement of neutralizing antibody in animals immunized with rNDV-F in the presence of RSV-neutralizing antibody, an enhancement which remained stable at the 9 month time point. This study suggests that, in addition to the ability of this vaccine to give long-lasting protection, rNDV-F is also efficacious in those with pre-existing antibody.

(237) 6.1.3 Discussion

(238) The data presented in this example demonstrates that a Newcastle disease virus vectored RSV vaccine, designed to stimulate robust IFN production simultaneous with RSV F protein presentation to the immune system, protects against RSV infection and induces a long-lived humoral immune response. Delivery of a protective dose of rNDV-F was not associated with adverse histopathology. Lymphoplasmacytic infiltrates observed in immunized animals in response to the boosting rNDV-F dose and subsequent challenge are consistent with an appropriate adaptive immune response (FIG. **1**). Additionally, the increase in lung eosinophils detected in cotton rats that been mock vaccinated prior to primary and secondary RSV challenge was not detected in the lungs of rNDV-F vaccinated cotton rats. This finding is of particular interest when considered in light of mounting evidence that severe RSV lung disease during infancy is associated with asthma and recurrent wheezing later in childhood [1-4].

(239) As shown here, the eosinophilic response to RSV infection in the cotton rat was abrogated by rNDV-F vaccination. Without being bound by any theory, the adjuvant effect of the type I IFN induction, in addition to the prolongation of antibody responses by the rNDV-F vaccines described in this example, may also decrease T.sub.H2 responses to inhaled allergens encountered during RSV infections in young children.

(240) RSV-specific secretory and serum antibodies have been correlated with protection of the upper and lower airways, respectively, against re-infection with RSV [9, 10]. A recent study suggests that the ability of this virus to re-infect immunocompetent adults is correlated with a defect in B cell memory. Neutralizing serum and nasal antibody levels in experimentally infected healthy adult volunteers increased post-infection, but returned to baseline levels 6 months later [5]. This differs markedly from the lifelong persistence of influenza specific IgG that follows this infection [11]. Thus, it is essential that any RSV vaccine candidate induce both systemic and mucosal RSV-specific antibodies, but do so in a manner that induces a B cell memory response superior to that induced by RSV infection. It is this requirement that recommends consideration of a vectored RSV vaccine.

(241) In this example, rNDV-F vaccination induced serum and mucosal F-specific antibodies that were maintained for at least 7 months. Importantly, the mucosal F-specific antibody response, which correlates most closely with protection against reinfection [5], was more robust and longer lived in rNDV-F immunized cotton rats than that induced by RSV infection alone. The ability of NDV-F to boost neutralizing antibody titers in RSV seropositive animals indicates that vaccination of older children and adults may provide an avenue for protecting a population while avoiding the difficulties associated with vaccination of young infants.

6.1.4 REFERENCES CITED IN THIS EXAMPLE 6.1

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6.2 Example 2: Optimized Recombinant Ndv Constructs

(243) This example demonstrates the production of optimized recombinant NDV constructs. In particular, the example demonstrates the enhanced expression of RSV F protein by the optimized recombinant NDV constructs.

(244) 6.2.1 Materials & Methods

(245) 6.2.1.1 Generation of Recombinant Newcastle Disease Virus (rNDV) Expressing the F Protein of Human Respiratory Syncytial Virus.

(246) The generation and characterization of the first version of rNDV-RSV-F has been described in detail in reference Martinez-Sobrido et al. (Journal of virology. 2006; 80(3):1130-9). This first version will be referred here as rNDV-F. Briefly, the sequence coding for the F protein of RSV (strain Long) was inserted in the cDNA of the full length genome of NDV strain Hitchner B1 (a

non-virulent vaccine strain of NDV), between the P and M genes. The inserted sequence contained NDV gene end and gene start sequences to make it a functional transcription unit, and a Kozak sequence for efficient translation.

(247) The plasmid obtained was used to rescue an infectious rNDV-F following a well-established protocol that has been recently described in Ayllon et al. (J Vis Exp. 80:50830 (2013)). The next versions of rNDV—RSV-F were prepared in a similar way, but using a full length cDNA of NDV vaccine strain LaSota and a codon optimized sequence of the RSV-F protein. The codon optimized sequence was purchased from Genewiz (see the website for Genewiz) and used to generate 2 different versions of rNDV-RSV-F that will be referred here as rNDV-Fopt and rNDV-F.sub.chim and are described in detail in the following paragraphs. NDV-Fopt was generated in a similar way to the original rNDV-F. The synthetic, codon optimized, sequence of RSV-F was used as template to PCR amplify an insert that contained the F open reading frame flanked by the necessary restriction sites, gene end and gene start regulatory sequences, and a Kozak sequence for efficient translation. The codon-optimized sequence of RSV-F sequence is shown in SEQ ID NO:2. The PCR product was directly cloned into the plasmid containing the full length NDV cDNA, between the P and M genes, and used to rescue an infectious rNDV-Fopt as previously described. The full length NDV cDNA sequence of the NDV strain LaSota with the codon-optimized RSV-F sequence inserted is shown in SEQ ID NO:3.

