HUMAN ANTIBODIES TO RESPIRATORY SYNCYTIAL VIRUS F PROTEIN AND METHODS OF USE THEOF

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Field of Classification Search
None
See application file for complete search history.

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ABSTRACT
The present invention provides fully human antibodies that bind to respiratory syncytial virus F protein, compositions comprising the antibodies and methods of use. The antibodies of the invention are useful for preventing fusion of the virus with the cell membrane and preventing cell to cell spread of the virus, thereby providing a means of preventing the infection, or treating a patient suffering from the infection and ameliorating one or more symptoms or complications associated with the viral infection. The antibodies may also be useful for diagnosis of an infection by RSV.

46 Claims, 2 Drawing Sheets
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OTHER PUBLICATIONS


Figure 1
Figure 2

A. **Attachment**

![Attachment graph]

B. **Fusion**

![Fusion graph]
HUMAN ANTIBODIES TO RESPIRATORY SYNCYTIAL VIRUS F PROTEIN AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 (e) of U.S. provisional application Nos. 61/782,215, filed Mar. 14, 2013 and 61/911,093, filed Dec. 3, 2013, both of which are herein specifically incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind to Respiratory Syncytial Virus F protein (RSV-F), comprising compositions these antibodies and methods of using these antibodies.

STATEMENT OF RELATED ART


RSV can infect the adult population as well. In this population, RSV causes primarily an upper respiratory tract disease, although elderly patients may be at greater risk for a serious infection and pneumonia (Evans, A. S., eds., 1989, Viral Infections of Humans: Epidemiology and Control, 3rd ed., Plenum Medical Book, New York at pages 525-544), as well as adults who are immunosuppressed, particularly bone marrow transplant patients (Hertz et al., 1989, Medicine 68:269-281). Other at risk patients include those suffering from congestive heart failure and those suffering from chronic obstructive pulmonary disease (ie, COPD). There have also been reports of epidemics among nursing home patients and institutionalized young adults (Falsley, A. R., 1991, Infect. Control Hosp. Epidemiol. 12:602-608; and Garvie et al., 1980, Br. Med. J. 281:1253-1254).

While treatment options for established RSV disease are limited, more severe forms of the disease of the lower respiratory tract often require considerable supportive care, including administration of humidified oxygen and respiratory assistance (Fields et al., eds, 1990, Fields Virology, 2nd ed., Vol. 1, Raven Press, New York at pages 1045-1072).

Riboavirin, which is the only drug approved for treatment of infection, has been shown to be effective in the treatment of pneumonia and bronchiolitis associated with RSV infection, and has been shown to modify the course of severe RSV disease in immunocompetent children (Smith et al., 1991, New Engl. J. Med. 325:24-29). The use of riboavirin is limited due to concerns surrounding its potential risk to pregnant women who may be exposed to the aerosolized drug while it is being administered in a hospital environment.

Similarly, while a vaccine may be useful, no commercially available vaccine has been developed to date. Several vaccine candidates have been abandoned and others are under development (Murphy et al., 1994, Virus Res. 32:13-36). The development of a vaccine has proven to be problematic. In particular, immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory tract disease occurs at 2-5 months of age. However, it is known that the neonatal immune response is immature at that time. Plus, the infant at that point in time still has high titers of maternally acquired RSV antibody, which might reduce vaccine immunogenicity (Murphy et al., 1988, J. Virol. 62:3907-3910; and Murphy et al., 1991, Vaccine 9:185-189).

Two glycoproteins, F and G, on the surface of RSV have been shown to be targets of neutralizing antibodies (Fields et al., 1990, supra; and Murphy et al., 1994, supra). These two proteins are also primarily responsible for viral recognition and entry into target cells; G protein binds to a specific cellular receptor and the F protein promotes fusion of the virus with the cell. The F protein is also expressed on the surface of infected cells and is responsible for subsequent fusion with other cells leading to syncytia formation and cell to cell virus spread.

Currently, the only approved approach to prophylaxis of RSV disease is passive immunization. For example, the humanized antibody, palivizumab (SYNAGIS®), which is specific for an epitope on the F protein, is approved for intramuscular administration to pediatric patients for prevention of serious lower respiratory tract disease caused by RSV at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNAGIS® is a composite of human (95%) and murine (5%) antibody sequences. See, Johnson et al., (1997), J. Infect. Diseases 176:1215-1224 and U.S. Pat. No. 5,824,307, the entire contents of which are incorporated herein by reference.

Although SYNAGIS® has been successfully used for the prevention of RSV infection in pediatric patients, multiple intramuscular doses of 15 mg/kg of SYNAGIS® are required to achieve a prophylactic effect. The necessity for the administration of multiple intramuscular doses of antibody requires repeated visits to the doctor's office, which is not only inconvenient for the patient but can also result in missed doses.

Efforts were made to improve on the therapeutic profile of an anti-RSV-F antibody, and this led to the identification and development of motavizumab, also referred to as NUMAX™. However, clinical testing revealed that certain of the patients being administered motavizumab were having severe hypersensitivity reactions. Further development of this humanized anti-RSV-F antibody was then discontinued.

Other antibodies to RSV-F protein have been described and can be found in U.S. Pat. No. 6,656,467; U.S. Pat. No.
The invention provides isolated fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that bind specifically to Respiratory Syncytial Virus F protein (RSV-F). Given the role that the F protein plays in fusion of the virus with the cell and in cell to cell transmission of the virus, the antibodies described herein provide a method of inhibiting that process and as such, may be used for preventing infection of a patient exposed to, or at risk for acquiring an infection with RSV, or for treating and/or ameliorating one or more symptoms associated with RSV infection in a patient exposed to, or at risk for acquiring an infection with RSV, or suffering from infection with RSV.

The antibodies described herein may also be used to prevent or to treat an RSV infection in a patient who may experience a more severe form of the RSV infection due to an underlying or pre-existing medical condition. A patient who may benefit from treatment with an antibody of the invention may be a pre-term infant, a full-term infant born during RSV season (approximately late fall (November) through early spring (April)) that is at risk because of other pre-existing or underlying medical conditions including congenital heart disease or chronic lung disease, a child greater than one year of age with or without an underlying medical condition, an institutionalized or hospitalized patient, or an elderly adult (>65 years of age) with or without an underlying medical condition, such as congestive heart failure (CHF), or chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), bronchopulmonary dysplasia, congestive heart failure (CHF), or congenital heart disease.

Because the antibodies of the invention are more effective at neutralization of RSV compared to known antibodies, lower doses of the antibodies or antibody fragments could be used to achieve a greater level of protection against infection with RSV, and more effective treatment and/or amelioration of symptoms associated with an RSV infection. Accordingly, the use of lower doses of antibodies or fragments thereof which immuno-specifically bind to RSV-F antigen may result in fewer or less severe adverse events. Likewise, the use of more effective neutralizing antibodies may result in a diminished need for frequent administration of the antibodies or antibody fragments than previously envisioned as necessary for the prevention of infection, or for virus neutralization, or for treatment or amelioration of one or more symptoms associated with an RSV infection. Symptoms of RSV infection may include a bluish skin color due to lack of oxygen (hypoxia), breathing difficulty (rapid breathing or shortness of breath), cough, coughy cough (‘seal bark’ cough), fever, nasal flaring, nasal congestion (stuffy nose), apnea, decreased appetite, dehydration, poor feeding, altered mental status, or wheezing.

Such antibodies may be useful when administered prophylactically (prior to exposure to the virus and infection with the virus) to lessen the severity, or duration of a primary infection with RSV, or ameliorate at least one symptom associated with the infection. The antibodies may be used alone or in conjunction with a second agent useful for treating an RSV infection. In certain embodiments, the antibodies may be given therapeutically (after exposure to and infection with the virus) either alone, or in conjunction with a second agent to lessen the severity or duration of the primary infection, or to ameliorate at least one symptom associated with the infection. In certain embodiments, the antibodies may be used prophylactically as stand-alone therapy to protect patients who are at risk for acquiring an infection with RSV, such as those described above. Any of these patient populations may benefit from treatment with the antibodies of the invention, when given alone or in conjunction with a second agent, including for example, an anti-viral therapy, such as ribavirin, or other anti-viral vaccines.

The antibodies of the invention can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, F(ab')2, or scFv fragment), and may be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al., 2000, J. Immunol. 164:1925-1933).

Accordingly, in a first aspect, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F).

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody has one or more of the following characteristics:

(a) is a fully human monoclonal antibody;
(b) interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354;
(c) interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354.
NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354;
(d) is capable of neutralizing respiratory syncytial virus subtype A and subtype B strains in vitro;
(e) demonstrates the ability to significantly reduce the nasal and/or lung viral load in vivo in an animal model of RSV infection; or
(f) inhibits fusion of the virus to the cell.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354.

In one embodiment, the antibody is a fully human monoclonal antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or an antigen-binding fragment thereof interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354, and wherein the antibody neutralizes respiratory syncytial virus subtype A and/or subtype B strains in vitro and in vivo.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates the ability to significantly reduce the lung viral load in a mouse model of RSV infection when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates a 1-2 logs greater reduction of nasal and/or lung viral titers as compared to palivizumab in a cotton rat model of RSV infection when administered at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{90} of about 0.15 mg/kg or less when administered in a mouse model of RSV subtype A infection.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{90} of about 0.62 mg/kg or less when administered in a cotton rat model of RSV subtype A infection.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{90} of about 2.5 mg/kg or less when administered in a cotton rat model of RSV subtype B infection.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates an ED_{90} that is about 2 to 5 fold lower than the ED_{90} for palivizumab or motvirizumab.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a half maximal inhibitory concentration (IC_{50}) of about 2 pH to about 600 pH in a microneutralization assay specific for RSV subtype A strains of RSV.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a half maximal inhibitory concentration (IC_{50}) of about 6 pH to about 100 pH in a microneutralization assay specific for RSV subtype B strains of RSV.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to RSV-F protein demonstrates a neutralization potency against one or more subtype A laboratory strains of RSV that is about a 15 to 17 fold improvement over palivizumab, or demonstrates a neutralization potency against one or more subtype A clinical strains of RSV that is about a 10 to 20 fold improvement over palivizumab.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to RSV-F protein demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2 to 5 fold improvement over palivizumab.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a neutralization potency against one or more subtype A laboratory strains or subtype A clinical strains of RSV that is about a 0.5 to 2 fold improvement over AM-22.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2.5 to 17 fold improvement over AM-22.

In one embodiment, the isolated human antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), exhibits a K_{D} ranging from 1x10^{-7} M to 6x10^{-10} M, as measured by surface plasmon resonance.

In one embodiment, the isolated human antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), exhibits a K_{D} ranging from 1x10^{-7} M to 9x10^{-10} M, as measured by surface plasmon resonance.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR amino acid sequence selected from the group consisting of SEQ ID Nos: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR amino acid sequence selected from the group consisting of SEQ ID Nos: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition,
In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 30, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 278, 290, 306, 322 and 338.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 30, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338; and a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 30, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338; and a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a heavy chain amino acid sequence of SEQ ID NO: 363 and the light chain amino acid sequence of SEQ ID NO: 364.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.
(f) a LCRD3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 288 and 352.

In one embodiment, the isolated human antibody or antigen binding fragment thereof that specifically binds to RSV-F comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NOs: 276, 278 and 280, respectively and LCRD1, LCRD2 and LCRD3 amino acid sequences of SEQ ID NOs: 284, 286 and 288, respectively.

In one embodiment, the isolated human antibody or antigen binding fragment thereof that specifically binds to RSV-F comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NOs: 340, 342 and 344, respectively and LCRD1, LCRD2 and LCRD3 amino acid sequences of SEQ ID NOs: 348, 350 and 352, respectively.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F) competes for specific binding to RSV-F with an antibody or antigen-binding fragment comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof, which comprises heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, and which specifically binds to Respiratory Syncytial Virus F protein (RSV-F), does not compete for specific binding to RSV-F with palivizumab, motavizumab, or AM-22.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F) binds the same epitope on RSV-F that is recognized by an antibody comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof, which comprises heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, and which specifically binds to Respiratory Syncytial Virus F protein (RSV-F), does not bind the same epitope on RSV-F as palivizumab or motavizumab.

In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds to RSV-F, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 98% or at least 99% sequence identity; and a LCRD3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vi) a LCRD1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 352 and 348, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vii) and a LCRD2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (viii) exhibits a $K_{D}$ ranging from about $1 	imes 10^{-5} \text{M}$ to about $6 \times 10^{-10} \text{M}$ as measured by surface plasmon resonance; (ix) is capable of neutralizing respiratory syncytial virus subtype A and/or subtype B strains in vitro; (x) demonstrates the ability to significantly reduce the viral load in a mouse model of RSV infection when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg; (xi) demonstrates a 1 to 2 logs greater reduction of nasal and/or lung viral titers in a cotton rat model of RSV infection at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg when compared to palivizumab; (xii) demonstrates an effective dose 99 (ED$_{99}$) ranging from about 0.15 mg/kg to about 2.5 mg/kg when administered in an animal model of RSV infection (e.g. a mouse model or a cotton rat model); or (xiii) demonstrates a half maximal inhibitory concentration (IC$_{50}$) of about 2 pM to about 15 pM in a microneutralization assay specific for RSV subtype A strains of RSV and a half maximal inhibitory concentration (IC$_{50}$) of about 6 pM to about 100 pM in a microneutralization assay.
at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vi) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vii) and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (viii) exhibits a K_{d}, ranging from about 1×10^{-9} M to about 6×10^{-10} M; (ix) is capable of neutralizing respiratory syncytial virus subtype A and/or subtype B strains in vitro; (x) demonstrates the ability to significantly reduce the viral load in a animal model of RSV infection (e.g. a mouse model) when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg; (xi) demonstrates a 1 to 2 logs greater reduction of nasal and/or lung viral titer in an animal model of RSV infection (e.g. a cotton rat model) at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg when compared to palizumab; (xii) demonstrates an effective dose 95 (ED_{50}) ranging from about 0.05 mg/kg to about 2.5 mg/kg when administered in an animal model of RSV infection (e.g. a mouse model or a cotton rat model); (xiii) demonstrates an ED_{50} that is about 2 to 3 fold lower than the ED_{50} for palizumab or motavizumab; (xiv) demonstrates a neutralization potency against one or more subtype A laboratory strains of RSV that is about 10 to 20 fold improvement over palizumab; (xv) demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about 2 to 5 fold improvement over palizumab; (xvi) demonstrates a neutralization potency against one or more subtype A laboratory strains or subtype A clinical strains of RSV that is about 0.5 to 2 fold improvement over AM-22; (xvii) demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about 2.5 to 17 fold improvement over AM-22.

In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds to RSV-F, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCDR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338, or a substantially similar sequence thereof having at least 90%, at least 95% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 95% or at least 99% sequence identity; (iv) comprises a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) a LCDR1 domain having an amino acid acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vi) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vii) and a LCDR2 domain having an amino acid acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (viii) exhibits a K_{d}, ranging from about 1×10^{-9} M to about 6×10^{-10} M; (ix) is capable of neutralizing respiratory syncytial virus subtype A and/or subtype B strains in vitro; (x) demonstrates the ability to significantly reduce the viral load in a animal model of RSV infection; (xi) interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354; (xii) interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354, and the threonine at position 174 of SEQ ID NO:
354; (xiii) inhibits fusion of RSV to the host cell; (xiv) does not cross-compete with palivizumab or AM-22 for binding to RSV-F.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds Respiratory Syncytial Virus F protein (RSV-F), or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid sequence ranging from about position 161 to about position 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NO: 355 and 356.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within SEQ ID NO: 355 or SEQ ID NO: 356.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354, and wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282.

In one embodiment, the invention provides an isolated human monoclonal antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or antigen-binding fragment thereof comprises:

(a) a HCDR1 domain comprising the amino acid sequence of SEQ ID NO: 276;
(b) a HCDR2 domain comprising the amino acid sequence of SEQ ID NO: 278;
(c) a HCDR3 domain comprising the amino acid sequence of SEQ ID NO: 280;
(d) a LCDR1 domain comprising the amino acid sequence of SEQ ID NO: 284;
(e) a LCDR2 domain comprising the amino acid sequence of SEQ ID NO: 286; and
(f) a LCDR3 domain comprising the amino acid sequence of SEQ ID NO: 288.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NO: 355 and 356.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within SEQ ID NO: 355 or SEQ ID NO: 356.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not cross-compete for binding to RSV-F with palivizumab, or motavizumab.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not cross-compete for binding to RSV-F with AM-22.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not bind the same epitope on RSV-F as palivizumab.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not bind the same epitope on RSV-F as motavizumab.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof that does not bind to an epitope on RSV-F
ranging from about amino acid residue 255 to about amino acid residue 276 of SEQ ID NO: 354.

In one embodiment, the isolated human monoclonal antibody, or an antigen-binding fragment thereof does not bind to the same epitope on RSV-F as palivizumab, wherein the epitope ranges from about amino acid residue 255 to about amino acid residue 276 of SEQ ID NO: 354.

In a second aspect, the invention provides nucleic acid molecules encoding antibodies or fragments thereof that specifically bind to RSV-F. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, and 357 or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

In one embodiment, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 273 and 337.

In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, and 345, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 281 and 345.

In one embodiment, the invention also provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 23, 39, 55, 71, 87, 103, 119, 135, 151, 167, 183, 190, 215, 231, 247, 263, 279, 295, 311, 327, and 343 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 31, 47, 63, 79, 95, 111, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, 287, 303, 319, 335, and 351, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

In one embodiment, the invention provides an antibody or fragment thereof further comprising a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, and 339, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 293, 309, 325, and 341, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 27, 43, 45, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 351, and 347, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, and 349, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

In a third aspect, the invention features a human antibody or antigen-binding fragment specific for RSV-F comprising a HCVR encoded by nucleotide sequence segments derived from V_{\kappa}, D_{\kappa} and J_{\kappa} germline sequences, and a LCVR encoded by nucleotide sequence segments derived from V_{\kappa} and J_{\kappa} germline sequences.

The invention encompasses antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or, e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

In a fourth aspect, the invention provides a pharmaceutical composition comprising at least one isolated fully human monoclonal antibody or antigen-binding fragment thereof that binds to RSV-F and a pharmaceutically acceptable carrier or diluent. In one embodiment, the invention provides a pharmaceutical composition comprising two fully human monoclonal antibodies or antigen-binding fragments thereof, which either bind to the same epitope or bind to two different epitopes on RSV-F and a pharmaceutically acceptable carrier or diluent. It is to be understood that any combination of antibodies as described herein may be used in a pharmaceutical composition to achieve the desired results in the patient population in need of such therapy. For example, two antibodies that recognize and/or bind RSV-F may be used in a composition. Alternatively, two antibodies, one that recognizes and/or binds RSV-F and a second antibody that binds to another antigen on RSV (e.g. RSV-G) may be used in a composition. In one embodiment, two antibodies, one that recognizes and/or binds RSV-F and a second antibody that binds to a metapneumovirus antigen may be used in a composition. Alternatively, two or more antibodies may be used in a composition, one that recognizes and/or binds RSV-F, one that binds to a metapneumovirus antigen and one that binds to an influenza virus antigen or to any other virus that causes respiratory diseases.

In one embodiment, the pharmaceutical composition comprises an antibody that binds RSV-F and has a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the pharmaceutical composition comprises an antibody that binds RSV-F and has a HCVR/LCVR amino acid sequence pair consisting of SEQ ID NOs: 274/282.

In one embodiment, the pharmaceutical composition comprises an antibody that binds RSV-F and has a HCVR/LCVR amino acid sequence pair consisting of SEQ ID NOs: 358/346.

In one embodiment, the pharmaceutical composition comprises at least one antibody that binds RSV-F, wherein the antibody comprises the three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 274 and 338; and the three light chain complementarity determining regions (LCDR1,
LCCR2 and LCCR3) contained within any one of the light chain variable region (LCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 282 and 346.

In one embodiment, the antibodies of the invention, or compositions containing one or more antibodies of the invention may be used to neutralize RSV from any subtype A or subtype B strain of RSV.

In one embodiment, the invention features a composition, which is a combination of an antibody or antigen-binding fragment of an antibody of the invention, and a second therapeutic agent.

The second therapeutic agent may be a small molecule drug, a protein/polypeptide, an antibody, a nucleic acid molecule, such as an anti-sense molecule, or a siRNA. The second therapeutic agent may be synthetic or naturally derived.

The second therapeutic agent may be any agent that is advantageously combined with the antibody or fragment thereof of the invention, for example, an antiviral agent (e.g., ribavirin), a vaccine specific for RSV, or a vaccine specific for influenza virus, or a vaccine specific for metabatuvirus (MPV), an siRNA specific for an RSV antigen, an siRNA specific for an influenza virus antigen, an siRNA specific for a metapneumovirus (MPV) antigen, a second antibody specific for an RSV antigen, or a metapneumovirus (MPV) antigen, or an influenza antigen, an anti-IL4R antibody, an anti-RSV-G antibody or a NSAID. In certain embodiments, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with the antibody or antigen-binding fragment of an antibody of the invention, if such side effect(s) should occur.

It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutic or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control) of any adverse effects. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art.

A fifth aspect of the invention provides a method for preventing infection with respiratory syncytial virus in a patient in need thereof, or for treating a patient suffering from an infection with RSV, or for ameliorating at least one symptom or complication associated with the RSV infection, the method comprising administering one or more antibodies or antigen-binding fragments thereof as described herein, or a pharmaceutical composition comprising one or more antibodies of the invention or fragments thereof, as described herein, to a patient in need thereof, such that the RSV infection is prevented, or at least one symptom or complication associated with the infection is ameliorated, alleviated or reduced in severity and/or duration.

In a related embodiment, the invention provides a pharmaceutical composition comprising one or more antibodies of the invention, alone or in combination with a second therapeutic agent, for use in preventing a respiratory syncytial virus (RSV) infection in a patient in need thereof, or for treating a patient suffering from an RSV infection, or for ameliorating at least one symptom or complication associated with the infection, wherein the infection is either prevented, or at least one symptom or complication associated with the infection is prevented, ameliorated, or lessened in severity and/or duration.

In one embodiment, the invention provides a pharmaceutical composition comprising one or more antibodies of the invention, alone or in combination with a second therapeutic agent in the manufacture of a medicament for preventing a respiratory syncytial virus (RSV) infection in a patient in need thereof, or for treating a patient suffering from an RSV infection, or for ameliorating at least one symptom or complication associated with the infection, wherein the infection is either prevented, or at least one symptom or complication associated with the infection is prevented, ameliorated, or lessened in severity and/or duration.

In one embodiment, a patient in need of treatment with an antibody of the invention, or an antigen-binding fragment thereof is a patient who may experience a more severe form of the RSV infection due to an underlying or pre-existing medical condition. In one embodiment, the method provides for preventing the development of infection with RSV in a patient at risk thereof, the method comprising administering to the patient an effective amount of an antibody or an antigen-binding fragment thereof that binds to the F protein of RSV, or a pharmaceutical composition comprising an effective amount of an antibody or an antigen-binding fragment thereof that binds to the F protein of RSV such that the infection is either prevented, ameliorated, or lessened in severity and/or duration, or at least one symptom or complication associated with the infection is prevented, or ameliorated, or lessened in severity or duration. In one embodiment, the administering of the isolated human RSV-F antibody or an antigen-binding fragment thereof results in prevention of recurrent wheezing in the patient. In one embodiment, the administering of the isolated human RSV-F antibody or an antigen-binding fragment thereof results in prevention of RSV-associated asthma in a child. In one embodiment, the administering of the isolated human RSV-F antibody or an antigen-binding fragment thereof results in prevention of an RSV infection caused by a subtype A or a subtype B respiratory syncytial virus.

In one embodiment, the at least one symptom or complication associated with the RSV infection that may be treated with an antibody of the invention, or an antigen-binding fragment thereof, may be selected from the group consisting of hypoxia, a bluish skin color due to lack of oxygen, breathing difficulty (e.g., rapid breathing or shortness of breath), cough, coughy cough (“seal bark” cough), fever, nasal flaring, stuffy nose, wheezing, pneumonia, apnea, dehydration, poor feeding, altered mental status, decreased appetite, or bronchiolitis.

In one embodiment, the patient at risk of developing an RSV infection, who may benefit from treatment with the antibodies of the invention, or with a composition comprising one or more antibodies of the invention, may be selected from the group consisting of a pre-term infant, a full term infant who is compromised due to some other underlying medical condition and/or is exposed during the peak season
for RSV, a child greater than or equal to one year of age with
or without an underlying medical condition (e.g. congenital
heart disease, chronic lung disease, cystic fibrosis, immu-
nodficiency, a neuromuscular disorder), an institutionalized
or hospitalized patient, an elderly patient 65 years of age
with or without an underlying medical condition such as
congestive heart failure or chronic obstructive pulmonary
disease), a patient who is immunocompromised due to
underlying illness or due to administration of immuno-
suppressive therapeutics, a patient who has some underlying
medical condition that may pre-dispose them to acquiring an
RSV infection, for example, chronic obstructive pulmonary
disease (COPD), congestive heart failure, cystic fibrosis,
bronchopulmonary dysplasia, airway malfunction, chronic
lung disease, a cancer patient, or a transplant patient who is
on immuno-suppressive therapy.

In one embodiment, a patient who is a candidate for
therapy with an antibody of the invention may suffer from
a condition resulting from a compromised pulmonary, cardio-
vascular, neuromuscular, or immune system. The condition
may be selected from the group consisting of an abnormality
of the airway, a chronic lung disease, a chronic heart disease,
a neuromuscular disease that compromises the handling of
respiratory secretions and immunosuppression. The chronic
lung disease may be chronic obstructive pulmonary disease
(COPD), cystic fibrosis, or bronchopulmonary dysplasia.
The chronic heart disease may be congestive heart failure
(CHF), or congenital heart disease. The neuromuscular
disease or condition may be a neurodegenerative disease, or
an inability to handle and/or eliminate respiratory secretions
due to an injury or accident to the nervous system, e.g., a
stroke, or a spinal cord injury. The immunosuppression may
be the result of severe combined immunodeficiency or
severe acquired immunodeficiency, or may be a result of any
other infectious disease or cancerous condition that leads to
immunosuppression, or is a result of treatment with immu-
notropic drug therapy or radiation therapy.

In one embodiment, the antibody is administered prophyl-
actically (administered prior to development of the infec-
tion) to a patient at risk for developing an RSV infection, or
at risk for developing at least one symptom or complication
associated with the RSV infection. The patients who are
candidates for treatment with the antibodies of the invention
may be administered the compositions comprising one or
more antibodies by any route of delivery suitable for admin-
istration, including but not limited to intravenous injection,
intradural injection, or subcutaneous injection.

In one embodiment, the antibody is administered therape-
utically (administered after the development of the infec-
tion) to a patient to ameliorate or reduce the severity and/or
duration of at least one symptom or complication associated
with the RSV infection.

In one embodiment, the antibodies of the invention may
be administered to the patient in combination with one or
more therapeutic agents useful for treating an RSV infection.
The one or more therapeutic agents may be selected from the
group consisting of an antiviral agent; a vaccine specific for
RSV, a vaccine specific for influenza virus, or a vaccine
specific for metapneumovirus (MPV); an siRNA specific for
an RSV antigen or a metapneumovirus (MPV) antigen; a
second antibody specific for an RSV antigen or a metap-
neumovirus (MPV) antigen; an anti-IL-4R antibody, an anti-
body specific for an influenza virus antigen, an anti-RSV-G
antibody and a NSAIAD.

A sixth aspect of the invention provides an immunogenic
composition, or a vaccine, that when administered to an
individual, preferably a human, induces an immune response
in such individual to a Respiratory Syncytial Virus (RSV)
antigen.

In one embodiment, the immunogenic composition, or
vaccine, comprises an RSV antigen, for example, an RSV-F
protein, polypeptide, or an immunogenic fragment thereof,
or an epitope contained within and/or obtained from an
antigen of the RSV-F polypeptide or a fragment thereof,
and/or comprises DNA and/or RNA which encodes and
expresses an epitope from an antigen of the RSV-F polypep-
tide, or other polypeptides of the invention.

In one embodiment of the invention, the immunogenic
composition, or vaccine, may comprise the RSV-F protein
as shown in SEQ ID NO: 354. In one embodiment of the
invention, the immunogenic composition, or vaccine, may
comprise a RSV-F polypeptide fragment comprising resi-
dues 161 through 188 of SEQ ID NO: 354. In one embodi-
ment of the invention, the immunogenic composition, or vaccine,
may comprise one or more amino acid residues contained
within SEQ ID NO: 355 and/or SEQ ID NO: 356. In one
embodiment of the invention, the immunogenic composition,
or vaccine, may comprise SEQ ID NO: 355 and/or SEQ ID
NO: 356.

In a related aspect, the invention provides a method for
inducing an immune response in an individual, particularly
a mammal, preferably humans, by administering to an
individual an immunogenic composition, or a vaccine,
comprising a RSV-F protein, or an immunogenic fragment
thereof, or a RSV-F antigen or an immunogenic fragment
thereof comprising one or more epitopes contained within
the RSV-F antigen or fragment thereof, adequate to produce
an antibody and/or a T cell immune response to protect the
individual from infection, particularly infection with Respi-
atory Syncytial Virus (RSV).

In one embodiment, methods are provided for using the
immunogenic compositions, or vaccines of the invention for
inducing an immune response that results in inhibiting, or
slowing the progression of cell to cell viral spread. Methods
are also provided for ameliorating at least one symptom
associated with RSV infection by administering an immu-
ogenic composition, or a vaccine, comprising at least one
RSV-F antigen, or one or more epitopes contained within
the RSV-F antigen, which when administered will induce an
immune response in the individual.

For example, in one embodiment the invention provides
a method of inducing an immune response in an individual
comprising delivering to the individual an immunogenic
composition, or vaccine comprising, an RSV-F antigen (e.g.,
the amino acid sequence shown in SEQ ID NO: 354), or an
antigenic fragment thereof, (e.g. a polypeptide comprising
residues 161 through 188 of SEQ ID NO: 354), or a nucleic
acid vector comprising a nucleotide sequence to direct
expression of such viral polypeptide, or a fragment or a
variant thereof, in vivo in order to induce an immune
response.

In one embodiment of the invention, the polypeptide to be
used in an immunogenic composition or in a vaccine for
inducing an immune response in an individual comprises
residues 161 through 188 of SEQ ID NO: 354. In one
embodiment of the invention, the polypeptide to be used in
an immunogenic composition or in a vaccine for inducing an
immune response in an individual comprises one or more
amino acid residues contained within SEQ ID NO: 355 and/or
SEQ ID NO: 356. In one embodiment of the invention,
the polypeptide to be used in an immunogenic
composition or in a vaccine for inducing an immune response
in an individual comprises SEQ ID NO: 355 and/or SEQ ID
NO. 356. In one embodiment of the invention, the immunogenic composition, or vaccine, may elicit an antibody response or a T cell response specific for the RSV-F antigen of RSV, wherein the antibodies generated interact with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In certain embodiments of the invention, the immunogenic composition, or vaccine may comprise an immunogenic polypeptide and/or polynucleotide of the invention, or a combination thereof, together with a suitable carrier/ excipient, such as a pharmaceutically acceptable carrier/ excipient. The immunogenic composition, or vaccine of the invention may also include adjuvants for enhancing the immunogenicity of the formulation.

In certain embodiments, it is advantageous for the RSV-F antigens or fragments thereof to be formulated into immunogenic compositions, or vaccines that comprise immunogenic, preferably immunologically effective, amounts of additional antigens to elicit immunity to other pathogens, preferably viruses and/or bacteria. Such additional antigens may include an influenza virus antigen, an antigen from metapneumovirus or from a coronavirus, an antigen from Haemophilus influenzae, Streptococcus pneumoniae, or Bordetella pertussis. Other RSV antigens may be included in the immunogenic compositions, or vaccines, such as the RSV-G glycoprotein, or immunogenic fragments thereof, the HN protein, or derivatives thereof.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. A schematic diagram of the RSV-F protein.

FIGS. 2A and 2B. Demonstrates that HIHI35923P blocks viral entry by inhibiting fusion of virus and cell membranes.

DETAILED DESCRIPTION

Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term “about,” when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression “about 100” includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

DEFINITIONS

“Respiratory Syncytial Virus-F protein”, also referred to as “RSV-F” is a type I transmembrane surface protein, which has an N terminal cleaved signal peptide and a membrane anchor near the C terminus (Collins, P. L. et al., (1984), PNAS (USA) 81:7683-7687). The RSV-F protein is synthesized as an inactive 67 kDa precursor denoted as F0 (Caldar, L. J.; et al., Virology (2000), 271, 122-131. The F0 protein is activated proteolytically in the Golgi complex by a furin-like protease at two sites, yielding two disulfide linked polypeptides, F2 and F1, from the N and C terminal, respectively. There is a 27 amino acid peptide released called “preP27”. There are furin cleavage sites (FCS) on either side of the pep27 (Collins, P. L.; Mottert, G. (1991), J. Gen. Virolog., 72: 3095-3101; Sugne, R. J. et al. (2001), J. Gen. Virolog., 82, 1375-1386). The F2 subunit consists of the Heptad repeat C (HRC), while the F1 contains the fusion polypeptide (FP), heptad repeat A (HRA), domain I, domain II, heptad repeat B (HRB), transmembrane (TM) and cytoplasmic domain (CP) (See Sun, Z. et al. Viruses (2013), 5:211-225). The RSV-F protein plays a role in fusion of the virus particle to the cell membrane, and is expressed on the surface of infected cells, thus playing a role in cell to cell transmission of the virus and syncytia formation. The amino acid sequence of the RSV-F protein is provided in GenBank as accession number AAX23994 and is also referred to herein as SEQ ID NO: 354.

A genetically engineered construct of the RSV-F protein is shown herein as having the amino acid sequence of SEQ ID NO: 353.

The term “laboratory strain” as herein refers to a strain of RSV (subtype A or B) that has been passaged extensively in in vitro cell culture. A “laboratory strain” can acquire adaptive mutations that may affect their biological properties. A “clinical strain” as herein refers to an RSV isolate (subtype A or B), which is obtained from an infected individual and which has been isolated and grown in tissue culture at low passage.

The term “effective dose” or “ED50” refers to the dosage of an agent that produces a desired effect of 50% reduction of viral forming plaques relative to the isotype (negative) control. In the present invention, the ED50 refers to the dosage of the anti-RSV-F antibodies that will neutralize the virus infection (i.e. reduce 99% of viral load) in vivo, as described in Example 5.

The term “IC50” refers to the “half maximal inhibitory concentration”, which value measures the effectiveness of compound (e.g., anti-RSV-F antibody) inhibition towards a biological or biochemical utility. This quantitative measure indicates the quantity required for a particular inhibitor to inhibit a given biological process by half.

“Paliuzumab”, also referred to as “SYNALTIS®”, is a humanized anti-RSV-F antibody with heavy and light chain variable domains having the amino acid sequences as set forth in U.S. Pat. No. 7,635,568 and U.S. Pat. No. 5,824,307 (also shown herein as SEQ ID NO: 361 for the heavy chain of the antibody and SEQ ID NO: 362 for the light chain of the antibody). This antibody, which immunospecifically binds to the RSV-F protein, is currently FDA-approved for the passive immunoprophylaxis of serious RSV disease in high-risk children and is administered intramuscularly at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNALTIS® is composed of 95% human and 5% murine antibody sequences. See also Johnson et al., (1997), J. Infect. Diseases 176:1215-1224.

“Motavizumab”, also referred to as “NUMAX™”, is an enhanced potency RSV-F-specific humanized monoclonal antibody derived by in vitro affinity maturation of the complementarity-determining regions of the heavy and light chains of paliuzumab. For reference purposes, the amino acid sequence of the NUMAX™ antibody is disclosed in

As used herein, the terms "treat," "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition related thereto (such as asthma, wheezing, or a combination thereof) resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents). In specific embodiments, such terms refer to the reduction or inhibition of the replication of RSV, the inhibition or reduction in the spread of RSV to other tissues or subjects (e.g., the spread to the lower respiratory tract), the inhibition or reduction of infection of a cell with a RSV, or the amelioration of one or more symptoms associated with an upper and/or lower respiratory tract RSV infection or otitis media.

As used herein, the terms "prevent," "preventing," and "prevention" refer to the prevention or inhibition of the development or onset of an upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto in a subject, the prevention or inhibition of the progression of an upper respiratory tract RSV infection to a lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto resulting from the administration of a therapy (e.g., a prophylactic or therapeutic agent), the prevention of a symptom of an upper and/or lower tract RSV infection, otitis media or a respiratory condition related thereto, or the administration of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents).

The term "antibody," as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds (i.e., "full antibody molecules"), as well as multimers thereof (e.g., IgM) or antigen-binding fragments thereof. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "VH") and a heavy chain constant region (comprised of domains Cα1, Cα2 and Cα3). Each light chain is comprised of a light chain variable region ("LCVR" or "VL") and a light chain constant region (Cλ). The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity-determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR).

Each VH and VL is comprised of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In certain embodiments of the invention, the FRs of the antibody (or antigen binding fragment thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan et al. (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos et al. 2002 J Mol Biol 320:415-428).

CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDR12 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

The fully human monoclonal antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the VH and/or VL domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

The present invention also includes fully monoclonal antibodies comprising variants of any of the HCVR, LCVR,
and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

The term “human antibody”, as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term “human antibody”, as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences.

The term “recombinant” generally refers to any protein, polypeptide, or cell expressing a gene of interest that is produced by genetic engineering methods. The term “recombinant” as used with respect to a protein or polypeptide, means a polypeptide produced by expression of a recombinant polynucleotide. The proteins used in the immunogenic compositions of the invention may be isolated from a natural source or produced by genetic engineering methods.