(248) rNDV-F.sub.chim was designed to express a chimeric F protein with the transmembrane and cytoplasmic domains of the RSV F protein replaced by the corresponding sequences of the NDV F protein. The rationale for this was that the chimeric F protein is predicted to be efficiently incorporated in the envelope of the viral particle and result in better immunogenicity. To obtain the rescue plasmid for rNDV-F.sub.chim we proceeded in two steps, summarized in FIG. **8**. First, the codon optimized synthetic sequence was used as template to PCR amplify the ectodomain, flanked by the appropriate restriction sites and Kozak sequence. The PCR product was cloned into plasmid pShuttle LaSota that contained the required gene end and gene start sequences, as well as the sequence coding for the transmembrane and cytoplasmic domains of the NDV F protein. The fusion in frame of the RSV-F ectodomain and rNDV-F transmembrane and cytoplasmic domains resulted in the chimeric F protein. In the second step, after sequence confirmation, the insert in plasmid pShuttle LaSota was excised and cloned into the plasmid containing the full length NDV cDNA, between the P and M genes, and used to rescue the infectious rNDV-chimF. The chimeric RSV-F sequence is shown in SEQ ID NO:4. The full length NDV cDNA sequence of the NDV strain LaSota with the codon-optimized RSV-F sequence inserted is shown in SEQ ID NO:5. A schematic representation of the different rNDV-F, rNDV-F.sub.opt, rNDV-F.sub.chim are shown in FIG. **9**.

(249) 6.2.1.2 Animals

(250) 6-10 week old female cotton rats (*Sigmodon hispidus*) were used in this study (Sigmovir Biosystems, Inc., Bethesda, MD, USA). Animals were housed in groups of 3 in a BSL 2 facility and were offered a commercial pelleted rat chow and water ad libitum. Animals were acclimated for 7 to 10 days prior to vaccination or viral challenge. Animal housing and experimental procedures were approved by the Institutional Animal Care and Use Committee at the New York University School of Medicine and the Rutgers—New Jersey Medical School. All procedures used here were conducted humanely. Data were collected from 3-5 cotton rats per cohort per time point, unless otherwise specified.

(251) 6.2.1.3 Vaccination

(252) NDV-F was constructed as previously described (33) then amplified in 10-day-old embryonated chicken eggs. While under isoflurane anesthesia, cotton rats were intranasally (i.n.) vaccinated with 1×10.sup.6 pfu NDV-F, 1×10.sup.6 pfu NDV vector alone, or allantoic fluid as a mock control in a 100 μl total volume divided equally between nares. Twenty-eight days after the priming vaccination, cotton rats were boosted in the same manner.

(253) 6.2.1.4 RSV Challenge
(254) Human RSV strain A2, originally obtained from ATCC (VR-1540), was passaged on murine STAT1.sup.−/− fibroblast monolayers as previously described (54). The challenge dose of 1×10.sup.6 pfu RSV was instilled into the nasal cavities of cotton rats under isoflurane anesthesia in a 50 μl total volume, divided equally between nares. The inoculum was delivered slowly, over approximately 15 seconds, to restrict initial virus infection to the upper airway.
(255) 6.2.1.5 Plaque Assay
(256) Cotton rats were euthanized by CO.sub.2 asphyxiation, and lungs were collected immediately after euthanasia and stored at −80° C. until use in viral plaque assay. Viral plaque assay was performed on murine STAT1−/−fibroblast monolayers as previously described (Gitiban et al., Journal of Virology 2005; 79(10):6035-42).
(257) 6.2.1.6 Flow Cytometry Assay
(258) With respect to the data shown in FIG. **18**: Vero cells growing in 6 well plates were infected with dilutions of the viral stocks by adding 250 μl of virus diluted in PBS per well. After 1 h adsorption, 2 ml of complete medium (DMEM supplemented with 1% antibiotics and 10% fetal bovine serum) was added per well and cells were incubated at 37° C. in a CO2 incubator. At 24 h post infection cells were resuspended by trypsin treatment and fixed with 4% formaldehyde for 30 min. at room temperature. After fixation, approximately 10.sup.5 cells (1/10 of the sample) were labelled with RSV F specific humanized monoclonal antibody Synagis followed by fluorescently labelled anti-human secondary antibody. Fluorescently labelled cells were detected using a flow cytometer Canto II.
(259) With respect to the data shown in FIGS. **9**A-**9**B: Serum samples at a 1/800 dilution were incubated with rg-RSV [37] at a concentration of 3×10.sup.5 pfu/ml. in DMEM+5% fetal calf serum for 1 hour at 37° C. The serum-virus mixture was then used to inoculate, in duplicate, monolayers of Vero cells (10.sup.5 cells plated in 2 cm2 wells). After a 20 hour incubation, cells were resuspended and analyzed by flow cytometry. Only infected cells will express gfp. Percent neutralization was calculated as 100 (1−fs/f0) where fs=fraction of gfp+ cells in the sample, and f0=the fraction of gfp+ cells in the no-serum control.
(260) 6.2.1.7 Rt-PCR and Immunofluorescence Assay
(261) RT-PCR: Viral RNA was purified from the viral stocks using the kit E.Z.N.A. viral RNA kit (OMEGA bio-tek) and conditions recommended by the manufacturer. 5 μl of purified RNA were used as template in a 50 μl RT-PCR reaction using the kit Superscript III high-fidelity RT-PCR kit (Invitrogen, 12574-035) and the following primers specific for NDV genome sequences flanking the insert site. pNDV/3102+5′-CTGTCCACTCGGCATCACAC-3′ (SEQ ID NO:62) and pNDV/3231-5′-CTAGATTAATTACGGTTACGC-3′ (SEQ ID NO:63). The amplified band was purified from an agarose gel using the kit E.Z.N.A. gel extraction kit (OMEGA bio-tek) and sequenced using the same primers.
(262) Immunofluorescence Microscopy: Vero cells growing in 96 well plates were infected with dilutions of the viral stocks by adding 50 μl of virus diluted in PBS per well. After 1 h adsorption, 200 μl of complete medium (DMEM supplemented with 1% antibiotics and 10% fetal bovine serum) was added per well and cells were incubated at 37° C. in a C02 incubator. At 24 h post infection cells were fixed with 4% formaldehyde for 30 min. at room temperature and then labelled with RSV F specific humanized monoclonal antibody Synagis and/or NDV specific mouse serum, followed by fluorescently labelled anti-human and/or anti-mouse secondary antibodies. Fluorescently labelled cells were observed and photographed in a fluorescent microscope.
(263) 6.2.1.8 RSV-F Specific ELISA
(264) Purified RSV F glycoprotein, whose transmembrane anchor was replaced with a 6His tag (SEQ ID NO:61), was produced by transfection of HEK293F cells and purified as described (56). For RSV F-specific ELISA, Nunc maxisorb immunoplates (ThermoScientific, Waltham, MA, USA) were coated overnight at 4° C. with 0.3 μg purified F protein diluted in 0.1M sodium