The antibodies of the invention may, in some embodiments, be recombinant human antibodies. The term “recombinant human antibody”, as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the Vg, and Vc, regions of the recombinant antibodies are sequences that, while derived from and related to human germline Vg, and Vc, sequences, may not naturally exist within the human antibody germline repertoire in vivo.

The term “specifically binds,” or “binds specifically to”, or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about $1 \times 10^{-3}$ M or less (e.g., a smaller $K_d$ denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. As described herein, antibodies have been identified by surface plasmon resonance, e.g., BIACORE™, which bind specifically to RSV-F. Moreover, multi-specific antibodies that bind to RSV-F protein and one or more additional antigens or a bi-specific that binds to two different regions of RSV-F are nonetheless considered antibodies that “specifically bind”, as used herein.

The term “high affinity” antibody refers to those mAbs having a binding affinity to RSV-F, expressed as $K_d$, of at least $10^{-8}$ M; more preferably $10^{-9}$ M, more preferably $10^{-10}$ M, more preferably $10^{-11}$ M, more preferably $10^{-12}$ M as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

By the term “slow off rate”, “Koff” or “kd” is meant an antibody that dissociates from RSV-F, with a rate constant of $1 \times 10^{-3}$ s$^{-1}$ or less, preferably $1 \times 10^{-4}$ s$^{-1}$ or less, as determined by surface plasmon resonance, e.g., BIACORE™.

The terms “antigen-binding portion” of an antibody, “antigen-binding fragment” of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms “antigen-binding portion” of an antibody, or “antibody fragment”, as used herein, refers to one or more fragments of an antibody that retains the ability to bind to RSV-F.

The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety (“immunoconjugate”), such as an antibiotic, a second anti-RSV-7 antibody, a vaccine, or a toxoid, or any other therapeutic moiety useful for treating a RSV infection.

An “isolated antibody”, as used herein, is intended to refer to an antibody that is substantially free of other antibodies (Abs) having different antigenic specificities (e.g., an isolated antibody that specifically binds RSV-F, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than RSV-F).

A “blocking antibody” or a “neutralizing antibody”, as used herein (or an “antibody that neutralizes RSV-F activity”), is intended to refer to an antibody whose binding to RSV-F results in inhibition of at least one biological activity of RSV-F. For example, an antibody of the invention may aid in blocking the fusion of RSV to a host cell, or prevent syncytin formation, or prevent the primary disease caused by RSV. Alternatively, an antibody of the invention may demonstrate the ability to ameliorate at least one symptom of the RSV infection. This inhibition of the biological activity of RSV-F can be assessed by measuring one or more indicators of RSV-F biological activity by one or more of several standard in vitro assays (such as a neutralization assay, as described herein) or in vivo assays known in the art (for example, animal models to look at protection from challenge with RSV following administration of one or more of the antibodies described herein).

The term “surface plasmon resonance”, as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alternations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.)

The term $K_d$, as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

The term “epitope” refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term “epitope” also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen
that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phospho- ryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331, which is herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleu- cine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) Science 256: 1443-45, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutant thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) supra). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, e.g., Altschul et al. (1990) J. Mol. Biol. 215: 403-410 and (1997) Nucleic Acids Res. 25:3389-402, each of which is herein incorporated by reference.

In specific embodiments, the antibody or antibody fragment for use in the method of the invention may be monospecific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C\textsubscript{\alpha}3 domain and a second Ig C\textsubscript{\alpha}3 domain, wherein the first and second Ig C\textsubscript{\alpha}3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C\textsubscript{\alpha}3 domain binds Protein A and the second Ig C\textsubscript{\alpha}3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H1435R by EU numbering). The second Ig C\textsubscript{\alpha}3 may further comprise an Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C\textsubscript{\alpha}3 include: D16E, L18M, N44S, K52N, V57M, and V821 (by IMGT; D356E, L358M, N384S, K392N, V397M, and V4221 by EU) in the case of IgG1 mAbs; N44S, K52N, and V821 (IMGT; N384S, K392N, and V4221 by EU) in the case of IgG2 mAbs; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V821 (by IMGT; Q55SR, N834S, K922N, V937M, R409K, E419Q, and V4221 by EU) in the case of IgG4 mAbs. Variations in the bi-specific antibody format described above are contemplated within the scope of the present invention.

By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

An "immunogenic composition" relates to a composition containing an antigen/immunogen, e.g., a microorganism, such as a virus or a bacterium, or a component thereof, a protein, a polypeptide, a fragment of a protein or polypeptide, a whole cell inactivated, subunit or attenuated virus, or a polysaccharide, or combination thereof, administered to stimulate the recipient's humoral and/or cellular immune systems to one or more of the antigens/immunogens present in the immunogenic composition. The immunogenic compositions of the present invention can be used to treat a
human susceptible to RSV infection, by means of administering the immunogenic compositions via a systemic route. These administrations can include injection via the intramuscular (i.m.), intradermal (i.d.), intranasal or inhalation route, or subcutaneous (s.c.) routes; application by a patch or other transdermal delivery device. In one embodiment, the immunogenic composition may be used in the manufacture of a vaccine or in the elicitation of polyclonal or monoclonal antibodies that could be used to passively protect or treat a mammal.

The terms “vaccine” or “vaccine composition”, which are used interchangeably, refer to a composition comprising at least one immunogenic composition that induces an immune response in an animal.

In one embodiment of the invention, the protein of interest comprises an antigen. The terms “antigen,” “immunogen,” “antigenic,” “immunogenic,” “antigenically active,” and “immunologically active” when made in reference to a molecule, refer to any substance that is capable of inducing a specific humoral and/or cell-mediated immune response. In one embodiment, the antigen comprises an epitope, as defined above.

“Immunologically protective amount”, as used herein, is an amount of an antigen effective to induce an immunogenic response in the recipient that is adequate to prevent or ameliorate signs or symptoms of disease, including adverse health effects or complications thereof. Either humoral immunity or cell-mediated immunity or both can be induced. The immunogenic response of an animal to a composition can be evaluated, e.g. indirectly through measurement of antibody titers, lymphocyte proliferation assays, or directly through monitoring signs and symptoms after challenge with the microorganism. The protective immunity conferred by an immunogenic composition or vaccine can be evaluated by measuring, e.g. reduction of shed of challenge organisms, reduction in clinical signs such as mortality, morbidity, temperature, and overall physical condition, health and performance of the subject. The immune response can comprise, without limitation, induction of cellular and/or humoral immunity. The amount of a composition or vaccine that is therapeutically effective can vary, depending on the particular organism used, or the condition of the animal being treated or vaccinated.

“Immune response”, or “immunological response” as used herein, in a subject refers to the development of a humoral immune response, a cellular-immune response, or a humoral and a cellular immune response to an antigen/immunogen. A “humoral immune response” refers to one that is at least in part mediated by antibodies. A “cellular immune response” is one mediated by T-lymphocytes or other white blood cells or both, and includes the production of cytokines, chemokines and similar molecules produced by activated T-cells, white blood cells, or both. Immune responses can be determined using standard immunassays and neutralization assays, which are known in the art. “Immunogenicity”, as used herein, refers to the capability of a protein or polypeptide to elicit an immune response directed specifically against a bacteria or virus that causes the identified disease.

General Description

Respiratory syncytial virus (RSV) is a negative sense, single stranded RNA virus that is the leading cause of serious respiratory tract infections in infants and children, with the primary infection occurring in children from 6 weeks to 2 years of age and uncommonly in the first 4 weeks of life during nosocomial epidemics (Hall et al., 1979, New Engl. J. Med. 300:393-396). (Feigen et al., eds., 1987, In:


RSV can infect the adult population as well. In this population, RSV causes primarily an upper respiratory tract disease, although elderly patients may be at greater risk for a serious infection and pneumonia (Evans, A. S., eds., 1989, Viral Infections of Humans. Epidemiology and Control, 3rd ed., Plenum Medical Book, New York at pages 525-544), as well as adults who are immunosuppressed, particularly bone marrow transplant patients (Herz et al., 1989, Medicine 68:269-281). Other at risk patients include those suffering from congestive heart failure and those suffering from chronic obstructive pulmonary disease (i.e. COPD). There have also been reports of epidemics among nursing home patients and institutionalized young adults (Falsone, A. R., 1991, Infect. Control Hosp. Epidemiol. 12:602-608; and Garvie et al., 1980, Br. Med. J. 281:1253-1254).

While treatment options for established RSV disease are limited, more severe forms of the disease of the lower respiratory tract often require considerable supportive care, including administration of humidified oxygen and respiratory assistance (Fields et al., eds., 1990, Fields Virology, 2nd ed., Vol. 1, Raven Press, New York at pages 1045-1072).

Ribavirin, which is the only drug approved for treatment of infection, has been shown to be effective in the treatment of pneumonia and bronchiolitis associated with RSV infection, and has been shown to modify the course of severe RSV disease in immunocompetent children (Smith et al., 1991, New Engl. J. Med. 325:24-29). However, the use of ribavirin is limited due to concerns surrounding its potential risk to pregnant women who may be exposed to the aerosolized drug while it is being administered in a hospital environment. Its use is also limited due to its relatively high cost.


Other small molecule inhibitors of RSV infection have also been identified, but have been discontinued for various reasons, some of which may be due to toxic side effects (Wyde, P. R., et al. (1998), Antiviral Res. 38:31-42; Nakanishita, A. A. et al. (2001), Bioorg Med Chem Lett 11:1041-1044; Douglas, J. L., et al. (2003), J. Virol 77:5054-5064; Bonfanti, J. F. et al. (2008), J. Med Chem 51:875-896).

Similarly, while a vaccine may be useful, no commercially available vaccine has been developed to date. Several vaccine candidates have been abandoned and others are
31 under development (Murphy et al., 1994, Virus Res. 32:13-36). The development of a vaccine has proven to be problematic. In particular, immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory tract disease occurs at 2-5 months of age. However, it is known that the neonatal immune response is immature at that time. Plus, the infant at that point in time still has high titers of maternally acquired RSV antibody, which might reduce vaccine immunogenicity (Murphy et al., 1988, J. Virol. 62:3907-3910; and Murphy et al., 1991, Vaccine 9:185-189).

Currently, passive immunization appears to be the only approved approach to prophylaxis of RSV disease. Initial evidence that suggested a protective role for IgG was obtained from studies demonstrating maternal antibody in ferrets (Prince, G. A., Ph.D. diss., University of California, Los Angeles, 1975) and humans (Lambrechts et al., 1976, J. Infect. Dis. 134:211-217; and Glezen et al., 1981, J. Pediatr. 98:708-715).

Hemming et al. (Morel) et al., eds., 1986, Clinical Use of Intravenous Immunoglobulin, Academic Press, London at pages 285-294) recognized the possible utility of RSV antibody in treatment or prevention of RSV infection during studies involving the pharmacokinetics of an intravenous immune globulin (IVIG) in newborns suspected of having neonatal sepsis. This same group of investigators then examined the ability of hyperimmune serum or immune globulin, enriched for RSV neutralizing antibody, to protect cotton rats and primates against RSV infection (Prince et al., 1985, Virus Res. 3:193-206; Prince et al., 1990, J. Virol. 64:3091-3092; Hemming et al., 1985, J. Infect. Dis. 152: 1083-1087; Prince et al., 1983, Infect. Immun. 42:81-87; and Prince et al., 1985, J. Virol. 55:517-520). Results of these studies suggested that RSV neutralizing antibody given prophylactically inhibited respiratory tract replication of RSV in cotton rats. When given therapeutically, RSV antibody reduced pulmonary viral replication both in cotton rats and in a neonatal primate model.

More recent studies have concentrated on the role of two glycoproteins, designated F and G, which are found on the surface of RSV, as targets of neutralizing antibodies, due to the role of these glycoproteins in viral attachment and fusion with the host cell (Fields et al., 1990, supra; and Murphy et al., 1994, supra). The G protein binds to a specific cellular receptor and the F protein promotes fusion of the virus with the cell. The F protein is also expressed on the surface of infected cells and is responsible for subsequent fusion with other cells leading to syncytia formation. Thus, antibodies to the F protein may directly neutralize virus, or block fusion of the virus with the cell, or prevent cell to cell spread by preventing syncytia formation.

The first humanized antibody approved for use in pediatric patients for prevention of serious lower respiratory tract disease caused by RSV was palivizumab (SYNAGIS®), which immunospecifically binds to the F protein and is administered intramuscularly at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNAGIS® is comprised of 95% human and 5% murine antibody sequences. See, Johnson et al., 1997, J. Infect. Diseases 176:1215-1224 and U.S. Pat. No. 5,824,307, the entire contents of which are incorporated herein by reference.

While SYNAGIS® has been successfully used for the prevention of RSV infection in pediatric patients, the need for multiple visits to the doctor’s office for multiple intramuscular doses of 15 mg/kg of SYNAGIS® was not only inconvenient for the patient but could also result in missed doses. Thus, there was a need for development of antibodies that retained the immunospecificity for the RSV antigen, but which were more potent, with an improved pharmacokinetic profile, and thus have an overall improved therapeutic profile. Such an antibody is described in U.S. Patent Publication 2003/0091584 and is known as motavizumab (NUMAX™). Although NUMAX™ has improved binding characteristics that may overcome the higher dosing requirements described above for SYNAGIS®, it also had a 3- to 5-fold increase in the frequency and severity of hypersensitivity reactions compared to SYNAGIS®. NUMAX™ was then withdrawn from future development.

Accordingly, there is still a need for effective therapies against RSV infections, and in particular, there is a need to identify a more potent antibody for preventing and treating RSV infections, but without the adverse side effects associated with those described above. The antibodies described herein, while exhibiting a lower binding affinity for RSV-F (i.e., the antibodies of the present invention do not bind as tightly to RSV-F as palivizumab) than that described for palivizumab or motavizumab appears to exhibit better neutralization capabilities and addresses those needs.

In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a whole RSV particle, either live, attenuated, or inactivated, or with a recombinant form of the virus, or with a purified F protein (See GenBank accession number AAX23994.1 (SEQ ID NO: 354)), or a recombinantly produced F protein (See SEQ ID NO: 353), followed by immunization with a secondary immunogen (whole virus, or purified F protein), or with an immunogenically active fragment of the F protein.

The immunogen may be DNA encoding the F protein or an active fragment thereof.

The immunogen may be derived from the N-terminal or C-terminal domain of either the 67 KD precursor (F0), or from either of the two fragments generated from the precursor by a furin-like protease yielding two disulfide linked polypeptides, designated as F2 and F1, from the N and C terminal, respectively. The fragment may be derived from any of the known regions of RSV-F protein (See Sun, Z. et al. (2013), Viruses 5:211-225).

The full-length amino acid sequence of RSV-F is shown as SEQ ID NO: 354 and is also shown in GenBank accession number AAX23994.1.

A genetic construct containing the F protein of RSV is shown as SEQ ID NO: 353.

In certain embodiments, antibodies that bind specifically to RSV-F may be prepared using fragments of the above-noted regions, or peptides that extend beyond the designated regions by about 5 to about 20 amino acid residues from either, or both, the N or C terminal ends of the regions described herein. In certain embodiments, any combination of the above-noted regions or fragments thereof may be used in the preparation of RSV-F specific antibodies. In certain embodiments, any one or more of the above-noted regions of RSV-F, or fragments thereof may be used for preparing monospecific, bispecific, or multispecific antibodies.

Antigen-Binding Fragments of Antibodies

Unless specifically indicated otherwise, the term “antibody,” as used herein, shall be understood to encompass antibody molecules comprising two immunoglobulin heavy chains and two immunoglobulin light chains (i.e., “full antibody molecules”) as well as antigen-binding fragments thereof. The terms “antigen-binding portion” of an antibody, “antigen-binding fragment” of an antibody, and the like, as
used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms “antigen-binding portion” of an antibody, or “antibody fragment”, as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to RSV-F. An antibody fragment may include a Fab fragment, a F(ab')2 fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR. Antibody-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and (optionally) constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression “antigen-binding fragment,” as used herein.

An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a VH domain associated with a VL domain, the VH and VL domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain VH,VH, VH,VL, or VL,VL dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric VH or VL domain.

In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) VH,C1; (ii) VH,C2; (iii) VH,C3; (iv) VH,C12; (V) VH,C12; (vi) VH,C12; (vii) VH,C12; (viii) VH,C12; (ix) VH,C12; (x) VH,C12; (xi) VH,C12; (xii) VH,C12; (xiii) VH,C12; (xiv) VH,C12. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or heterodimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric VH or VL domain (e.g., by disulfide bond(s)).

As with full antibody molecules, antigen-binding fragments may be mono-specific or multi-specific (e.g., bi-specific). A multi-specific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multi-specific antibody format, including the exemplary bi-specific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

Preparation of Human Antibodies

Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to RSV-F. Using VELOCEMMUNE® technology (see, for example, U.S. Pat. No. 6,596,541, Regeneron Pharmaceuticals, VELOCEMMUNE®) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to RSV-F are initially isolated having a human variable region and a mouse constant region. The VELOCEMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

Generally, a VELOCEMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.
In certain embodiments, the antibodies of the instant invention possess affinities (Kₐ) ranging from about 1.0x 10⁻⁷ M to about 1.0x 10⁻¹⁰ M, when measured by binding to antigen either immobilized on solid phase or in solution phase. In certain embodiments, the antibodies of the invention possess affinities (Kₐ) ranging from about 1x 10⁻⁶ M to about 6x 10⁻⁸ M, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region. Surprisingly, certain antibodies of the present invention, while demonstrating lower affinities than motavizumab, are more potent in terms of virus neutralization.

Bioequivalents

The anti-RSV-F antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind RSV-F. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antibody or antibody fragment that is essentially bioequivalent to an antibody or antibody fragment of the invention.

Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutically equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or a different effective labor when compared to continued therapy without such switching.

In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

Bioequivalence may be demonstrated by in vivo and/or in vitro methods. Bioequivalence measures include, e.g., (a) an in vivo test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an in vitro test that has been correlated with and is reasonably predictive of human in vivo bioavailability data; (c) an in vivo test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody. Bioequivalent variants of the antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, e.g., mutations that eliminate or reduce glycosylation. Biological Characteristic of the Antibodies

In general, the antibodies of the present invention may function by binding to RSV-F and in so doing act to block the fusion of the viral membrane with the host cell membrane. The antibodies of the present invention may also function by binding to RSV-F and in so doing block the cell to cell spread of the virus and block syncytia formation associated with RSV infection of cells.

In certain embodiments, the antibodies of the present invention may function by blocking or inhibiting RSV fusion to the cell membrane by binding to any other region or fragment of the full length native F protein, the amino acid sequence of which is shown in SEQ ID NO: 354, also shown as Gen Bank accession number AAX23994.1. The antibodies may also bind to any region which is found in SEQ ID NO: 353, or to a fragment found within SEQ ID NO: 353.

In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds to the F protein of RSV subtype A or B, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (a) is a fully human monoclonal antibody; (b) exhibits a Kₐ ranging from about 1x 10⁻⁷ M to about 6x 10⁻⁸ M, (c) is capable of neutralizing respiratory syncytial virus subtype A or subtype B strains in vitro; (d) demonstrates the ability to significantly reduce the viral load in an animal model of RSV infection (e) demonstrates a 1-2 logs greater reduction of nasal and/or lung viral titers when compared to palivizumab; (f) demonstrates an effective dose 99 (ED₉₉) of about 0.15 mg/kg or less when administered subcutaneously in a mouse model of RSV subtype A infection, or an ED₉₉ of about 0.62 mg/kg or less when administered in a cotton rat model of RSV subtype A infection, or an ED₉₉ of about 2.5 mg/kg or less when administered in a cotton rat model of RSV subtype B infection; (g) demonstrates an ED₉₉ that is about 2 to 3 fold lower than the ED₉₉ for palivizumab or motavizumab; (h) demonstrates a neutralization potency against one or more clinical strains of RSV that is about 15 to 17 fold improvement over palivizumab, or demonstrates a neutralization potency against one or more clinical strains of RSV that is about 10 to 22 fold improvement over palivizumab; (i) demonstrates a neutralization potency against a subtype B laboratory strain of RSV that is about 3 to 5 fold improvement over palivizumab (j) demonstrates a neutralization
potency against a subtype A laboratory strain or clinical strain of RSV that is about a 0.5 to 2 fold improvement over AM-22; (k) demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2.5 to 17 fold improvement over AM-22; (l) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (m) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 28, 28, 74, 90, 106, 122, 138, 151, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (n) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity and a LLCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (o) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 130, 156, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCVR domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 352 and 348, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LLCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (p) interacts with an amino acid sequence comprising residues ranging from about position 161 to about position 188 of SEQ ID NO: 354; (q) interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354; (r) does not cross compete for binding to RSV-F protein with palivizumab or motavizumab; (s) inhibits fusion of the virus to the cell.

Certain anti-RSV-F antibodies of the present invention are able to bind to the F protein of RSV and neutralize the infectivity of both subtypes A and B of RSV as determined by in vitro assays. The ability of the antibodies of the invention to bind to and neutralize the infectivity of the subtypes of RSV may be measured using any standard method known to those skilled in the art, including binding assays, or neutralization assays, or in vivo protection assays, as described herein.

Non-limiting, exemplary in vitro and in vivo assays for measuring binding activity and in vitro neutralization and in vivo efficacies are illustrated in Examples 3, 4, 5, 7, 8, 9, 10, 11 and 12 herein. In Example 3, the binding affinities and kinetic constants of human anti-RSV-F antibodies were determined by surface plasmon resonance and the measurements were conducted on a Biacore 4000 or T200 instrument. In Example 4, the potency of the antibodies was tested in a RSV micro-neutralization assay. Example 5 demonstrates the ability of the antibodies of the invention to neutralize an RSV infection in vivo in two different animal models. Examples 7 and 8 demonstrate the interaction of the antibodies of the invention with particular binding sites on RSV-F protein. Examples 9 and 10 demonstrate the neutralization capabilities of the antibodies with several laboratory and clinical strains of RSV subtypes A and B. Example 11 demonstrates the ability of the antibodies of the invention to inhibit fusion of the virus to cells. Example 12 demonstrates the cross-competition of various antibodies for binding to RSV-F.

Epitope Mapping and Related Technologies

Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody “interacts with one or more amino acids” within a polypeptide or protein. Exemplary techniques include, for example, a routine cross-blocking assay such as that described Anti-bodies, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., N.Y.) can be performed. Other methods include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol Biol 248:443-63), peptide cleavage analysis crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of the interface.

As a result, amino acids that form part of the protein/antibody interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues that correspond to the specific amino acids with which the antibody interacts. See, e.g., Elrington (1999) Analytical Biochemistry 267(2):252-259; Engen and Smith (2001) Anal. Chem. 73:256-A-265A.

The term “epitope” refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with
denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (US 2004/0101920, herein specifically incorporated by reference in its entirety). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce mAbs having the desired characteristics. MAP may be used to sort the antibodies of the invention into groups of antibodies binding different epitopes.

In certain embodiments, the antibodies or antigen-binding fragments of the invention interact with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354. In certain embodiments, the antibodies of the invention may interact with amino acid residues that extend beyond the region identified above by about 5 to 10 amino acid residues, or by about 10 to 15 amino acid residues, or by about 15 to 20 amino acid residues towards either the amino terminal or the carboxy terminal of the RSV-F protein.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NO: 355 and 356.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

The present invention includes anti-RSV-F antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein in Table 1, Likewise, the present invention also includes anti-RSV-F antibodies that compete for binding to RSV-F fragment with any of the specific exemplary antibodies described herein in Table 1.

In certain embodiments, the antibodies of the present invention do not cross-compete for binding to RSV-F with palivizumab, motavizumab, or AM-22.
Immunon conjugates

The invention encompasses a human RSV-F monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an agent that is capable of reducing the severity of primary infection with RSV, or to ameliorate at least one symptom associated with RSV infection, including coughing, fever, pneumonia, or the severity thereof. Such an agent may be a second different antibody to RSV-F, or a vaccine. The type of therapeutic moiety that may be conjugated to the anti-RSV-F antibody and will take into account the condition to be treated and the desired therapeutic effect to be achieved. Alternatively, if the desired therapeutic effect is to treat the sequelae or symptoms associated with RSV infection, or any other condition resulting from such infection, such as, but not limited to, pneumonia, it may be advantageous to conjugate an agent appropriate to treat the sequelae or symptoms of the condition, or to alleviate any side effects of the antibodies of the invention. Examples of suitable agents for forming immunon conjugates are known in the art, see for example, WO 05/103081.

Multi-Specific Antibodies

The antibodies of the present invention may be mono-specific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tut et al., 1991, J. Immunol. 147:60-69; Kufler et al., 2004, Trends Biotechnol. 22:238-244. The antibodies of the present invention can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multi-specific antibody with a second binding specificity.

An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) Fc Ig domain and a second Ig Fc domain, wherein the first and second Ig Fc domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A compared to a bispecific antibody lacking the amino acid difference. In one embodiment, the first Ig Fc domain binds Protein A and the second Ig Fc domain contains a mutation that reduces or abolishes Protein A binding such as an E95R modification (by IMGT ex numbering; H435R by EU numbering). The second Ig Fc may further comprise a Y96F modification (by IMGT; V436F by EU), further modifications that may be found within the second Ig Fc include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, I358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R60K, E79Q, and V82I (by IMGT; Q55R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bispecific antibody format described above are contemplated within the scope of the present invention.

Therapeutic Administration and Formulations

The invention provides therapeutic compositions comprising the anti-RSV-F antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFEC TIN™), DNA conjugates, adsorptive material pastes, oil-in-water and water-in-oil emulsions, emulsions, carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. “Compendium of excipients for parenteral formulations” PDA (1998) J Pharm Sci Technol 52:238-311.

The dose of each of the antibodies of the invention may vary depending upon the age and size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibodies of the present invention are used for treating a RSV infection in a patient, or for treating one or more symptoms associated with a RSV infection, such as the cough or pneumonia associated with a RSV infection in a patient, or for lessening the severity of the disease, it is advantageous to administer each of the antibodies of the present invention intravenously or subcutaneously normally at a single dose of about 0.01 to about 30 mg/kg body weight, more preferably about 0.1 to about 20 mg/kg body weight, or about 0.1 to about 15 mg/kg body weight, or about 0.02 to about 7 mg/kg body weight, about 0.03 to about 5 mg/kg body weight, or about 0.05 to about 3 mg/kg body weight, or about 1 mg/kg body weight, or about 3.0 mg/kg body weight, or about 10 mg/kg body weight, or about 20 mg/kg body weight. Multiple doses may be administered as necessary. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. In certain embodiments, the antibodies or antigen-binding fragments thereof of the invention can be administered as an initial dose of at least about 0.1 mg to about 800 mg, about 1 to about 600 mg, about 5 to about 300 mg, or about 10 to about 150 mg, or about 100 mg, or about 50 mg. In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of the antibodies or antigen-binding fragments thereof in an amount that can be approximately the same or less than that of the initial dose, wherein the subsequent doses are separated by at least 1 day to 3 days; at least one week; at least 2 weeks; at least 3 weeks; at least 4 weeks; at least 5 weeks; at least 6 weeks; at least 7 weeks; at least 8 weeks; at least 9 weeks; at least 10 weeks; at least 12 weeks; or at least 14 weeks.

Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al. (1987) J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, transdermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral routes. The composition may be administered by any convenient route, for example by infusion at the site of injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, nasal mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. It may be delivered as an aerosolized formulation (See US2011/0311515 and US2012/0128669). The delivery of agents useful for treating respiratory diseases by inhalation
is becoming more widely accepted (See A. J. Bitonti and J. A. Dumont, (2006), Adv. Drug Deliv. Rev., 58:1106-1118). In addition to being effective at treating local pulmonary disease, such a delivery mechanism may also be useful for systemic delivery of antibodies (See Maillot et al. (2008), Pharmaceutical Research, Vol. 25, No. 6, 2008).

The pharmaceutical composition can also be delivered in a vesicle, in particular a liposome (see, for example, Langer (1990) Science 249:1527-1533).

In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the composition’s target, thus requiring only a fraction of the systemic dose.

The injectable preparations may include dosage forms for intravenous, subcutaneous, intramuscular and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant (e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil), etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes profiled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to, AUTOPIEN™ (Owen Mumford Ltd, Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIORM™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, N.J.), OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTART™ pen (sanofi-aventis), the FLEXIPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, Calif.), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L. P.) and the HUMIRA™ Pen (Abbott Labs, Abbott Park, Ill.), to name only a few.

Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suitable to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Administration Regimens

According to certain embodiments of the present invention, multiple doses of an antibody to RSV-F may be administered to a subject over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a subject multiple doses of an antibody to RSV-F. As used herein, “sequentially administering” means that each dose of antibody to RSV-F is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an antibody to RSV-F, followed by one or more secondary doses of the antibody to RSV-F and optionally followed by one or more tertiary doses of the antibody to RSV-F.

The terms “initial dose,” “secondary doses,” and “tertiary doses,” refer to the temporal sequence of administration of the antibody to RSV-F. Thus, the “initial dose” is the dose which is administered at the beginning of the treatment regimen (also referred to as the “baseline dose”); the “secondary doses” are the doses which are administered after the initial dose; and the “tertiary doses” are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of antibody to RSV-F, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of antibody to RSV-F contained in the initial, secondary and/or tertiary doses vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (e.g., 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as “loading doses” followed by subsequent doses that are administered on a less frequent basis (e.g., “maintenance doses”).

In one exemplary embodiment of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (e.g., 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14, 14.5, 15, 15.5, 16, 16.5, 17, 17.5, 18, 18.5, 19, 19.5, 20, 20.5, 21, 21.5, 22, 22.5, 23, 23.5, 24, 24.5, 25, 25.5, 26, 26.5, or more) weeks after the immediately preceding dose. The phrase “the immediately preceding dose,” as used herein, means, in a sequence of multiple administrations, the dose of
antibody to RSV-F which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

The methods according to this aspect of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of an antibody to RSV-F. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

Therapeutic Uses of the Antibodies

Due to their binding to interaction with, the RSV fusion protein (RSV-F), the present antibodies are useful for preventing fusion of the virus with the host cell membrane, for preventing cell to cell virus spread, and for inhibition of syncytia formation. As such, the antibodies of the present invention are useful for preventing an infection of a subject with RSV when administered prophylactically. Alternatively, the antibodies of the present invention may be useful for ameliorating at least one symptom associated with the infection, such as coughing, fever, pneumonia, or for lessening the severity, duration, and/or frequency of the infection. The antibodies of the invention are also contemplated for prophylactic use in patients at risk for developing or acquiring an RSV infection. These patients include pre-term infants, full-term infants born during RSV season (late fall to early spring), the elderly (for example, in anyone 65 years of age or older), or patients immunocompromised due to illness or treatment with immunosuppressive therapeutics, or patients who may have an underlying medical condition that predisposes them to an RSV infection (for example, cystic fibrosis patients, patients with congestive heart failure or other cardiac conditions, patients with airway impairment, patients with COPD). It is contemplated that the antibodies of the invention may be used alone, or in conjunction with a second agent, or third agent for treating RSV infection, or for alleviating at least one symptom or complication associated with the RSV infection, such as the fever, coughing, bronchiolitis, or pneumonia associated with, or resulting from such an infection. The second or third agents may be delivered concurrently with the antibodies of the invention, or they may be administered separately, either before or after the antibodies of the invention. The second or third agent may be an anti-viral such as ribavirin, an NSAI or other agents to reduce fever or pain, another second but different antibody that specifically binds RSV-F, an agent (e.g. an antibody) that binds to another RSV antigen, such as RSV-G, a vaccine against RSV, an siRNA specific for an RSV antigen.

In yet a further embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for treating patients suffering from a RSV infection. In yet another embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for reducing the severity of a primary infection with RSV, or for reducing the duration of the infection, or for reducing at least one symptom associated with the RSV infection. In a further embodiment of the invention the present antibodies are used as adjunct therapy with any other agent useful for treating an RSV infection, including an antiviral, a toxoid, a vaccine, a second RSV-F antibody, or any other antibody specific for an RSV antigen, including an RSV-G antibody, or any other palliative therapy known to those skilled in the art.

Combination Therapies

As noted above, the methods of the present invention, according to certain embodiments, comprise administering to the subject one or more additional therapeutic agents in combination with an antibody to RSV-F. As used herein, the expression “in combination with” means that the additional therapeutic agents are administered before, after, or concurrently with the pharmaceutical composition comprising the anti-RSV-F antibody. The term “in combination with” also includes sequential or concomitant administration of the anti-RSV-F antibody and a second therapeutic agent.

For example, when administered “before” the pharmaceutical composition comprising the anti-RSV-F antibody, the additional therapeutic agent may be administered about 72 hours, about 60 hours, about 48 hours, about 36 hours, about 24 hours, about 12 hours, about 10 hours, about 8 hours, about 6 hours, about 4 hours, about 2 hours, about 1 hour, about 30 minutes, about 15 minutes or about 10 minutes prior to the administration of the pharmaceutical composition comprising the anti-RSV-F antibody. When administered “after” the pharmaceutical composition comprising the anti-RSV-F antibody, the additional therapeutic agent may be administered about 10 minutes, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours or about 72 hours after the administration of the pharmaceutical composition comprising the anti-RSV-F antibodies. Administration “concurrent” or with the pharmaceutical composition comprising the anti-RSV-F antibody means that the additional therapeutic agent is administered to the subject in a separate dosage form within less than 5 minutes (before, after, or at the same time) of administration of the pharmaceutical composition comprising the anti-RSV-F antibody, or administered to the subject as a single combined dosage formulation comprising both the additional therapeutic agent and the anti-RSV-F antibody.

Combination therapies may include an anti-RSV-F antibody of the invention and any additional therapeutic agent that may be advantageously combined with an antibody of the invention, or with a biologically active fragment of an antibody of the invention.

For example, a second or third therapeutic agent may be employed to aid in reducing the viral load in the lungs, such as an antiviral, for example, ribavirin. The antibodies may also be used in conjunction with other therapies, as noted above, including a toxoid, a vaccine specific for RSV, a
second antibody specific for RSV-F, or an antibody specific for another RSV antigen, such as RSV-G.

Diagnostic Uses of the Antibodies

The anti-RSV antibodies of the present invention may also be used to detect and/or measure RSV in a sample, e.g., for diagnostic purposes. It is envisioned that confirmation of an infection thought to be caused by RSV may be made by measuring the presence of the virus through use of any one or more of the antibodies of the invention. Exemplary diagnostic assays for RSV may comprise, e.g., contacting a sample, obtained from a patient, with an anti-RSV-F antibody of the invention, wherein the anti-RSV-F antibody is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate the virus containing the F protein from patient samples. Alternatively, an unlabeled anti-RSV-F antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as $^{3}$H, $^{125}$I, $^{14}$C, $^{35}$P, $^{32}$S, or $^{125}$I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, $\beta$-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure RSV containing the F protein in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

Samples that can be used in RSV diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of RSV-F protein, or fragments thereof, under normal or pathological conditions. Generally, levels of RSV-F in a particular sample obtained from a healthy patient (e.g., a patient not afflicted with a disease or condition associated with the presence of RSV-F) will be measured to initially establish a baseline, or standard, level of the F protein from RSV. This baseline level of RSV-F can then be compared against the levels of RSV-F measured in samples obtained from individuals suspected of having an RSV infection, or symptoms associated with such infection.

Vaccines and Immunogenic Compositions

One aspect of the invention provides an immunogenic composition, or a vaccine, that when administered to an individual, preferably a human, induces an immune response in such individual to a Respiratory Syncytial Virus (RSV) antigen, for example, a RSV-F polypeptide, wherein the composition may comprise a recombinant RSV-F protein, or a polypeptide fragment of a RSV-F protein, or an epitope contained within and obtained from an antigen of the RSV-F polypeptide or a fragment thereof, and/or comprises DNA and/or RNA which encodes and expresses an epitope from an antigen of the RSV-F polypeptide, or other polypeptides of the invention. The immunogenic composition or vaccine may be used therapeutically or prophylactically and may be used to elicit antibody immunity and/or cellular immunity, such as cellular immunity arising from CTL or CD4+ T cells.

In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise the RSV-F protein as shown in SEQ ID NO: 354. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise a RSV-F polypeptide fragment comprising residues 161 through 188 of SEQ ID NO: 354. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise one or more amino acid residues contained within SEQ ID NO: 355 and/or SEQ ID NO: 356.

In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise SEQ ID NO: 355 and/or SEQ ID NO: 356. In a related aspect, the invention provides a method for inducing an immune response in an individual, particularly a mammal, preferably humans, by administering to an individual an immunogenic composition, or a vaccine, comprising a RSV-F protein, or an immunogenic fragment thereof, or a RSV-F antigen or an immunogenic fragment thereof comprising one or more epitopes contained within the RSV-F antigen or fragment thereof, adequate to produce an antibody and/or a T cell immune response to protect the individual from infection, particularly infection with Respiratory Syncytial Virus (RSV). Also provided are methods of using the immunogenic compositions, or vaccines of the invention for inducing an immune response that results in inhibiting, or slowing the progression of cell to cell viral spread. Methods are also provided for ameliorating at least one symptom associated with RSV infection by administering an immunogenic composition, or a vaccine, comprising at least one RSV-F antigen, or one or more epitopes contained within the RSV-F antigen, which when administered will induce an immune response in the individual.

For example, in one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises residues 161 through 188 of SEQ ID NO: 354, or an antigenic fragment thereof, (e.g. a polypeptide comprising residues 161 through 188 of SEQ ID NO: 354), or a nucleic acid vector comprising a nucleotide sequence to direct expression of such viral polypeptide, or a fragment of a variant thereof, in vivo in order to induce an immune response.