carbonate buffer. Plates were washed with PBS containing 0.05% Tween 20 (PBS-T) then blocked with PBS containing 10% fetal calf serum (PBS-F). Plates were washed with PBS-T then samples, serially diluted in PBS-F, were added followed by incubation at 25° C. for 60 minutes. Wells were washed with PBS-T and secondary antibody diluted in PBS-F was added (chicken anti-cotton rat IgG, Immunology Consultants Laboratory, Inc., Portland, OR, USA). Plates were incubated at 25° C. for 60 minutes. After washing with PBS-T, tertiary antibody diluted in PBS-F was added (goat anti-chicken IgG conjugated to HRP, Southern Biotech, Birmingham, AL, USA). Following a second incubation at 25° C. for 60 minutes, plates were again washed with PBS-T followed by the addition of tetramethylbenzidine peroxidase substrate (ScyTek, Logan, UT, USA). After incubation at 25° C. for 30 minutes, the reaction was stopped by addition of 2N H.sub.2SO.sub.4. Absorbance at 450 nm (A.sub.450) was determined using an Epoch Microplate Spectrophotomer (BioTek, Winooki, VT, USA). Titers were defined as the highest dilution of the sample resulting in A.sub.450 four-fold greater than background (PBS-F alone).

(265) 6.2.1.9 RSV Neutralization Assay

(266) The potent RSV neutralizing monoclonal antibody Synagis® (concentration 100 mg/ml) was serially diluted in tissue culture medium (DMEM supplemented with 1% fetal bovine serum and 1% antibiotics). Dilutions tested were 1:1000, 1:5000, 1:25000, 1:125000, 1:625000, as indicated in FIGS. **14** and **15**.

(267) Next, the antibody dilutions were distributed in 96 well plates, (50 μl per well), and the indicated viruses were added, in duplicate rows (see table below). Viral stocks were diluted in tissue culture medium to give an approximate titer of 10.sup.2-10.sup.3 infectious particles per 50 μl. Virus and antibody dilutions were mixed by pipetting up and down and incubated at 37° C. for 2 h. After the 2 h incubation, 100 μl of medium containing 10.sup.4 cells was added to each well and the plates were incubated at 37° C. for 24 h. For the RSV-GFP virus cells were the HEp2 cell line, for all the recombinant NDVs we used Vero cells.

(268) At 24 h post infection cells were fixed with 10% paraformaldehyde in PBS for 15 minutes at room temperature and then overlaid with 1×PBS.

(269) Cells infected with GFP expressing viruses (RSV-GFP and NDV-GFP) were visualized directly by fluorescence microscopy. For the recombinant NDV viruses, infected cells were visualized by immuno-fluorescence using a commercial monoclonal antibody that recognizes the NDV HN protein followed by a fluorescent anti-mouse secondary antibody. Representative microscopic fields were photographed to prepare FIGS. **14** and **15**.