In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises residues 161 through 188 of SEQ ID NO: 354. In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises one or more amino acid residues contained within SEQ ID NO: 355 and/or SEQ ID NO: 356. In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises one or more amino acid residues contained within SEQ ID NO: 355 and/or SEQ ID NO: 355.

In certain embodiments, it is advantageous for the RSV-F antigens or fragments thereof to be formulated into immunogenic compositions, or vaccines that comprise immunogenic, preferably immunologically effective, amount of additional antigens to elicit immunity to other pathogens, preferably viruses and/or bacteria. Such additional antigens may include an influenza virus antigen, an antigen from metapneumovirus or from a coronavirus, an antigen from Haemophilus influenzae, Streptococcus pneumoniae, or Borrelia pertussis. Other RSV antigens may be included in the immunogenic compositions, or vaccines, such as the RSV-G glycoprotein, or immunogenic fragments thereof, the HN protein, or derivatives thereof. In certain embodiments, influenza virus antigens to be included in the immunogenic
compositions or vaccines of the invention may include whole, live or inactivated virus, split influenza virus, grown in eggs or MDCK cells, or Vero cells or whole flu virosomes, or purified or recombinant proteins thereof, such as HA, NP, NA, or M proteins, or combinations thereof.

In certain embodiments of the invention, the immunogenic composition, or vaccine formulation may comprise an immunogenic recombinant polypeptide and/or polynucleotide of the invention, or a combination thereof, together with a suitable carrier/exipient, such as a pharmaceutically acceptable carrier/exipient. The immunogenic composition and/or vaccine is preferably administered parenterally, including, for example, administration that is subcutaneous, intramuscular, intravenous, or intradermal. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostatic compounds and solutes which render the formulation isotonic with the bodily fluid, preferably the blood, of the individual; and aqueous and non-aqueous sterile suspensions which may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use.

The immunogenic composition, or vaccine formulation of the invention may also include adjuvants for enhancing the immunogenicity of the formulation. At this time, the only adjuvant widely used in humans has been alum (aluminum phosphate or aluminum hydroxide) and calcium phosphate gels. Freund's complete adjuvant and other adjuvants used in research and veterinary applications have toxicities, which limit their potential use in human vaccines. However, chemically defined preparations such as oil emulsions and surfactant based formulations, e.g., MF59 (microfluidized detergent stabilized oil-in-water emulsion), QS21 (purified saponin), AS02 [SBAS2] (oil-in-water emulsion+MPL+Q5S21), Montanide ISA-51 and ISA-720 (stabilized water-in-oil emulsion), are also in development. Furthermore, microbial derivatives (natural and synthetic), e.g., muramyl dipeptide, monophosphoryl lipid A (e.g. 3 De-O-acetylated monophosphoryl lipid A, also known as 3D-MPL, which is manufactured by Ribi Immunochem, Montana), Detox (MPL+M. Phleicell wall skeleton), AGP [RC-529] (synthetic acylated monosaccharide), DCClO1 (lipidal immunostimulators able to self organize into liposomes), OM-174 (lipid A derivative), CpG motifs (synthetic oligonucleotides containing immunostimulatory CpG motifs), modified LT and CT (genetically modified bacterial toxins to provide non-toxic adjuvant effects), and QS21, an Hple purified non-toxic fraction derived from the bark of Quillaja Saponaria Molina, have all been developed for human use.

A preferred form of 3 De-O-acetylated monophosphoryl lipid A is disclosed in European Patent 0 689 454 B1 (SmithKline Beecham Biologicals SA).

Other particulate adjuvants include, e.g., virosomes (unilamellar liposomal vehicles incorporating a viral antigen), AS04 [SBAS4] AI salt with MPL, ISCOMS (structured complex of saponins and lipids), polyacrylate co-glycolide (PLG).

Other suitable adjuvants include all acceptable immunostimulatory compounds, such as cytokines, chemokines, or colony stimulating factors. For example, these may include the interleukins IL-1, IL-2, IL-4, IL-7, IL-12, gamma-interferon, and hGM-CSF.

It is to be understood that the adjuvant and/or immunostimulatory compound to be used will depend on the subject to which the vaccine or immunogenic composition will be administered, the route of injection and the number of injections to be given.

While the invention has been described with reference to certain RSV-F polypeptides, it is to be understood that this covers fragments of the naturally occurring polypeptides, and similar polypeptides with additions, deletions or substitutions which do not substantially affect the immunogenic properties of the recombinant polypeptides or polynucleotides.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Generation of Human Antibodies to RSV-F Protein

An immunogen comprising any one of the following can be used to generate antibodies to RSV-F protein. In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a whole respiratory syncytial virus isolate, either live, attenuated or killed/inactivated. The mice may be given one or more booster shots containing either the same virus isolate, or they may be boosted with the RSV-F protein itself. In certain embodiments, the mice are injected with live virus, followed by boosting with the construct shown as SEQ ID NO: 353, or with isolated RSV-F protein, obtained from a virus isolate or prepared recombinantly. (See also GenBank accession number AA235994.1.)

In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a biologically active RSV, subtype A or B, and/or the RSV fusion (F) protein, or an immunogenic fragment of the RSV fusion (RSV-F) protein, or DNA encoding the full length protein or the active fragment thereof. The immunogen may be delivered to the animal via any route including but not limited to intramuscularly, subcutaneously, intravenously or intranasally.

In certain embodiments, whole virus, or the RSV-F protein or fragments thereof may be used for preparing monospecific, bispecific, or multispecific antibodies.

The whole virus, or full length proteins, or fragments thereof, that were used as immunogens, as noted above, were administered directly, with an adjuvant to stimulate the immune response, to a VELOIMMUNE® mouse comprising DNA encoding human immunoglobulin heavy and kappa light chain variable regions. The antibody immune response was monitored by a RSV-F immunoassay. When a desired immune response was achieved, splenocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce RSV-F-specific antibodies. Using this tech-
nique, and the various immunogens described above, several chimERIC antibodies (i.e., antibodies possessing human variable domains and mouse constant domains) were obtained; certain exemplary antibodies generated in this manner were designated as H1M3621N, H1M3622N, H1M2634N and H1M3627N.

Anti-RSV-F\textsuperscript{-}F antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. 2007/0280945 A1, herein specifically incorporated by reference in its entirety. Using this method, several fully human anti-RSV-F\textsuperscript{-}F antibodies (i.e., antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1H3564P, H1H3565P, H1H3566P, H1H3567P, H1H3581P, H1H3583P, H1H3589P, H1H3591P, H1H3592P, H1H3597P, H1H3598P, H1H3603P, H1H3604P, H1H3605P, H1H3607P, H1H3608P, H1H3592P2, H1H3592P3.

The biological properties of the exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2

Heavy and Light Chain Variable Region Amino Acid Sequences

Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected antibodies specific for RSV-F\textsuperscript{-}F protein and their corresponding antibody identifiers. Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (e.g., “H4F”, “H1M”, “H2M”), followed by a numerical identifier (e.g., “3117” as shown in Table 1), followed by a “P” or “N” suffix. Thus, according to this nomenclature, an antibody may be referred to as, e.g., “H1H3117”. The H4F, H1M, and H2M prefixes on the antibody designations used herein indicate the particular Fc region of the antibody. For example, an “H2M” antibody has a mouse IgG2 Fc, whereas an “H4F” antibody has a human IgG4 Fc. As will be appreciated by a person of ordinary skill in the art, an H1M or H2M antibody can be converted to an H4H antibody, and vice versa, but in any event, the variable domains (including the CDRs), which are indicated by the numerical identifiers shown in Table 1, will remain the same. Antibodies having the same numerical antibody designation, but differing by a letter suffix of N, B or P refer to antibodies having heavy and light chains with identical CDR sequences but with sequence variations in regions that fall outside of the CDR sequences (i.e., in the framework regions). Thus, N, B and P variants of a particular antibody have identical CDR sequences within their heavy and light chain variable regions but differ from one another within their framework regions.

Antibody Comparators

Anti-RSV-F antibody controls were included in the following Examples for comparative purposes. Isotype matched negative controls were also used in the Examples. One anti-RSV-F control antibody is designated herein as Control I and is a humanized anti-RSV-F antibody with heavy and light chain variable domain sequences of the polivizumab (SYNAGIS®) humanized antibody as set forth in U.S. Pat. No. 7,635,568 and U.S. Pat. No. 5,824,307. The variable light and heavy chains were expressed with human kappa and gamma-1 constants, respectively. One anti-RSV-F antibody is designated herein as Control II and is a humanized anti-RSV-F antibody variant of polivizumab, with heavy and light chain variable domain sequences of the matovizumab (NUMAX™) humanized antibody described in US2003/0091584 and by Wu et al. (2007), J. Mol. Biol. 368:652-665. The variable light and heavy chains were expressed with human kappa and gamma-1 constants, respectively. Another anti-RSV-F antibody is designated as Control III (also referred to as AM-22) and is described in U.S. Pat. No. 8,568,726. The amino acid sequence of the heavy and light chain of AM-22 is shown in SEQ ID NO: 357 (for the heavy chain of the antibody) and SEQ ID NO: 358 (for the light chain of the antibody).

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<tr>
<th>Antibody</th>
<th>SEQ ID NOs</th>
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<td>H1H3567P</td>
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<tr>
<td>H1H3581P</td>
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<td>H1H3583P</td>
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<td>H1H3589P</td>
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<tr>
<td>H1M3627N</td>
<td>338 340 342 344 346 348 350 352</td>
</tr>
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</table>
Example 3

Antibody Binding Affinities and Kinetic Constants of Human Monoclonal Anti-RSV-F Antibodies as Determined by Surface Plasmon Resonance

Binding affinities and kinetic constants of human monoclonal anti-RSV-F antibodies were determined by surface plasmon resonance at 25°C (Tables 2-3). Measurements were conducted on a Biacore 4000 or T-200 instrument. Antibodies, expressed with either mouse Fe (AbPID prefix H1M; H2M) or human IgG1 Fe (AbPID prefix H1H), were captured onto an anti-mouse or anti-human Fe sensor surface (Mab capture format), and soluble monomeric (RSV-F.mAb; SEQ ID NO: 353) protein was injected over the surface. All Biacore binding studies were performed in HBST running buffer (0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% v/v surfactant F20). Different concentrations of RSV-F.mAb prepared in HBST running buffer were injected over the anti-RSV-F monoclonal antibody captured surface at a flow rate of 30 μl/min (Biacore 4000) or at a flow rate of 50 μl/min (Biacore T-200) and the association of RSV-F.mAb to captured monoclonal antibody was monitored for 6 min or 5 min respectively. The dissociation of RSV-F.mAb from the monoclonal antibody in HBST running buffer was monitored for 8-10 min at 25°C. Kinetic association (kₐ) and dissociation (k₈) rate constants were determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0 curve fitting software. Binding dissociation equilibrium constants (K₈) and dissociative half-lives (t₈/₂) were calculated from the kinetic rate constants as: K₈ = k₈/kₐ, and t₈/₂ = (ln 2/60k₈).

Anti-RSV-F antibodies of the invention displayed a broad range of affinities for RSV-F.mAb. Control I, produced based on the public sequence of palivizumab set forth in U.S. Pat. No. 7,635,568, and Control II, produced on the public sequence of montalizumab as described in Wu et al. (2007), (J. Mol. Biol. 368:652-665) displayed the approximately ~70-fold difference (control 1; 38 nM vs control II; 0.43 nM) in affinity that has been previously reported.

### TABLE 2

<table>
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<tr>
<th>Biacore Binding Affinities of Hybridoma mAbs at 25°C</th>
<th>Binding at 25°C Mab Capture Format</th>
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<tr>
<td>AbPID</td>
<td>kₐ (1/1M)</td>
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<td>1.79E+05</td>
</tr>
<tr>
<td>H1M3627N</td>
<td>2.59E+05</td>
</tr>
</tbody>
</table>

Example 4

Respiratory Syncytial Virus Fusion (RSV-F) Protein Antibodies Display Potent Neutralization Capabilities Across RSV Subtypes a and Subtype B Strains

Purified antibodies were tested in a RSV micro-neutralization assay to determine potency. Briefly, 10⁶ HEP-2 cells cultured in MEM high glucose medium, supplemented with 5% Hyclone FBS, L-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours (37°C, 5% CO₂). Next, various concentrations of antibodies, starting at 666 nM with subsequent 1:5 dilutions in media, were incubated with the RSV 1540 (A2) strain at an MOI of 0.04 for 2 hours (37°C, 5% CO₂). Virus-free and irrelevant isotype controls were included.

Post incubation, the antibody-virus mixture was added to the HEP-2 cells and infection was maintained for 3 days. The degree of infection was determined by fixing cells in 2% PFA and performing an ELISA with Goat anti-RSV/anti-Goat HRP antibodies. Luminescence reagents were added to the wells and signal was detected using a plate reader (VICTor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

The antibodies of the invention displayed a broad range of neutralization activities against the RSV A2 (1540) strain (Table 4-5). Several antibodies displayed lower IC₅₀ values than control I while only a few exemplary antibodies H1HI3526N, H1HI3591P, H1HI3529P and H1HI3592P showed better neutralization than control II. Select antibodies (H1HI3267N, H1HI3592P) were also tested for their ability to neutralize RSV subtype B strains (Table 6).

This example demonstrates the efficacy of the antibodies of this invention to neutralize several strains of RSV-F, across two subtypes, in vitro, with greater potency than previously demonstrated for established controls.

### TABLE 3

<table>
<thead>
<tr>
<th>Biacore binding affinities of human Fe mAbs at 25°C</th>
<th>Binding at 25°C Mab Capture Format</th>
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<tbody>
<tr>
<td>AbPID</td>
<td>kₐ (1/1M)</td>
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<td>H1HI354P</td>
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### TABLE 4

Neutralization potency for selected mAbs against RSV A2 (1540)

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<td>H1H13633P</td>
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<tr>
<td>H1H13634P</td>
<td>&gt;10000</td>
<td>—</td>
<td>—</td>
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<tr>
<td>H1H13635P</td>
<td>&gt;10000</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>H1H13637P</td>
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<td>H1H13638P</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
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<td>1820</td>
<td>950</td>
<td>290</td>
<td>530</td>
<td>160</td>
<td>500</td>
<td>250</td>
</tr>
<tr>
<td>Control 2</td>
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<td>23</td>
<td>20</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

### TABLE 5

Neutralization potency for selected mAbs against RSV subtype A

| Subtype A Neutralization: IC50 & Fold Improvement Relative to Control 1 |
|---------------------------|--------------------------|--------------------------|
| Ab/PID     | IC50 [pM] | Fold | IC50 [pM] | Fold |
| H1H13627N  | 2.6     | 138    | 7.3     | 73      |
| H1H13592P  | 10      | 36     | 15      | 35      |
| Control 1  | 360     | —      | 536     | —       |
| Control 2  | 14      | 25     | 65      | 8.2     |

### TABLE 6

Neutralization potency for selected mAbs against RSV subtype B

| Subtype B Neutralization: IC50 & Fold Improvement Relative to Control 1 |
|---------------------------|--------------------------|--------------------------|
| RSV - 1580 | Neutral. | RSV-9230 | Neutral. | IC50 [pM] | Fold |
| Ab/PID     | IC50 [pM] | Fold | IC50 [pM] | Fold |
| H1H13627N  | 6.7     | 55     | 11      | 42      |
| H1H13592P  | 31      | 12     | 100     | 4.6     |
| Control 1  | 375     | —      | 460     | —       |
| Control 2  | 43      | 8.7    | 56      | 8.2     |

### Example 5

**Selected Anti-RSV-F Antibodies Display Potent Neutralization of RSV Infection in Vivo**

**A. Mouse Model**

The exemplary antibodies H1H13627N and H1H13592P3 were selected for in vivo RSV neutralization studies using Balb/c mice. Briefly, 7 week old Balb/c mice (n=4-5) were injected SC at two doses (0.15 or 0.05 mg/kg) using either H1H13627N, H1H13592P3, control 1, control II or isotype-matched antibody. The use of carrier antibody (1 mg/kg) was utilized in all experiments to minimize the loss of anti-RSV-F antibody.

One day post-injection, mice were challenged intranasally with 50 ul (10⁶ pfu) of RSV A2 (1540) strain. Four days post-infection, sera was drawn, mice were sacrificed, and lungs were extracted and homogenized in 1 ml of PBS using an OmniGiL II homogenizer. Lung homogenates were centrifuged to remove cellular debris and a portion of supernatant was used to determine anti-RSV-F mAb concentration in the lung. The remaining supernatant was used to make serial dilutions which were incubated with HEp-2 cells for 2 hours, to allow viral entry. Subsequently, supernatant was removed and the cells were overlaid with 1% methylcellulose. Six days later, cells were stained with crystal violet and plaques were counted and the log₁₀ viral reduction was calculated relative to isotype control.

Exemplary antibodies H1H13627N and H1H13592P3 were more efficacious in reducing the viral load in vivo than control I or control II anti-RSV-F antibodies (Tables 7a-7e). Specifically, at the 0.15 mg/kg dose, antibodies H1H13627N, H1H13592P5 and control II all effectively reduced RSV infection in the lung to near undetectable levels compared to control I (viral reduction log(10) fold change ≥2.10). Total human IgG measurements in the lungs and serum confirmed that antibody levels were relatively consistent between groups.

At a lower administrated dose, greater differentiation in neutralization efficacy between the three antibodies compared to control I was evident. At 0.05 mg/kg, H1H13592P3 showed the greatest reduction in viral load, with fold changes ranging from 1.49 to ≥2.07 logs, compared with viral load reduction fold changes of 1.08 to 1.36 logs for H1H13627N and 0.01 to 0.65 logs for control II. Control I at this lower dose was only moderately effective with viral load reduction changes of 0.03 to 1.03 logs.
The results indicate that both H1H3627N and H1H3592P3 are potent RSV neutralizing antibodies in vivo, with the latter showing a trend of being a more effective neutralizer of RSV infection at lower doses.

A dosing range experiment was performed following the same protocol described above, injecting SC 4 different doses of control I antibody (0.6, 0.3, 0.15 and 0.05 mg/kg), and two doses (0.15 and 0.05 mg/kg) of H1H3592P3 and control II. Viral reduction in the lungs was calculated as a percentage of isotype control (Exp M4, Tables 7d-e).

Exemplary antibody H1H3592P3 was more efficacious in reducing the viral load in vivo (in mouse) than control I or control II anti-RSV-F antibodies. In addition, the dose of control I required to reach a 99% viral reduction in the lungs was 3-4 fold higher than the dose of H1H3592P3. Tables 7a-e: RSV viral reduction (log10) in mice after administration of Anti-RSV-F antibodies

### TABLE 7a

<table>
<thead>
<tr>
<th>PID</th>
<th>Dose: 0.15 mg/kg</th>
<th>Dose: 0.05 mg/kg</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mice per group</td>
<td>(log10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lungs</td>
</tr>
<tr>
<td>H1H3627N</td>
<td>5</td>
<td>&gt;2.10</td>
</tr>
<tr>
<td>H1H3592P3</td>
<td>5</td>
<td>&gt;2.10</td>
</tr>
<tr>
<td>Control I</td>
<td>5</td>
<td>1.02</td>
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<tr>
<td>Control II</td>
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### TABLE 7b

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<th>Dose: 0.05 mg/kg</th>
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<tbody>
<tr>
<td></td>
<td>Mice per group</td>
<td>(log10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lungs</td>
</tr>
<tr>
<td>H1H3627N</td>
<td>5</td>
<td>&gt;2.51</td>
</tr>
<tr>
<td>H1H3592P3</td>
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<tr>
<td>Control I</td>
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<td>0.79</td>
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<tr>
<td>Control II</td>
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<td>2.51</td>
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### TABLE 7c

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<th>Dose: 0.05 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mice per group</td>
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<tr>
<td></td>
<td></td>
<td>Lungs</td>
</tr>
<tr>
<td>H1H3627N</td>
<td>4</td>
<td>2.7</td>
</tr>
<tr>
<td>H1H3592P3</td>
<td>4</td>
<td>&gt;2.83</td>
</tr>
<tr>
<td>Control I</td>
<td>4</td>
<td>1.00</td>
</tr>
<tr>
<td>Control II</td>
<td>4</td>
<td>2.35</td>
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<tr>
<td>Isotype Ctrl</td>
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### TABLE 7d

<table>
<thead>
<tr>
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<th>Dose: 0.6 mg/kg</th>
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</tr>
</thead>
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<tr>
<td></td>
<td>Mice per group</td>
<td>(log10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum</td>
</tr>
<tr>
<td>Control I</td>
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</tbody>
</table>
TABLE 7e

<table>
<thead>
<tr>
<th>Exp M4 (ED50)</th>
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<th>Dose: 0.05 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PID</td>
<td>Mice per group</td>
<td>Viral Reduction (%)</td>
</tr>
<tr>
<td>H1H3592P3</td>
<td>5</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Control I</td>
<td>5</td>
<td>57.9</td>
</tr>
<tr>
<td>Control II</td>
<td>5</td>
<td>96.7</td>
</tr>
<tr>
<td>Isotype Ctrl</td>
<td>5</td>
<td>NA</td>
</tr>
</tbody>
</table>

ND: Not determined

B. Cotton Rat Model

The exemplary antibodies H1H3627N and H1H3592P3 were selected for in vivo RSV neutralization studies using cotton rats. Briefly, 6-8 week old cotton rats (n=5) were injected IM at two doses (5 or 0.6 mg/kg) using either H1H3627N, H1H3592P3, control I, control II or isotype-matched antibody.

One day post-injection, rats were challenged intranasally with 100 ul (10⁵ pfu) of RSV A2 strain. Four days post-infection, sera was drawn, rats were sacrificed, and lung and nasal tissues were extracted for viral titration. Lung homogenates were centrifuged to remove cellular debris and a portion of supernatant was used to determine anti-RSV-F mAb concentration in the lung. The remaining supernatant was used to make serial dilutions, which were incubated with HEp-2 cells to allow viral entry. Subsequently, supernatant was removed and the cells were overlaid with 1% methylcellulose. Six days later, cells were stained and plaques were counted and the log₁₀ viral reduction was calculated relative to isotype control.

Exemplary antibody H1H3592P3 was more efficacious in reducing the viral load in the lungs and nose than control I, and as efficacious as control II in lungs and better in the nose. Exemplary antibody H1H3627N was only better than control I and as efficacious as control II in the nose (Table 8). Specifically, at the 5 mg/kg dose, antibodies H1H3627N, H1H3592P3, control I and control II all effectively reduced RSV infection in the lung to near undetectable levels compared to isotype control (viral reduction log₁₀ fold change ±2.33). However, in the nose, greater differentiation in neutralization efficacy between H1H3627N, H1H3592P3, control II compared to control I was evident. H1H3592P3 showed the greater reduction in viral load (2.65 logs) compared to H1H3627N (1.46 logs) or control II (1.33 logs).

At a lower administrated dose, greater differentiation in neutralization efficacy between the three antibodies compared to control I was evident in the lungs. At 0.6 mg/kg, H1H3592P3 showed similar reduction in viral load than control I (1.5 logs) and they were both more efficacious than control I (0.624 logs). H1H3627N showed less efficacy than the other three antibodies.

Exemplary anti-RSV-F antibody H1H3592P3 was next selected for testing its ability to neutralize RSV subtype B in vivo using the cotton rat model. As with RSV/A, 6- to 8-week old cotton rats (n=4-6/group/experiment) were intramuscularly administered either 5 or 0.6 mg/kg of H1H3592P3, Control I or Control II. The next day, animals were challenged with 10⁵ pfu of RSV/B strain 18537. Four days post-challenge, viral titers in the lungs and nose were determined along with serum antibody titers. The results shown in Table 9 were data pooled from two independent experiments.

H1H3592P3 showed efficacy in reducing RSV/B viral load in lungs at both high and low doses (Table 9). At 0.6 mg/kg, RSV/B viral load in the lungs was reduced by 2.21 logs with H1H3592P3, compared with a reduction of 2.11 logs by Control I and 2.18 logs by Control II. At 0.6 mg/kg, RSV/B viral load in the lungs was reduced by 1.29 logs with H1H3592P3, compared with a reduction of 0.75 logs by Control I and 0.83 logs by Control II.

Overall, H1H3592P3 showed superiority in neutralization of RSV Subtype B in the lungs over both Control I and Control II at 0.6 mg/kg. At 5 mg/kg, H1H3592P3 showed comparable neutralizing ability than Control I and Control II in reducing viral load in the lungs.

The results indicate that H1H3592P3 is a potent neutralizer of RSV subtype strains A and B in vivo in cotton rats, being a more effective neutralizer of RSV infection at high doses in the nose and at lower doses in the lungs. The efficacy at low doses indicates the possibility of a lower dose regimen in the clinic.

TABLE 8

<table>
<thead>
<tr>
<th>Exp R1</th>
<th>Dose: 0.6 mg/kg</th>
<th>Dose: 5.0 mg/kg</th>
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<tr>
<td></td>
<td>Rates per group (log₁₀)</td>
<td>Reduction lung (log₁₀)</td>
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<tr>
<td>PID</td>
<td>Viral</td>
<td>mAb</td>
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<tr>
<td>H1H3627N</td>
<td>5</td>
<td>0.34</td>
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<tr>
<td>H1H3592P3</td>
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<td>1.66</td>
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<tr>
<td>Control I</td>
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<td>0.62</td>
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<td>Control II</td>
<td>5</td>
<td>1.50</td>
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<tr>
<td>Isotype Ctrl</td>
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<td>NA</td>
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</tbody>
</table>
TABLE 9

RSV-B viral reduction (log 10) in cotton rats after administration of Anti-RSV-F antibodies

<table>
<thead>
<tr>
<th>Dose: 0.6 mg/kg</th>
<th>Dose: 5.0 mg/kg</th>
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<tr>
<td><strong>Env R2</strong></td>
<td><strong>Env R2</strong></td>
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<td>Virus</td>
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<td>Reduction lung (log10)</td>
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<tr>
<td>HH3592P3</td>
<td>1.29 ± 0.21</td>
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<tr>
<td>Control I</td>
<td>0.75 ± 0.15</td>
</tr>
<tr>
<td>Control II</td>
<td>0.83 ± 0.10</td>
</tr>
<tr>
<td>Isotype Ctrl</td>
<td>NA</td>
</tr>
</tbody>
</table>

C. Cotton Rat Model—Determination of the ED₉₀ of an Exemplary Antibody HH3592P3

Dose-ranging studies using the cotton rat were performed to determine at which dose an exemplary antibody HH3592P3 would reduce viral load by >99% (i.e. the ED₉₀). Cotton rats were prophylactically administered an IM dose of HH3592P3 or Control 1 antibody at either 10, 25, 50, 125, or 250 mg/kg. Additionally an isotype control antibody was dosed in at either 10 or 0.62 mg/kg to bracket the active agents in this study. Following antibody treatments, an intranasal RSV challenge of either subtype A (RSV A2 strain) or subtype B (RSV B strain 18537) was performed. Four days post-infection, sera was drawn, rats were sacrificed, and lung tissue was extracted for viral titration. HH3592P3 at a dose of 0.62 mg/kg achieved >99% viral load reduction in the lungs as compared to Control 1 which required a dose of 2.5 mg/kg to reach the same >99% viral reduction (Table 10). The mean terminal Control 1 concentration (27 μg/mL) at the calculated ED₉₀ correlated well with previously published work (Scott and Lamb, 1999), which indicated that a serum palivizumab concentration (i.e. Control 1) of 30-40 mg/mL, at the time of RSV infection, was associated with a 99% reduction in lung viral load. The mean terminal HH3592P3 concentration (4.9 μg/mL) correlated well with the 4-fold lower dose delivered at its ED₉₀. Results against subtype B challenge were similar (Table 11) in that an ED₉₀ for HH3592P3 was achieved at 2.5 mg/kg while Control 1 required roughly a 4x greater dose (10 mg/kg) to obtain that same >99% viral lung reduction.

In summary these studies support that less frequent dosing of HH3592P3 may confer the same level of protection as the current monthly dosing paradigm used with palivizumab.

TABLE 10

Determination of the ED₉₀ for Anti RSV-F Antibodies After RSV Subtype A Challenge

<table>
<thead>
<tr>
<th>PID</th>
<th>10 mg/kg</th>
<th>5 mg/kg</th>
<th>2.5 mg/kg</th>
<th>1.25 mg/kg</th>
<th>0.62 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH3592P3</td>
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<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
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<td>Control</td>
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<td>&gt;99</td>
<td>&gt;99</td>
<td>98.9</td>
<td>95.0</td>
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<tr>
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<td>NA</td>
<td>NA</td>
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</tr>
</tbody>
</table>

Antibody Serum Concentration (μg/mL)

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<tr>
<th>PID</th>
<th>107.2 ± 3.4</th>
<th>48.44 ± 6.1</th>
<th>20.15 ± 1.8</th>
<th>10.55 ± 1.5</th>
<th>4.91 ± 0.7</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>89.16 ± 6.5</td>
<td>58.07 ± 6.3</td>
<td>26.93 ± 3.3</td>
<td>12.72 ± 2.2</td>
<td>6.65 ± 0.5</td>
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<tr>
<td>Isotype</td>
<td>90.57 ± 12.6</td>
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<td>—</td>
<td>—</td>
<td>5.39 ± 0.5</td>
</tr>
</tbody>
</table>

TABLE 11

Determination of the ED₉₀ for Anti RSV-F Antibodies After RSV Subtype B Challenge

<table>
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<tr>
<th>PID</th>
<th>10 mg/kg</th>
<th>5 mg/kg</th>
<th>2.5 mg/kg</th>
<th>1.25 mg/kg</th>
<th>0.62 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HH3592P3</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>&gt;99</td>
<td>98.4</td>
<td>96.7</td>
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<td>Control</td>
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<td>98.4</td>
<td>96.3</td>
<td>88.2</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Antibody Serum Concentration (μg/mL)

<table>
<thead>
<tr>
<th>PID</th>
<th>98.04 ± 18.4</th>
<th>50.99 ± 7.8</th>
<th>27.82 ± 4.9</th>
<th>10.49 ± 1.7</th>
<th>7 ± 0.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>98.89 ± 10.9</td>
<td>42.74 ± 8.9</td>
<td>26.46 ± 3.3</td>
<td>16.06 ± 2.2</td>
<td>7.58 ± 1.1</td>
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<tr>
<td>Isotype</td>
<td>90.72 ± 17.4</td>
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<td>NA</td>
<td>NA</td>
<td>5.38 ± 0.5</td>
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Example 6

Generation of a Bi-Specific Antibody

Various bi-specific antibodies are generated for use in practicing the methods of the invention. For example, RSV-F specific antibodies are generated in a bi-specific format (a “bi-specific”) in which variable regions binding to distinct domains of the RSV-F protein are linked together to confer dual-domain specificity within a single binding molecule. Appropriately designed bi-specifics may enhance overall virus neutralization efficacy through increasing both specificity and binding avidity. Variable regions with specificity for individual domains are paired on a structural scaffold that allows each region to bind simultaneously to separate epitopes, or to different regions within one domain. In one example for a bi-specific, heavy chain variable regions (V\text{H}) from a binder with specificity for one domain are recombined with light chain variable regions (V\text{L}) from a series of binders with specificity for a second domain to identify non-cognate V\text{H} partners that can be paired with an original V\text{H} without disrupting the original specificity for that V\text{H}. In this way, a single V\text{H} segment (e.g., V\text{H}1) can be combined with two different V\text{L} domains (e.g., V\text{L1} and V\text{L2}) to generate a bi-specific comprised of two binding “arms” (V\text{H1-L1} and V\text{H2-L2}). Use of a single V\text{H} segment reduces the complexity of the system and thereby simplifies and increases efficiency in cloning, expression, and purification processes used to generate the bi-specific (See, for example, U.S. Ser. No. 13/022,759 and US20100331527).

Alternatively, antibodies that bind RSV-F and a second target, such as, but not limited to, for example, a second different anti-RSV-F antibody, or a toxin, or a vaccine, may be prepared in a bi-specific format using techniques described herein, or other techniques known to those skilled in the art. Antibody variable regions binding to distinct regions may be linked together with variable regions that bind to relevant sites on, for example, a different viral antigen to confer dual-antigen specificity within a single binding molecule. Appropriately designed bi-specifics of this nature serve a dual function. For example, in the case of a bi-specific antibody that binds i.e., RSV-F and RSV-G one may be able to better neutralize the virus, without the need for administration of a composition containing two separate antibodies. Variable regions with specificity for RSV-F, are combined with a variable region with specificity for RSV-G and are paired on a structural scaffold that allows each variable region to bind to the separate antigens.

The bi-specific binders are tested for binding and functional blocking of the target antigens, for example, RSV-F and RSV-G, in any of the assays described above for antibodies. For example, standard methods to measure soluble protein binding are used to assess the bispecific interaction, such as Biacore, ELISA, size exclusion chromatography, multi-angle laser light scattering, direct scanning calorimetry, and other methods. Binding of bi-specific antibodies to both RSV-F and RSV-G is determined through use of an ELISA binding assay in which synthetic peptides representing the different antigens are coated onto the wells of microtiter plates, and binding of a bi-specific is determined through use of a secondary detection antibody. Binding experiments can also be conducted using surface plasmon resonance experiments, in which real-time binding interaction of peptide to antibody is measured by flowing a peptide or bi-specific across a sensor surface on which bi-specific or peptide, respectively, is captured. Functional

in vitro blocking of both RSV-F and RSV-G by a bi-specific is determined using any bioassay such as the neutralization assay described herein, or by in vivo protection studies in appropriate animal models, such as those described herein, or in an in vivo model of lung inflammation.

Example 7

In Vitro Generation of RSV Escape Mutants to Determine the Binding Epitope of H1H3592P3

Generation of Escape Mutants to H1H3592P3

3x10^4 Hep-2 cells/well were plated in a 6-well plate for 24 h. Concentrations of H1H3592P3, ranging from 50 ng/mL to 0.016 ng/mL were mixed with RSV subtype A strain 1540 or RSV subtype B strain 1580 for 1 h at 37°C. After incubation, the RSV/antibody mixture was added to the previously seeded Hep-2 cells at a multiplicity of infection (MOI) of 10 plaque-forming units (pfu)/cell. Cells were incubated for 6 days, and cytopathic effects were monitored daily using light microscopy. At day 6, contents of each well were harvested, adjusted to initial concentration of antibody and used to infect freshly seeded Hep-2 cells. This serial passage was repeated until obvious cytopathic effects were observed at high concentrations of H1H3592P3 (50 ng/mL), which is approximately 2 logs greater than the IC50 of the antibody, suggesting the presence of viral mutants. Supernatants from these wells were confirmed from the presence of resistant virus via a micro-neutralization assay (described below) and plaque isolation was performed in 10 cm tissue culture dishes. 10 individual plaques were expanded in 6-well plates and virus were re-tested for resistance via microneutralization. Sequencing was then performed on these viral mutants.

Microneutralization Assay

To confirm whether escape mutants generated under the pressure of H1H3592P3 were resistant to neutralization, a microneutralization assay in Hep-2 cells was performed. Briefly, 10^5 Hep-2 cells cultured in DMEM 1× medium, supplemented with 5% Hyclone FBS, 1-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours (37°C, 5% CO2).

Next, various concentrations of antibodies, starting at 666 nM and diluted 1:5 in media, were incubated for 2 hours (37°C, 5% CO2) with RSV wild-type (subtype A or B) or escape mutants from both subtype A and B, at an MOI from 0.04 to 0.4. Controls not containing virus or controls containing virus but no antibodies were included. All dilutions of antibody were conducted in quadruplicates. After incubation, the antibody/virus mixture was added to cells and infection was allowed for 3 days. Infection was determined by fixing the cells in 2% PFA and an ELISA with Goat anti-RSV/anti-Goat HRP antibodies was performed. Luminescence reagents were added to the wells and signal was detected using a plate reader (Victor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

Results

Respiratory syncytial virus escape mutants were generated to map the specific binding region of H1H3592P3 to RSV-F. Briefly, Hep-2 cells infected with RSV strains 1540 (subtype A) or 1580 (subtype B) were subjected to H1H3592P3 treatment ranging from 50 ng/mL to 0.016 ng/mL. After 6 days, contents from each well were used to infect freshly seeded Hep-2 cells. This serial passage continued until cytopathic effects were observed in Hep-2 cells even in the presence of the highest antibody dose, indicating
the presence of RSV viral mutants generated under selection pressure. Overall, viral mutants were isolated from ten distinct plaques, confirmed for neutralization resistance in the presence of H1H3592P3 and subsequently sequenced.

Sequence analysis confirmed that escape mutations for H1H3592P3 were found at amino acid positions 173 and 174 (S173Y and T174K) of RSV-F (SEQ ID NO: 354), indicating that these amino acids play an important role in antibody binding and viral neutralization. Prior reports have determined that the binding epitopes for anti-RSV Control I and Control II antibodies are located between S255-N276. The data from these studies suggest a binding site for H1H3592P3 on RSV-F that plays a major role in viral neutralization (see table 12) and is distinct from that required for previously established Control antibodies.