(270) TABLE-US-00009 TABLE 2 distribution of virus and antibody dilutions in the plate. Each virus was added to two replicate rows. dilution dilution dilution dilution dilution 1:1000 1:5000 1:25000 1:125000 1:625000 no antibody RSV-GFP.sup.1 NDV-GFP.sup.2 NDV-F.sup.3 NDV-Fopt.sup.4 NDV-Fchim.sup.5 NDV-LaSota wt.sup.6 NDV-boFopt.sup.7 NDV-boFchim.sup.8 .sup.1SV-GFP: recombinant RSV expressing the Green Fluorescent Protein, kindly provided by Dr. Megan Shaw (Mount Sinai). Positive control for neutralization. .sup.2NDV-GFP: recombinant NDV (strain LaSota) expressing the Green Fluorescent Protein. Negative control for neutralization. .sup.3NDV-F: original recombinant NDV (strain Hitchner B1) expressing the wild type version of the human RSV F protein. .sup.4NDV-Fopt: recombinant NDV (strain LaSota) expressing a codon optimized full length version of the human RSV F protein. .sup.5NDV-Fchim: recombinant NDV (strain LaSota) expressing a codon optimized chimeric version of the human RSV F protein ectodomain fused to the transmembrane and cytoplasmic domains of the NDV F protein. .sup.6NDV-LaSota wt: recombinant NDV with no insert. Negative control for neutralization. .sup.7NDV-boFopt: recombinant NDV (strain LaSota) expressing a codon optimized full length version of the bovine RSV F protein. .sup.8NDV-boFchim: recombinant NDV (strain LaSota) expressing a codon optimized chimeric version of the bovine RSV F protein ectodomain fused to the transmembrane and cytoplasmic domains of the NDV F protein.

6.2.2 Results

(271) Optimized versions of the rNDV-F construct have been produced as described in Section 6.2.1.1. These constructs are named rNDV-F.sub.opt and rNDV-F.sub.chim. FIG. **9** summarizes the main differences in the 3 recombinant NDVs expressing RSV-F. After rescue, all of the recombinant NDVs were amplified by inoculation in 8-10 old embryonated chicken eggs and characterized by RT-PCR and immunofluorescence (FIG. **13**).
(272) While inflammation is a necessary adjuvant in any vaccination strategy, it is important to limit inflammation in the respiratory tree when the vaccine is administered by the intranasal route. Both primary immunization and challenge with the optimized constructs, rNDV-F.sub.opt and rNDV-F.sub.chim, showed a decreased acute inflammatory response when compared with the original rNDV-F construct. In addition, the optimized constructs, rNDV-F.sub.opt and rNDV-F.sub.chim, show enhanced RSV F protein expression (FIG. **10**). Expression of the RSV F protein is enhanced in both NDV-F.sub.opt and NDV-F.sub.chim when compared with the original NDV-F construct. With being bound by any theory, it is possible that the relative reduction in RSV-F protein expression in the original NDV-F is related to the instability of the original rNDV-F construct. Initial observations indicate that the optimized constructs, NDV-F.sub.opt and NDV-F.sub.chim, appear to be much more stable than the original rNDV-F construct. The initial observations indicate that the original rNDV-F construct loses the RSV sequence upon passage.
(273) Cotton rats were mock treated or given priming and boosting doses of NDV, rNDV-F, rNDV-F.sub.opt or rNDV-F.sub.chim. Following RSV challenge, no RSV was detected in lung homogenates from animals receiving either rNDV-F.sub.opt or rNDV-F.sub.chim. Thus, the administration of rNDV-F.sub.opt and rNDV-F.sub.chim prior to challenge with RSV infection inhibited RSV replication. The administration of rNDV-Fopt to cotton rats resulted in a better protection against RSV challenge than administration rNDV-F to cotton rats.
(274) Another important measure of efficacy is the longevity of antibody protection. To determine whether rNDV-F.sub.opt and rNDV-F.sub.chim could also induce long-lived RSV-F specific antibody, animals were given allantoic fluid, rNDV vector, rNDV-F.sub.opt or rNDV-F.sub.chim, boosted one month later, and challenged with RSV on day 0. Serum samples were taken at day—31, and days 6, 13, 91 and 147 post-RSV challenge. The data in FIG. **12** demonstrates that the optimized constructs, unlike natural infection, can induce high titers of RSV F specific antibody that persist for 6 months after immunization. Titers are boosted by virus challenge, while protecting the host from infection, in the absence of disease.
(275) To assess the ability of Synagis®, a monoclonal antibody that binds to RSV F protein, to neutralize the recombination NDV constructs. As shown in FIG. **14**, the recombinant RSV-GFP was neutralized by Synagis®, but NDV-GFP was not inhibited. Similarly, the recombinant NDV constructs, rNDV-F, rNDV-Fopt, and rNDV-Fchim as well as wild-type NDV were not neutralized by Synagis® (FIG. **15**). For all the recombinant NDVs, no reduction in the percentage of infected cells at any of the dilutions tested was observed.
6.3 Example 3: Stability Assays for Recombinant NDV Constructs
(276) Stability of the recombinant NDVs expressing the F protein of RSV is evaluated by the ability to retain expression of the inserted gene after passage in eggs. The percentage of viruses retaining RSV-F expression is measured by simultaneous detection of the NDV protein HN and the RSV F protein by double immunofluorescence in cells infected with the different passages.
(277) Based on initial observations, the optimized versions (rNDV-F.sub.opt and rNDV-F.sub.chim) will retain a high percentage of cells with double labelling, while the original version (rNDV-F) will lose expression of the F protein in a high percentage of the infected cells after a few passages.
(278) Viruses rNDV-F, rNDV-F.sub.opt and rNDV-F.sub.chim are inoculated in triplicate at a 1:10000 dilution in chicken embryonated eggs (100 μl per egg). At 3 days post-infection the allantoic fluid is harvested, evaluated for hemagglutination and used to inoculate new eggs at 1:10000 dilution, as described above. This strategy is repeated for several passages.
(279) Serial dilutions of the harvested allantoic fluids is used to infect Vero cells in 96 well plates.

At 24 hours post infection cells are fixed and co-stained with a commercial mouse monoclonal antibody that recognizes the NDV HN protein and a humanized monoclonal antibody that recognize the RSV-F protein. Single and doubly labelled cells are quantified using a fluorescence plate reader (Celigo).

6.4 Example 4: Recombinant NDV Encoding Bovine RSV F Protein

(280) 6.4.1 Materials & Methods

(281) 6.4.1.1 Generation of Recombinant Newcastle Disease Virus (rNDV) Expressing the F Protein of Human Respiratory Syncytial Virus.

(282) 6.4.1.2 RSV Neutralization Assay

(283) This assay was performed as described in Section 6.2.1.9.

(284) 6.4.1.3 Generation of the Recombinant NDVs Expressing Bovine RSV F Proteins.

(285) The generation of the recombinant NDVs (LaSota strain) expressing a full length codon optimized F protein from bovine RSV (strain ATCC51908) (see SEQ ID NO:11 for the codon optimized nucleic acid sequence encoding bovine RSV F protein) and a chimeric F protein with the codon optimized ectodomain from bovine RSV (strain ATCC51908) fused to the transmembrane and cytoplasmic domains of NDV (strain LaSota) (see SEQ ID NO:14 for the nucleic acid sequence encoding chimeric F protein) was performed as described for the construction of the recombinant NDVs expressing the full length and chimeric F proteins from human RSV, respectively.

(286) 6.4.1.4 Characterization of the Recombinant NDVs Expressing Bovine RSV F Proteins.

(287) The presence of the inserted gene in the genome of the recombinant NDVs was confirmed by RT-PCR using viral RNA as template and primers flanking the insertion site. The amplified product was confirmed by sequencing.

(288) Expression of the recombinant bovine RSV F proteins was confirmed by double immunofluorescence in Vero cells infected with the recombinant NDVs as described for the human RSV F expressing NDVs, using the same antibodies (monoclonal antibodies Synagis recognizes the F protein from both human and bovine RSV).

(289) Absence of neutralization of the recombinant NDVs expressing bovine RSV F proteins by the potent RSV neutralizing Synagis antibody was performed as described for the recombinant NDVs expressing human RSV F proteins.

(290) 6.4.2 Results

(291) To assess the ability of Synagis®, a monoclonal antibody that binds to RSV F protein, to neutralize the recombination NDV constructs. As shown in FIG. **14**, the recombinant RSV-GFP was neutralized by Synagis®, but NDV-GFP was not inhibited. Similarly, the recombinant NDV constructs, rNDV-bovine RSV-Fopt, and rNDV-bovine RSV-Fchim as well as wild-type NDV were not neutralized by Synagis® (FIGS. **14** and **18**). For all the recombinant NDVs, no reduction in the percentage of infected cells at any of the dilutions tested was observed.

6.5 Example 5: Recombinant NDV Encoding Human Metapneumovirus F Protein

(292) 6.5.1 Generation of the Recombinant NDVs Expressing Human Metapneumovirus F Proteins.

(293) The generation of the recombinant NDVs expressing a full length codon optimized F protein from human MPV (strain CAN00-16) (see SEQ ID NO:18 for the codon optimized nucleic acid sequence encoding hMPV F protein) and a chimeric F protein with the codon optimized ectodomain from human MPV (strain CAN00-16) fused to the transmembrane and cytoplasmic domains of NDV (strain LaSota) (see SEQ ID NO:9 for the nucleic acid sequence encoding chimeric F protein) was performed as described for the construction of the recombinant NDVs expressing the full length and chimeric F proteins from human RSV, respectively.

(294) 6.5.2 Characterization of the Recombinant NDVs Expressing Human Metapneumovirus F Proteins.

(295) The presence of the inserted gene in the genome of the recombinant NDVs was confirmed by

RT-PCR using viral RNA as template and primers flanking the insertion site. The amplified product was confirmed by sequencing.

(296) Expression of the human MPV F protein by the recombinant NDVs was confirmed by double immunofluorescence in Vero cells infected with the recombinant NDVs as described for the human RSV F expressing NDVs, using human monoclonal antibody MPE8 to detect huMPV F protein and a commercial mouse monoclonal antibody to detect the NDV HN protein.

7. Embodiments

(297) Provided herein are the following exemplary embodiments:

(298) 1. A recombinant Newcastle disease virus (NDV) comprising a packaged genome comprising a transgene encoding a human respiratory syncytial virus ("RSV") F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:2, 26, 28, or 30.

(299) 2. A recombinant NDV comprising a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a human RSV F protein ectodomain and an NDV F protein transmembrane and cytoplasmic domains, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:4, 44, 45, or 46.

(300) 3. The recombinant NDV of embodiment 1, wherein the RSV F protein comprises the amino acid sequence set forth in SEQ ID NO:6.

(301) 4. The recombinant NDV of embodiment 2, wherein the chimeric F protein comprises the ectodomain of the amino acid sequence set forth in SEQ ID NO:7.

(302) 5. The recombinant NDV of embodiment 2 or 4, wherein the NDV virion comprises the chimeric F protein.

(303) 6. The recombinant NDV of embodiment 1 or 3, wherein the transgene is inserted between two transcription units of the packaged genome.