### TABLE 12

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<thead>
<tr>
<th>Virus</th>
<th>H1H3592P3 (EC50, pM)</th>
<th>Control I (EC50, pM)</th>
<th>Control II (EC50, pM)</th>
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<td>108</td>
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<tr>
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<tr>
<td>RSV/B T174K</td>
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<td>RSV/B S173T/T174K</td>
<td>Resistant</td>
<td>980</td>
<td>218</td>
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</table>

### Example 8

**Determination of the Binding Epitope of H1H3592P3 to RSV-F Using Hydrogen-Deuterium Exchange & Mass Spectrometry.**

Hydrogen/Deuterium Exchange (H/D exchange) in combination with peptic digests and mass spectrometry was conducted to determine the binding epitope of the anti-RSV-F antibody H1H3592P3 to recombinant RSV-F. Two H/D exchange formats (described in detail below) were employed: An ‘on-solution/off-beads’ method in which RSV-F peptide fragments that are protected by H1H3592P3 from back-exchange retain D₂O and yield higher molecule weights (m/z) values by mass spectrometry and an ‘on-beads/off-beads’ control method which establishes the baseline m/z values for all RSV-F peptides. Subtraction of the control m/z values from the m/z values obtained using the ‘on-solution/off-beads’ method yields certain amino acids regions that show non-zero delta m/z values i.e. residual D₂O that correspond to the binding epitope between H1H3592P3 and RSV-F.

**Methods**

**On Solution/Off Beads Format**

In the ‘on-solution/off-beads’ (on-exchange in solution followed by off-exchange on beads) format, RSV-F.mmh protein (SEQ ID NO: 353) was deuterated for 5 min or 10 min in PBS buffer prepared with D₂O and then bound to H1H3592P3 covalently attached to N-hydroxysuccinimide (NHS) agarose beads (GE LifeSciences) via a 2 min incubation. The RSV-F/H1H3592P3 bead complex was washed with PBS buffer (prepared with non-deuterated H₂O) and incubated in PBS buffer for half of the on-exchange time. After the off-exchange, the bound RSV-F was eluted from beads with an ice-cold low pH TFA solution. The eluted RSV-F was then digested with immobilized pepsin (Thermo Scientific) for 5 min. The resulting peptides were desalted using ZipTip chromatographic pipette tips and immediately analyzed by UltrafileXtreme matrix assisted laser desorption ionization time of flight (MALDI-TOF-TOF) mass spectrometry (MS).

**On-Beads/Off Beads Format**

In the ‘on-beads/off-beads’ (on-exchange on beads followed by off-exchange on beads) format, RSV-F.mmh (SEQ ID NO: 353) was first bound to H1H3592P3 agarose beads and then incubated for 5 min or 10 min in D₂O for on-exchange. The RSV-F/H1H3592P3 bead complex was washed with PBS buffer (prepared with non-deuterated H₂O) and incubated in PBS buffer for half of the on-exchange time. After the off-exchange, the bound RSV-F was eluted from beads with an ice-cold low pH TFA solution. The eluted RSV-F was then digested with immobilized pepsin (Thermo Scientific) for 5 min. The resulting peptides were desalted using ZipTip chromatographic pipette tips and immediately analyzed by MALDI-TOF-TOF mass spectrometry. The centroid values or average mass-to-charge ratios (m/z) of all the detected peptides were calculated and compared between this and the ‘on-solution/off-beads’ experiment.

### Peptide Identification

The identification of the peptides was carried out using liquid chromatography-Orbitrap Elite (Thermo Scientific).

**Results**

Table 13 is a detailed comparison of the delta centroid m/z values for all the RSV-F peptides detected by MALDI-TOF mass spectrometry following H/D exchange and peptic digest. Two segments corresponding to amino acids 161-171 (EGEVNVKIKSAL, (SEQ ID NO: 355)) and 172-188 (LSTNKAVVLSLSNGVSL, (SEQ ID NO: 356)) of SEQ ID NO: 354 had delta centroid values higher than 0.20, a threshold observed in-house to be considered indicative of antibody-protein contact and thus an epitope region. It should also be noted that the peptide signal corresponding to amino acids 161-171 was not quantified in the 10 min on-exchange experiment due to low signal to noise. However, the delta value of 0.88, detected at the 5 min on-exchange experiment, is far above the 0.2 threshold and can be attributed to the significant alteration in H/D exchange rate upon RSV-F binding to H1H3592P3.

Furthermore, the peptide segment corresponding to amino acids 172-188 contains the amino acids of the two RSV escape mutants (S173Y and T174K; see example 7), which were resistant to H1H3592P3 treatment, indicating that these two amino acids play a role in antibody binding and viral neutralization. Thus the combination of sequencing escape RSV mutants along with H/D exchange support amino acids 161-188 of SEQ ID NO: 354 defining at least in part the binding region in RSV-F for antibody H1H3592P3.
### TABLE 13

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<td>1189.72</td>
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Example 9

Respiratory Syncytial Virus Fusion (RSV-F) Protein Antibodies Display Potent Neutralization Capabilities Across RSV Subtype A and B Laboratory Strains

H3H3592P3 and controls I and II antibodies were tested in a RSV micro-neutralization assay to determine potency. Briefly, 10⁴ HEP-2 cells cultured in DMEM 1× medium, supplemented with 5% Hyclone FBS, L-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours at 37°C (5% CO₂). Next, various concentrations of antibodies, starting at 666 nM with subsequent 1:5 dilutions in media, were incubated with various RSV subtype A lab strains provided by ATCC at an MOI of 0.042 for 2 hours (37°C, 5% CO₂). Virus-free and irrelevant isotype controls were included. Post incubation, the antibody-virus mixture was added to the HEP-2 cells and infection was maintained for 3 days. The degree of infection was determined by fixing cells in 2% PFA and performing an ELISA with Goat anti-RSV/anti-Goat HRP antibodies. Luminescence reagents were added to the wells and signal was detected using a plate reader (Victor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

The antibodies of the invention displayed a broad range of neutralization activities against the RSV lab strains (Table 14). Antibodies H3H3592P3 and AM22 showed similar potency than control II for RSV subtype A lab strains. Compared to control I, H3H3592P3 showed 15-17 fold
more potency (IC50 44-140 pM), while AM22 showed 9-23 fold more potency (IC50 86-91 pM) (Table 14). For subtype B, antibody H1H3592P3 showed similar potency than control II, but superior than AM22 and control I. Compared to control I, H1H3592P3 showed 2-5 fold more potency (IC50 33-230 pM), while AM22 showed 0.13-2 fold more potency (IC50 190-2548 pM).

This example demonstrates the efficacy of the antibodies of this invention to neutralize several lab strains of RSV from both subtype A and B, in vitro, with greater potency than previously demonstrated for established controls.

<table>
<thead>
<tr>
<th>Subtype/strain</th>
<th>H1H3592P3 IC50 (pM)</th>
<th>Control I IC50 (pM)</th>
<th>Control II IC50 (pM)</th>
<th>Control III IC50 (pM)</th>
<th>Genbank</th>
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</table>

Example 10

Respiratory Syncytial Virus Fusion (RSV-F) Protein Antibodies Display Potent Neutralization Capabilities Across RSV Subtype A Clinical Isolates

H1H3592P3 and controls I, II and III antibodies were tested in a RSV micro-neutralization assay to determine potency. Briefly, 10^5 HEp-2 cells cultured in DMEM 1x medium, supplemented with 5% Hyclone FBS, L-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours (37°C, 5% CO2). Next, various concentrations of antibodies, starting at 666 nM with subsequent 1:5 dilutions in media, were incubated with various RSV subtype A clinical isolates provided by Dr. Moore (Emory University) at a range of MOIs from 0.015 to 0.128 for 2 hours (37°C, 5% CO2). Virus-free and irrelevant isotype controls were included. Post incubation, the antibody/virus mixture was added to the HEp-2 cells and infection was maintained for 3 days. The degree of infection was determined by fixing cells in 2% PFA and performing an ELISA with Goat anti-RSV/anti-Goat HRP antibodies. Luminescence reagents were added to the wells and signal was detected using a plate reader (Victor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

The antibodies of the invention displayed a broad range of neutralization activities against the RSV clinical isolates (Table 15). Antibody H1H3592P3 showed similar potency to controls II and III for most clinical isolates. Compared to control I, H1H3592P3 showed 10-22 fold more potency (IC50 34-66 pM) (Table 15).

This example demonstrates the efficacy of the antibodies of this invention to neutralize several clinical isolates of RSV, in vitro, with greater potency than previously demonstrated for established controls.

<table>
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<th>Control III</th>
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Example 11

H1H3592P3 Blocks Viral Entry by Inhibiting Fusion of Virus and Cell Membranes

A study was done to determine the mechanism by which the antibodies of the invention block respiratory syncytial virus (RSV) infection. One exemplary antibody of the invention, H1H3592P3, was tested to determine whether it acted to prevent/inhibit RSV fusion with host cells (FIGS. 2A and 2B). The mechanism of action for control I (the positive control mAb which is based on the sequence of palivizumab) was previously described as inhibition of viral fusion to the host cell (Huang et al., J. of Virol., 2010, August 84(16):8132-840). Because RSV-F is involved in both attachment to the cell via the interaction of the host receptor nucleolin, and fusion of the viral and plasma membranes, assays were performed to determine the mechanism of H1H3592P3.

The attachment assay (FIG. 2A) was performed by incubating RSV (subtype A strain A2) in the presence of either H1H3592P3 or the positive control antibody (control I), then incubating the mixture with HEp-2 cells at 4°C for one hour to allow binding of the virus to the cells. Unbound virus was washed out, cells were fixed and the percentage of attached virus was measured by ELISA. Heparin, which blocks RSV attachment, was used as a control.

Viral fusion was detected by allowing viral attachment at 4°C, washing out unbound virus, then incubating with H1H3592P3, positive Control I, or an isotype negative control antibody at 4°C and moving cells to 37°C to promote viral fusion and entry. Viral infection was measured 3 days later by ELISA (FIG. 2B). RU:Relative Luminescence Units.

H1H3592P3, like control I, blocks RSV fusion and not the attachment of RSV to the cell surface, while the isotype (negative) control mAb had no effect on viral fusion (FIG. 2B). Heparin effectively blocked RSV attachment to cells (Hallack et al., Virology (2000), 271(2):264-75), whereas neither antibody inhibited RSV attachment (FIG. 2A).

H1H3592P3 blocked viral fusion in this assay format with an IC50 of 230 pM, while the positive control mAb (control...
1) blocked viral fusion with an IC_{50} of 1 nM (FIG. 2B). Similar results were observed with an RSV subtype B strain (data not shown).

Example 12

Octet Cross Competition of Anti-RSV-F Antibodies for Binding to RSV-F

Binding competition between a panel of anti-RSV-F mAbs was determined using a real time, label-free bio-layer interferometry assay on an Octet® HTX biosensor (Pall ForteBio Corp.). The entire experiment was performed at 25° C. in HBST kinetics buffer (0.01 M HEPES pH7.4, 0.15M NaCl, 3 mM EDTA, 0.05% v/v Surfactant Tween-20, 0.1 mg/ml BSA) with the plate shaking at the speed of 1000 rpm. To assess whether two antibodies are able to compete with one another for binding to their respective epitopes on the recombinant RSV-F protein expressed with a C-terminal myc-mycx-hexahistidine tag (RSV-F-mmH), around 0.36 nm of RSV-F-mmH was first captured onto anti-Penta-His antibody coated Octet bioessors (Fortebio Inc, Cat#18-5079) by submerging the biosensors for 3 minutes into wells containing 10 μg/ml solution of recombinant RSV-F-mmH. The antigen captured biosensors were then saturated with the first anti-RSV-F monoclonal antibody (subsequently referred to as mAb-1) by dipping into wells containing 100-200 μg/mL solution of mAb-1 for 10 minutes. The biosensors were then subsequently dipped into wells containing 100-200 μg/mL solution of second anti-RSV-F monoclonal antibody (subsequently referred to as mAb-2) for 5 minutes to check for mAb-2 binding to RSV-F-mmH, which is pre-bound to mAb-1. The biosensors were washed in HBST kinetics buffer in between each step of the experiment. The real-time binding response was monitored throughout the course of the experiment and the maximum binding response for all the steps was recorded. The response of mAb-2 binding to RSV-F-mmH pre-bound with mAb-1 was measured and competitive/non-competitive behavior of different anti-RSV-F monoclonal antibodies was determined.

Results

Sequential binding studies performed on Octet® HTX demonstrate that none of the anti-RSV-F monoclonal antibodies compete with each other and are able to bind non-competitively to RSV-F-mmH. As shown in Table 16, dark grey boxes with black font indicate the binding response for self-competition. No competition between antibodies that suggest a distinct binding epitope is represented as a white box with black font. Binding of the first anti-RSV-F monoclonal antibody (mAb-1) to the anti-His-captured RSV-F-mmH protein does not prevent the binding of the second anti-RSV-F monoclonal antibody (mAb-2). For all the anti-RSV-F monoclonal antibodies in this study, the observed mAb-2 binding signal was found to be comparable to that observed in the absence of mAb-1 (No mAb). Moreover, the observed binding of mAb-2 for all the anti-RSV-F monoclonal antibodies was found to be independent of the order of binding of anti-RSV-F antibody; suggesting that all the anti-RSV-F antibodies under investigation have distinct binding epitopes.

| Cross-competition between anti-RSV-F monoclonal antibodies. |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Amount of            | Amount of            | Binding of mAb-2 to  |
| mAb-1                | Std Dev (nm)         | the Pre            |
|                      | Captured =           | complex of Captured |
|                      | Binding (nm)         | RSV-F-mmH & mAb-1  |
|----------------------|----------------------|----------------------|----------------------|----------------------|
| Comparator III       | 0.36 ± 0.01          | 0.33 ± 0.01          | 1 (0.01)             | 0.34 0.44 0.00      |
| (AM-22)              |                      |                      |                      |                      |
| HI13592F3            | 0.36 ± 0.01          | 0.35 ± 0.01          | 2 0.26 (0.00)        | 0.30 0.00           |
| Comparator I         | 0.39 ± 0.01          | 0.45 ± 0.02          | 3 0.29 0.23 (0.03)   | -0.01               |
| (Palivizumab)        |                      |                      |                      |                      |
| No mAb               | 0.36 ± 0.01          | -0.01 ± 0.01         | 4 0.20 0.17 0.36 (0.00) |                      |

SEQUENCE LISTING

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tctggcaag gcgttgagtg gttgaggggg ttcaacccgca ttcttgat tac tgcaacatc
agcgaaaggt tccagggagc aataaegatc acctgtggag ctcacagggg cccagttgct
agggactgta gcgtcaggtag acctgacgac aaggggtgtg attacgcccc gggactggag
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Thr Leu Ser Asn Asn
20  25  30
Ala Phe Ser Trp Val Gin Ala Pro Gly Gin Gly Leu Glu Trp Leu
35  40  45
Gly Gly Phe Asn Pro Ile Phe Asp Thr Ala Asn Tyr Ala Gin Lys Phe
50  55  60
Gln Gly Arg Ile Thr Ile Thr Leu Asp Ala Ser Thr Gly Thr Val Tyr
65  70  75  80
Met Gly Leu Ser Ser Leu Arg Ser Glu Asp Thr Gly Val Tyr Cys
85  90  95
Ala Gly Thr Gly Ala His Phe Glu Phe Trp Gly Gin Gly Thr Leu Val
100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
115 120

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<400> SEQUENCE: 3
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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ggaaaaacccc tcttgctcct gatctctatg gcactcaacgt tacaaagtgg ggttccatca 180
aggtcatctg gcaagctgctg tggcagcatgtctcctca cccacgcag ctctgcaacct 240
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Asp Arg Val Thr Ile Thr Cys Arg Thr Ser Gln Ser Ile Ser Thr Tyr
20 25 30
Leu Asn Trp Tyr Gln Gin Lys Pro Gly Lys Ala Pro Lys Phe Leu Ile
35 40 45
Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin Ser Val Ser Val Pro Tyr
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Thr Phe Gly Gin Gly Thr Lys Leu Glu Ile Lys
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 1   5

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 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
  20  25   30
Gly Met His Trp Val Arg Gin Ala Pro Gly Lys Gly Leu Glu Trp Val
  35  40   45
Thr Phe Ile Trp Ser Asp Gly Ser Asn Lys Tyr Tyr Leu Asp Ser Val
  50  55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Asn Ser Asn Thr Leu Tyr
  65  70   75   80
Leu Gin Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
  85  90   95
Ala Arg Ser Gly Leu Ala Ser Tyr Tyr Gly Met Asp Val Trp
 100 105 110
Gly Gin Gly Thr Val Thr Val Ser Ser
 115 120

Gln Gln Ser Val Ser Val Pro Tyr Thr
 1   5

Gln Val Gin Leu Val Glu Ser Gly Gly Val Val Gin Pro Gly Arg
 1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
  20  25   30
Gly Met His Trp Val Arg Gin Ala Pro Gly Lys Gly Leu Glu Trp Val
  35  40   45
Thr Phe Ile Trp Ser Asp Gly Ser Asn Lys Tyr Tyr Leu Asp Ser Val
  50  55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Ser Asn Ser Asn Thr Leu Tyr
  65  70   75   80
Leu Gin Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
  85  90   95
Ala Arg Ser Gly Leu Ala Ser Tyr Tyr Gly Met Asp Val Trp
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 22

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<210> SEQ ID NO 23
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<210> SEQ ID NO 24
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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 24

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1     5     10     15

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gggagaccc ctcagcgcct gatctatggt gcacccagtt tgcaasgtag ggtcgcgtca 180
aggtttcagcg caagtggtata gggcaagga aatctcttca ctaatcagcag cctgcagcct 240
gagagattgg ccacatttcg cttctacag cataaaggt aacgctggac gttcggccaa 300
gggcaccagg tggaacatcga a 321

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<212> TYPE: PRT
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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1  5 10 16
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Aen Amp
20 25 30
Leu Gly Trp Tyr Glu Gln Lys Pro Gly Ala Pro Lys Arg Leu Ile
35 40 45
Tyr Gly Ala Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Arg Phe Ala Thr Tyr Ser Cys Leu Glu His Aen Ser Tyr Pro Trp
85 90 95
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

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<210> SEQ ID NO 29
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<223> OTHER INFORMATION: Synthetic

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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<210> SEQ ID NO 31
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 31
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<210> SEQ ID NO 32
<211> LENGTH: 9
<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 32
Leu Gln His Asn Ser Tyr Pro Trp Thr
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<210> SEQ ID NO 33
<211> LENGTH: 366
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cgagggggg ggcgtggagtc gttggatatt ctatggagtg atgggaagtaa taacactat 180
gcagcttcg cgggggaggt atctacact ctccagaga atcctccagaa aacattgat 240
tggaattgta attgggttgag agcgaggagc agtgttggtag atactgtgct gagagttgaa 300
cgtgccctc actatata caagcgaggc gttggggggt aagggaccac ggtgcccgtc 360
tctca 366

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30
Gly Met His Thr Val Arg Gin Ala Pro Gly Lys Gly Leu Glu Trp Val
Val Phe Leu Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val
50 55 60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Cys
85 90 95
Ala Arg Ser Gly Leu Ala Ser Tyr Tyr Tyr Ser Met Asp Val Trp
100 105 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

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<212> TYPE: PRT
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<212> TYPE: DNA
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<212> TYPE: PRT
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<210> SEQ ID NO 41
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agcagcagag cagccagag cagccagag cagccagag cagccagag 240
gagcagcagag cagccagag cagccagag cagccagag cagccagag 300
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<400> SEQUENCE: 42