(304) 7. The recombinant NDV of embodiment 6, wherein the two transcription units of the packaged genome are the transcription units for the NDV P gene and the NDV M gene.

(305) 8. The recombinant NDV of embodiment 2, 4 or 5, wherein the transgene is inserted between two transcription units of the packaged genome.

(306) 9. The recombinant NDV of embodiment 8, wherein the two transcription units of the packaged genome are the transcription units for the NDV P gene and the NDV M gene.

(307) 10. The recombinant NDV of any one of embodiments 1 to 9 which comprises an NDV backbone which is lentogenic.

(308) 11. The recombinant NDV of any one of embodiments 1 to 9 which comprises an NDV backbone of LaSota strain.

(309) 12. The recombinant NDV of any one of embodiments 1 to 9 which comprises an NDV backbone of Hitchner B1 strain.

(310) 13. The recombinant NDV of embodiment 1 or 3, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO:3.

(311) 14. The recombinant NDV of embodiment 2, 4 or 5, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO:5.

(312) 15. An immunogenic composition comprising the recombinant NDV of any one of embodiments 1 to 14.

(313) 16. A method for inducing an immune response to RSV F protein, comprising administering the immunogenic composition of embodiment 15 to a subject.

(314) 17. A method for preventing an RSV disease, comprising administering the immunogenic composition of embodiment 15 to a subject.

(315) 18. A method for immunizing a subject against RSV, comprising administering the immunogenic composition of embodiment 15 to the subject.

(316) 19. The method of any one of embodiment 16 to 18, wherein the composition is administered

to the subject intranasally.
(317) 20. The method of any one of embodiments 16 to 19, wherein the subject is seropositive for anti-RSV F antibodies.
(318) 21. The method of any one of embodiments 16 to 19, wherein the subject is seronegative for anti-RSV F antibodies.
(319) 22. The method of any one of embodiments 16 to 21, wherein the subject is a human.
(320) 23. The method of any one of embodiments 16 to 21, wherein the subject is a human infant six months old or older.
(321) 24. The method of any one of embodiments 16 to 21, wherein the subject is a human child.
(322) 25. The method of any one of embodiments 16 to 21, wherein the subject is a human adult or an elderly human.
(323) 26. A recombinant NDV comprising a packaged genome comprising a transgene encoding a bovine respiratory syncytial virus ("RSV") F protein.
(324) 27. The recombinant NDV of embodiment 26, wherein bovine RSV F protein comprises the amino acid sequence of SEQ ID NO:10.
(325) 28. The recombinant NDV of embodiment 26 or 27, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:9 or 11.
(326) 29. The recombinant NDV of embodiment 26, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:40, 41, 42, or 43.
(327) 30. A recombinant NDV comprising a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises a bovine RSV F protein ectodomain and an NDV F protein transmembrane and cytoplasmic domains.
(328) 31. The recombinant NDV of embodiment 30, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:14, 31, 38 or 39.
(329) 32. The recombinant NDV of embodiment 30, wherein the chimeric F protein comprises the ectodomain of the amino acid sequence set forth in SEQ ID NO:10.
(330) 33. The recombinant NDV of embodiment 30, wherein the chimeric F protein comprises the amino acid sequence set forth in SEQ ID NO:33.
(331) 34. The recombinant NDV of any one of embodiments 30 to 33, wherein the NDV virion comprises the chimeric F protein.
(332) 35. The recombinant NDV of any one of embodiments 26 to 29, wherein the transgene is inserted between two transcription units of the packaged genome.
(333) 36. The recombinant NDV of embodiment 35, wherein the two transcription units of the packaged genome are the transcription units for the NDV P gene and the NDV M gene.
(334) 37. The recombinant NDV of any one of embodiments 30 to 34, wherein the transgene is inserted between two transcription units of the packaged genome.
(335) 38. The recombinant NDV of embodiment 37, wherein the two transcription units of the packaged genome are the transcription units for the NDV P gene and the NDV M gene.
(336) 39. The recombinant NDV of any one of embodiments 26 to 38 which comprises an NDV backbone which is lentogenic.
(337) 40. The recombinant NDV of any one of embodiments 26 to 39 which comprises an NDV backbone of LaSota strain.
(338) 41. The recombinant NDV of any one of embodiments 26 to 39 which comprises an NDV backbone of Hitchner B1 strain.
(339) 42. The recombinant NDV of embodiment 26, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO:12 or 13.
(340) 43. The recombinant NDV of embodiment 30, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO: 37 or 59.

(341) 44. An immunogenic composition comprising the recombinant NDV of any one of embodiments 26 to 43.
(342) 45. A method for inducing an immune response to RSV F protein, comprising administering the immunogenic composition of embodiment 44 to a bovine subject.
(343) 46. A method for preventing an RSV disease, comprising administering the immunogenic composition of embodiment 44 to a bovine subject.
(344) 47. A method for immunizing a subject against RSV, comprising administering the immunogenic composition of embodiment 44 to the bovine subject.
(345) 48. The method of any one of embodiment 45 to 47, wherein the composition is administered to the subject intranasally.
(346) 49. The method of any one of embodiments 45 to 48, wherein the subject is seropositive for anti-RSV F antibodies.
(347) 50. The method of any one of embodiments 45 to 48, wherein the subject is seronegative for anti-RSV F antibodies.
(348) 51. A method for inducing an immune response to RSV F protein in a human subject seropositive for anti-RSV F antibodies, comprising administering to the subject a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, wherein the transgene encodes a human RSV F protein.
(349) 52. A method for preventing an RSV disease in a human subject seropositive for anti-RSV F antibodies, comprising administering to the subject a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, wherein the transgene encodes a human RSV F protein.
(350) 53. A method for immunizing a subject against RSV in a human subject seropositive for anti-RSV F antibodies, comprising administering to the subject a recombinant NDV, wherein the recombinant NDV comprises a packaged genome comprising a transgene, wherein the transgene encodes a human RSV F protein.
(351) 54. The method of any one of embodiments 51 to 53, wherein the human RSV F protein comprises the amino acid sequence set forth in SEQ ID NO:6, 49, 50 or 58.
(352) 55. The method of embodiment 54, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO:1 or 2.
(353) 56. The method of embodiment 54, wherein the transgene comprises a codon optimized nucleic acid sequence encoding the RSV F protein.
(354) 57. The method of any one of embodiments 51 to 53, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence set forth in SEQ ID NO: 25, 26, 27, 28, 29 or 30.
(355) 58. The method of any one of embodiments 53 to 57, wherein the transgene is inserted between two transcription units of the packaged genome.
(356) 59. The method of embodiment 58, wherein the two transcription units of the packaged genome are the transcription units for the NDV P gene and the NDV M gene.
(357) 60. The method of any one of embodiments 51 to 59, wherein the recombinant NDV comprises an NDV backbone which is lentogenic.
(358) 61. The method of any one of embodiments 51 to 59, wherein the recombinant NDV comprises an NDV backbone of LaSota strain.
(359) 62. The method of any one of embodiments 51 to 59, wherein the recombinant NDV comprises an NDV backbone of Hitchner B1 strain.
(360) 63. The method of any one of embodiments 51 to 54, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO:3.
(361) 64. The method of any one of embodiments 51 to 63, wherein the composition is administered to the subject intranasally.
(362) 65. The method of any one of embodiments 51 to 64, wherein the human subject is an elderly

human.
(363) 66. The method of any one of embodiments 51 to 64, wherein the human subject is a human adult.
(364) 67. The method of any one of embodiments 51 to 64, wherein the human subject is a human child.
(365) 68. A recombinant NDV comprising a packaged genome comprising a transgene encoding a human metapneumovirus ("hMPV") F protein.
(366) 69. The recombinant NDV of embodiment 68, wherein the hMPV F protein comprises the amino acid sequence set forth in SEQ ID NO: 17.
(367) 70. The recombinant NDV of embodiment 68 or 69, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:16 or 18.
(368) 71. The recombinant NDV of embodiment 68, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO:52, 53, 54, 55, 56, or 57.
(369) 72. A recombinant Newcastle disease virus (NDV) comprising a packaged genome comprising a transgene encoding a chimeric F protein, wherein the chimeric F protein comprises an hMPV F protein ectodomain and an NDV F protein transmembrane and cytoplasmic domains.
(370) 73. The recombinant NDV of embodiment 72, wherein the chimeric F protein comprises the amino acid sequence of SEQ ID NO:15.
(371) 74. The recombinant NDV of embodiment 72, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 19, 32, 34, 35 or 36.
(372) 75. The recombinant NDV of embodiment 72, 73 or 74, wherein the NDV virion comprises the chimeric F protein.
(373) 76. The recombinant NDV of any one of embodiments 68 to 71, wherein the transgene is inserted between two transcription units of the packaged genome.
(374) 77. The recombinant NDV of embodiment 76, wherein the two transcription units of the packaged genome are the transcription units for the NDV P gene and the NDV M gene.
(375) 78. The recombinant NDV of any one of embodiments 72 to 75, wherein the transgene is inserted between two transcription units of the packaged genome.
(376) 79. The recombinant NDV of embodiment 78, wherein the two transcription units of the packaged genome are the transcription units for the NDV P gene and the NDV M gene.
(377) 80. The recombinant NDV of any one of embodiments 68 to 79 which comprises an NDV backbone which is lentogenic.
(378) 81. The recombinant NDV of any one of embodiments 68 to 79 which comprises an NDV backbone of LaSota strain.
(379) 82. The recombinant NDV of any one of embodiments 68 to 78 which comprises an NDV backbone of Hitchner B1 strain.
(380) 83. The recombinant NDV of embodiment 68, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO:20 or 21.
(381) 84. The recombination NDV of embodiment 72, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO: 22.
(382) 85. An immunogenic composition comprising the recombinant NDV of any one of embodiments 68 to 84.
(383) 86. A method for inducing an immune response to hMPV F protein, comprising administering the immunogenic composition of embodiment 85 to a human subject.
(384) 87. A method for preventing an hMPV disease, comprising administering the immunogenic composition of embodiment 85 to a human subject.
(385) 88. A method for immunizing a subject against hMPV, comprising administering the immunogenic composition of embodiment 85 to a human subject.

(386) 89. The method of any one of embodiments 86 to 88, wherein the composition is administered to the subject intranasally.
(387) 90. The method of any one of embodiments 86 to 89, wherein the subject is seropositive for anti-hMPV F antibodies.
(388) 91. The method of any one of embodiments 86 to 89, wherein the subject is seronegative for anti-hMPV F antibodies.
(389) 92. The method of any one of embodiments 86 to 91, wherein the subject is a human infant.
(390) 93. The method of any one of embodiments 86 to 91, wherein the subject is an elderly human.
(391) 94. A kit comprising the recombinant NDV of any one of embodiments 1 to 14, 26 to 43, or 68 to 84.
(392) 95. A cell line or chicken embryonated egg comprising the propagating the recombinant NDV of any one of embodiments 1 to 14, 26 to 43, or 68 to 84.
(393) 96. A method for propagating the recombinant NDV of any one of embodiments 1 to 14, 26 to 43, or 68 to 84, the method comprising culturing the cell or embryonated egg of embodiment 95.
(394) 97. The method of embodiment 96, wherein the method further comprises isolating the recombinant NDV from the egg or embryonated egg.
(395) The invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described will become apparent to those skilled in the art from the foregoing description and accompanying Figures. Such modifications are intended to fall within the scope of the appended claims.
(396) All references cited herein are incorporated herein by reference in their entirety and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

Claims

1. A recombinant Newcastle disease virus (NDV) comprising a packaged genome comprising (a) a transgene encoding a fusion (F) protein of a human virus of the family Pneumoviridae, wherein the transgene comprises (i) a ribonucleic acid (RNA) sequence corresponding to the negative sense of the complementary deoxyribonucleic acid (cDNA) sequence of SEQ ID NO: 2, 26, 28, or 30, or (ii) an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 18, 53, 55, or 57; (b) a transgene encoding a chimeric protein comprising an ectodomain of a F protein of a human virus of the family Pneumoviridae and a transmembrane domain and a cytoplasmic domain of a NDV F protein, wherein: (i) the human virus of the family Pneumoviridae is human respiratory syncytial virus (“RSV”), and the chimeric protein comprises the ectodomain of the amino acid sequence set forth in SEQ ID NO:7, (ii) the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 19, 32, 34, 35, or 36, or (iii) the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 4, 44, 45, or 46; or (c) a transgene encoding a bovine respiratory syncytial virus (“RSV”) F protein, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 11, 41, or 43; or (d) a transgene encoding a chimeric protein comprising a bovine Respiratory Syncytial Virus (RSV) F protein ectodomain and a transmembrane domain and a cytoplasmic domain of a NDV F protein, wherein: (i) the chimeric protein comprises the amino acid sequence set forth in SEQ ID NO:33, or (ii) the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 14, 31, 38, or 39.
2. The recombinant NDV of claim 1, wherein the human virus of the family Pneumoviridae is the RSV, and the chimeric protein comprises the ectodomain of the amino acid sequence set forth in

SEQ ID NO:7.
3. The recombinant NDV of claim 1, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO: 3, 5, 13, 37 or 59.
4. An immunogenic composition comprising the recombinant NDV of claim 1.
5. A method for inducing an immune response to an F protein of a human virus of the family Pneumoviridae in a subject, preventing a human virus of the family Pneumoviridae disease in a subject, or immunizing a subject against a human virus of the family Pneumoviridae, comprising administering the immunogenic composition of claim 4 to the subject.
6. The recombinant NDV of claim 1, wherein the chimeric protein comprises the amino acid sequence set forth in SEQ ID NO:33.
7. The recombinant NDV of claim 1, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 11, 14, 31, 38, 39, 41, or 43.
8. A method for inducing an immune response to RSV F protein to a bovine subject, preventing an RSV disease in a bovine subject, or immunizing a bovine subject against RSV, the method comprising administering the immunogenic composition of claim 1 to the bovine subject.
9. A method for inducing an immune response to RSV F protein in a human subject seropositive for anti-RSV F antibodies, preventing an RSV disease in a human subject seropositive for anti-RSV F antibodies, or immunizing a subject against RSV in a human subject seropositive for anti-RSV F antibodies, the method comprising administering the immunogenic composition of claim 1 to the human subject.
10. The recombinant NDV of claim 1, wherein (a) the F protein of a human virus of the family Pneumoviridae is a human metapneumovirus (“hMPV”) F protein; or (b) the ectodomain of a fusion (F) protein of a human virus of the family Pneumoviridae is a human metapneumovirus (hMPV) fusion (F) protein ectodomain.
11. The recombinant NDV of claim 10, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 18, 53, 55, 57, 19, 32, 34, 35 or 36.
12. The recombinant NDV of claim 10, wherein the genome comprises a negative sense RNA sequence transcribed from the cDNA sequence set forth in SEQ ID NO: 21, or 22.
13. An immunogenic composition comprising the recombinant NDV of claim 10.
14. A method for inducing an immune response to hMPV F protein, preventing an hMPV disease, or immunizing a subject against hMPV, the method comprising administering the immunogenic composition of claim 13 to a human subject.
15. A cell line or chicken embryonated egg comprising the propagating the recombinant NDV of claim 1.
16. A method for propagating the recombinant NDV of claim 1, the method comprising culturing the cell or embryonated egg of claim 15.
17. The recombinant NDV of claim 1, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 2, 26, 28, or 30.
18. The recombinant NDV of claim 1, wherein the transgene comprises an RNA sequence corresponding to the negative sense of the cDNA sequence of SEQ ID NO: 4, 44, 45, or 46.