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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20  25  30
Leu Ala Trp Tyr Gln Gln Pro Gly Lys Ala Pro Lys Arg Leu Ile
35  40  45
Tyr Gly Ala Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50  55  60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65  70  75  80
Glu Asp Phe Ala Thr Tyr Ser Cys Leu Gln His Asn Ser Tyr Pro Trp
85  90  95
Thr Phe Gly Gln Gly Thr Lys Val Gly Ile Lys
100 105

<210> SEQ ID NO 43
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 43

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<212> TYPE: PRT
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1   5   10   15
Ser Val Lys Val Ser Cys Ala Ser Gly Tyr Thr Leu Thr Gly Tyr
20  25  30
Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gin Gly Leu Glu Trp Met
35  40  45
Gly Trp Ile Asn Pro Thr Ser Gly Gin Gly Thr Asn Tyr Ala Gin Lys Phe
50  55  60
Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Ala Ala Phe
65  70  75  80
Met Glu Leu Ser Arg Leu Arg Ser Asp Thr Ala Val Tyr His Cys
85  90  95
Ala Arg Gln Phe Trp Pro His Gly Met Asp Val Trp Gly Gin Gly Thr
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Thr Val Thr Val Ser Ser
110 115

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<223> OTHER INFORMATION: Synthetic

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24

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<211> LENGTH: 8
<212> TYPE: PRT
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<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 52
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<223> OTHER INFORMATION: Synthetic

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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Ile Aen Pro Thr Ser Gly Gly Thr
1  5

gcgagagaaat ttgcccocca cggtatgagc gtc
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<210> SEQ ID NO: 55
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
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Ala Arg Glu Phe Trp Pro His Gly Met Asp Val
1  5  10

gccatcaggag tgaccaagtgc ctcatctccc ctgctgtgctc ctagagaga caagactgcc 60
atcactggt gcggcagctg aagattttag gctggtatcag gcagaaacc 120
gggaaagcc ctaatgctcttgcatc aactaagttgc ggctccctca 180
aggttctggct gcagagcttgat ctcagcttca ccaagctgac ccgctgctcc 240
gacctatttg cactttctta cctctctggag aatctacaa cagctggtgac gttggcacc 300
gggccacagg tggaaatcaca 321

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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 57

<210> SEQ ID NO: 58
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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Ala Ile Gin Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1  5  10  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Ala Ile Arg Aen Asp
20 25 30

Leu Gly Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ser Ser Ser Leu Gin Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Glu Asp Phe Ala Thr Tyr Cys Leu Ala Asp Tyr Lys Thr Trp
85  90  95
Thr Phe Gly Glu Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 59
<211> LENGTH: 18
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 59
cagggcatta gaaatgt

<210> SEQ ID NO 60
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 60
Gln Ala Ile Arg Arg Arg
1  5

<210> SEQ ID NO 61
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 61
gcttcatcc

<210> SEQ ID NO 62
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 62
Ala Ser Ser
1

<210> SEQ ID NO 63
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 63
cttgcaagtt acataaac gttgacg

<210> SEQ ID NO 64
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
Leu Ala Asp Tyr Lys Tyr Thr Trp Thr
<210> SEQ ID NO 65
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: Synthetic

<400> SEQUENCE: 65

gaggtgcacc ctggtaacgc ttggggagcc ttagtacacc cggggggttc cctgaaagtc 60
tcgtagaag ctctcgagtt cacacttagc agccatgtca tgacgccggt cgcccaaggt 120
ccagggcaag ggctcgagtt gatctggagt atacgtgggc ctgggttctag tcaaaagtat 180
ggacatcccg tgcaggggcg gttcaccaacc tccagagaca actcaaagaa caccctgtat 240
tccaaattg acacogctgtg acgcagagac ttgctgcat atacgtgcc gaaagggggg 300
ggtatagtgg gtagcagattg ggtcattttag tgcgtgttag gcgttcggggg ccaggagacc 360
acgctcacc tcctctca 378

<210> SEQ ID NO 66
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE: Synthetic

<400> SEQUENCE: 66

Glu Val Gin Leu Val Glu Gly Gly Leu Val His Pro Gly Gly
1  5  10  15
Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Ser Ser His
20  25  30
Val Met Ser Trp Val Arg Glu Val Pro Gly Lys Leu Glu Trp Val
35  40  45
Ser Arg Ile Ser Gly Pro Gly Gly Ser Thr Lys Tyr Ala Asp Ser Val
50  55  60
Gln Gly Arg Phe Thr Thr Ser Arg Asp Ser Lys Asn Thr Leu Tyr
65  70  75  80
Leu Gin Met Asn Ser Leu Ile Ala Glu Asp Ser Ala Ala Tyr Tyr Cys
85  90  95
Ala Lys Gly Gly Gly Tyr Ser Gly Tyr Asp Trp Asp Phe Tyr Tyr Gly
100 105
Met Asp Val Trp Gly Gin Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 67
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: Synthetic
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 67

gcattcacc tcagacgcc tgc 24

<210> SEQ ID NO 68
<211> LENGTH: 8
<212> TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE: 
OTHER INFORMATION: Synthetic

SEQUENCE: 68
Gly Phe Thr Leu Ser Ser His Val
1 5

SEQ ID NO 49
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: 
OTHER INFORMATION: Synthetic

SEQUENCE: 69
atcaagtgtc ctggggttag tagc 24

SEQ ID NO 70
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE: 
OTHER INFORMATION: Synthetic

SEQUENCE: 70
Ile Ser Gly Pro Gly Gly Ser Thr
1 5

SEQ ID NO 71
LENGTH: 57
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: 
OTHER INFORMATION: Synthetic

SEQUENCE: 71
gggaasgggg ggggataag tggctacag tgggactttt attacggtat gggagtc 57

SEQ ID NO 72
LENGTH: 19
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE: 
OTHER INFORMATION: Synthetic

SEQUENCE: 72
Ala Lys Gly Gly Tyr Ser Gly Tyr Asp Thr Asp Phe Tyr Tyr Gly
1 5 10 15
Met Asp Val

SEQ ID NO 73
LENGTH: 321
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE: 
OTHER INFORMATION: Synthetic

SEQUENCE: 73
gacaccaaa tgaccagtc tccatcttcc gtgtctgcag ctgtaggaga caggctcacc 60
atcaagtgtc ggggaggtca gggtagttag agctgtgatt gctggtatca gocgaaacc 120
gggaaagcc ctaagcttct gatctagct gcattcaggt tgcgaagttg ggctccctca 180
aggtttaggg gcaatgggtc tgtggcgagtt ttcctcttca cctccagcg ctgtagggct 240
gaagatttgt caaactacta tgctcaacag actaacagtt toctotoac ttctggcgga 300

<210> SEQ ID NO: 74
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 74
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly 1 5 10 15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ile Ser Ser Trp 20 25 30
Leu Ala Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile 35 40 45
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly 50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro 65 70 75 80
Glu Asp Phe Ala Thr Tyr Cys Gin Gin Thr Asn Ser Phe Pro Leu 85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys 100 105

<210> SEQ ID NO: 75
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 75
caggtataga gcagctggg 18

<210> SEQ ID NO: 76
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 76
Gln Gly Ile Ser Ser Trp 1 5

<210> SEQ ID NO: 77
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 77
gctgcatcc 9

<210> SEQ ID NO: 78
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 78
Ala Ala Ser
1

<210> SEQ ID NO: 79
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 79
cacactgacta acagtttcct tctcact 27

<210> SEQ ID NO: 80
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 80
gln gln thr asn ser phe pro leu thr
1 5

<210> SEQ ID NO: 81
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 81
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tctgtgcagc ctgggtgcagc ctgggtgcagc tgggtgcagc gttggaagct ctgggttcct gcgtgaggtc 120
cggtgaggtc cgggtgccgt gcgtgaggtc atctcccct ctccttggcct agggataa 180
gcactgaggtg cacggtgcagc gagcgtgaggtc atctcccct ctccttggcct agggataa 240
gcaggtgactgc tgggtgcagc gttggaagct ctgggttcct gcgtgaggtc atctcccct ctccttggcct agggataa 300
gcaggtgactgc tgggtgcagc gttggaagct ctgggttcct gcgtgaggtc atctcccct ctccttggcct agggataa 360
tcctca 366

<210> SEQ ID NO: 82
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 82
gln val gln leu val gln ser gly ala glu val lys lys ser gly ser
1 5 10 15
ser val lys ser ser cyr lys ala ser gly thr phe ser ser tyr
20 25 30
ala ile ser tyr val arg ala pro gly gln gly leu glu trp met
35 40 45
gly gly ile ile pro ile phe gly thr gly amn tyr ala gln lys phe
50 55 60
gln gly arg val thr ile thr thr arg ser thr thr ser thr ala tyr
65 70 75 80
<210> SEQ ID NO 83
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 83

ggagggccct tcagagcata tgtc 24

<210> SEQ ID NO 84
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 84

Gly Gly Thr Phe Ser Ser Tyr Ala
1 5

atcacccct tcttggctac agga 24

<210> SEQ ID NO 86
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 86

Ile Ile Pro Ile Phe Gly Thr Gly
1 5

<210> SEQ ID NO 87
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 87
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<210> SEQ ID NO 88
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
Ala Arg Asp Ser Ser Ser Ser Pro Arg Tyr Tyr Gly Met Asp Val
1 5 10 15

-G-SE-QUENCE: 89

<210> SEQ ID NO 89
<211> LENGTH: 121
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

-G-SE-QUENCE: 89

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tctcttcgca ggccagctca gagtcttacc agcactctag cctgttacc aacagaaaact 120
ggcccagctc cagctttctcc catctatgat gttacccaaga ggccacaggg cctcctcagc 180
gaggctagtg caagtggtcgt tgccacagac ttcactctca cccatcagccg ccctagcct 240
ggsatatttg ccactactta gttctcagcag cgtagcaact ggctctccac cctcgccaa 300
ggcccagcc cggagattaa a 321

-G-SE-QUENCE: 90

Glu Ile Val Leu Thr Gin Ser Pro Ala Thr Leu Ser Ser Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gin Ser Val Thr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gin Gin Lys Pro Gly Gin Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Val Ser Lys Arg Ala Thr Gin Gin Pro Arg Gin Pro Gin Lys
50 55 60

Ser Gin Ser Gin Thr Gin Ser Gin Ser Gin Pro Ser Ser Ser Leu Ser Glu Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin Arg Ser Asn Trp Pro Pro
85 90

Thr Phe Gin Gin Thr Gin Thr Gin Gin Thr Arg Leu Gin Ile Lys
100 105

-G-SE-QUENCE: 91

<210> SEQ ID NO 91
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

-G-SE-QUENCE: 91

cagactgtta ccagctac 19

-G-SE-QUENCE: 92

<210> SEQ ID NO 92
<211> LENGTH: 6
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 92
Gln Ser Val Thr Ser Tyr
1  5

<210> SEQ ID NO 93
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 93
gatgtatcc 9

<210> SEQ ID NO 94
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 94
Amp Val Ser
1

<210> SEQ ID NO 95
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 95
cagcaggtgaaactgagcc toccaccc 27

<210> SEQ ID NO 96
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 96
Gln Gln Arg Ser Aem Trp Pro Pro Thr
1  5

<210> SEQ ID NO 97
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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tcttctgaag cctcggatt cacctttgag acctattgga tgagttgggt cagccaggtc 120
cgagggagg gtcagaggtg gtcgagcaac ataaaaacag atgggaatgt gaatatcttt 180
gcagcttg tgaaggcccc atccaagccc tccagagaca acggcaagaa ctccctgtat 240
tctgcaatga acacgtctag agccggaagc acggctctgt atcactgtgc gagagagagg 300
cacaggggga gtaactagcc atcactagac ggtatggagc tctggggctca agggccacag 360
gtcaagctct cctca 375
Glu Val Gln Leu Val Gln Ser Gly Gly Leu Val Gln Pro Gly Gly
1    5    10    15
Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20   25   30
Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Leu Glu Trp Val
35   40   45
Ala Asn Ile Lys Gln Asp Gly Ser Val Lys Tyr Phe Val Asp Ser Val
50   55   60
Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Gln Thr Ala Leu Tyr His Cys
85   90   95
Ala Arg Glu Arg His Arg Gly Ser Tyr Tyr Gly Tyr Tyr Asp Gly Met
100 105 110
Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

ggattcaccct ttgtaacca ttcgg 24

Gly Phe Thr Phe Ser Thr Tyr Trp
1    5

ataaatcaag atggagatgt gaa 24

Gly Phe Thr Phe Ser Thr Tyr Trp
1    5

ataaatcaag atggagatgt gaa 24
<400> SEQUENCE: 102
Ile Lys Gin Asp Gly Ser Val Lys
1  5

<210> SEQ ID NO 103
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 103
ggcggagaga ggccagacgg agcttactac ggcttactcg acggtatgga cgtc 54

<210> SEQ ID NO 104
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 104
Ala Arg Glu Arg His Arg Arg Gly Ser Tyr Tyr Gly Tyr Tyr Asp Gly Met
1  5  10  15
Amp Val

<210> SEQ ID NO 105
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 105
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atccatggc gggcaagtca aaccattggc atctatttt atctgtaacct cggagggcca 120
ggggagcgtcc caatcctcttc ctgtctgct ctgtaaagtgg ggtcccatca 180
aggtctagag gcaggtgata ccgagcagat ttcatctcttc ccctcaatag tagctgcaacct 240
gacaggttgg cagccttacct acgtcagacg aagttacatt ccccttcctg cttcgccggc 300
ggacccaggg ttggagtccaa a 321

<210> SEQ ID NO 106
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 106
Amp Ile Gin Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1  5  10  15
Amp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Asn Ile Asp Ile Tyr
20  25  30
Leu Asn Thr Tyr Gin Glu Arg Pro Gly Lys Ala Pro Asn Leu Leu Ile
35  40  45
Tyr Ala Ala Ser Leu Gin Ser Gly Val Pro Ser Arg Phe Ser Gly
50  55  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
65  70  75  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin Ser Tyr Asn Thr Pro Phe
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 107
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 107

casacattg acatotat
18

<210> SEQ ID NO 108
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 108

Gln Asn Ile Asp Ile Tyr
1 5

<210> SEQ ID NO 109
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 109

gtgcacatcc
9

<210> SEQ ID NO 110
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 110

Ala Ala Ser
1

<210> SEQ ID NO 111
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 111

cacacaggtt acaatactcc gttcact
27

<210> SEQ ID NO 112
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 112

Gln Gin Ser Tyr Asn Thr Pro Phe Thr
<210> SEQ ID NO 113
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 113

gaagtgcagc tggtagagtc tgggggaggc tggatcacgc tggcagggc cctgagactc

<210> SEQ ID NO 114
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 114

Glu Val Gin Leu Val Glu Gly Gly Gly Leu Val Gin Pro Gly Arg
1   10
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Aep Tyr
10  25
Ala Met His Trp Val Arg Gin Thr Pro Gly Lys Glu Leu Glu Trp Ile
25  40
Ser Gly Ile Ser Trp Ser Ser Gly Thr Ile Val Tyr Ala Asp Ser Val
40  55
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
55  70
Leu Gin Met Asn Ser Leu Arg Gly Glu Asp Thr Ala Leu Tyr His Cys
70  90
Ala Lys Asp Gly Tyr Arg Trp Lys Ser Tyr Ser Tyr Gly Leu Aep Val
90 105
Trp Gly Gin Gly Thr Val Thr Val Ser Ser
105 120

<210> SEQ ID NO 115
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 115

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<400> SEQUENCE: 116
Gly Phe Thr Phe Asp Asp Tyr Ala
1  5

<210> SEQ ID NO 117
<211> LENGTH: 24
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<213> ORGANISM: Artificial Sequence
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<400> SEQUENCE: 117
attagttgga gtagtggtac cata 24

<210> SEQ ID NO 118
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 118
Ile Ser Trp Ser Ser Gly Thr Ile
1  5

<210> SEQ ID NO 119
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 119
gcaaagagtg ggtattggtg gaagtoctac tcgtaaggt tcgaagtc 48

<210> SEQ ID NO 120
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 120
Ala Lys Asp Gly Tyr Arg Trp Lys Ser Tyr Ser Tyr Gly Leu Asp Val
1  5  10  15

<210> SEQ ID NO 121
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 121
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cttctctgca ggccagctca gattgtttc aatacctag cttgtaacca gcagggccct 120
ggcggagctc ccaagactct cttctttggt gcctctctca gggcctcaggg tattccagcc 180
tagattagtt gctagtggtgc tgggcaagag ttatctctca cctcaagcag cttgagctc 240
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cagcagtata ataaatgacc gctcacc 27

<210> Seq ID No: 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 128

gln gln tyr aen aen trp pro leu thr 1 5

<210> Seq ID No: 129
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 129
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tctctgtgat cctcttgatt caccttgtat gattatgcca tgcacttggt cggccgact 120
cccagggaag gcgtggaagt ggtctcgagtt gtagttgaa gttgtagtac cgttagctat 180
ggccttgctg tcgagcctgc cttcagagac aagccccaga aacccattgt atccttgtat 240
tcacaatg gacgtgctgc agctgcaagc acggcctgtg attacgtggt aaagagcgcg 300
tataatcgtg gactacta taacgttttg gacgtctggg gccaaggggc caacgctcacc 360
gctctca 369

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<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 130

glu val gln leu val glu ser gly gly asp leu val gln pro gly arg 1 5 10 15
ser leu arg leu ser cys val ala ser gly phe thr phe asp tyr 20 25 30
ala met his trp val arg gln ala pro gly lys gly leu glu trp val 35 40 46
ser gly val ser trp gly ser thr val gly tyr ala asp ser val 50 55 60
lys gly arg phe thr val ser arg asp asn ala gln lys ser leu tyr 65 70 75 80
leu glu met asn ser leu arg ala glu asp thr ala leu tyr tyr cys 85 90 94
val lys asp ala tyr lys trp aen tyr tyr tyr gly leu asp val
Trp Gly Gin Gly Thr Thr Val Thr Val Ser Ser

115

120

<210> SEQ ID NO 131
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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 131

ggattcact ttgatgatta tgcc

24

<210> SEQ ID NO 132
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 132

Gly Phe Thr Phe Aep Aep Tyr Ala

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<210> SEQ ID NO 133
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 133

gttagtgga gtgtagtagc cgta

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<210> SEQ ID NO 134
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 134

Val Ser Trp Ser Gly Ser Thr Val

1

5

<210> SEQ ID NO 135
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 135

gttaaatcgcttcaatgtgacatcattacgttttgagtc

48

<210> SEQ ID NO 136
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 136

Val Lys Aep Ala Tyr Lys Trp Asn Tyr Tyr Tyr Gly Leu Aep Val

1

5

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<210> SRQ ID NO 137
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 121

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tccctctgca gggccagtca gactattcct agcaacctag cctagtacct acagaaacct 120
ggccagctc ccagctctct catctatgtg gcacccacca gggccacttg ttccgcagcc 180
aggtcagtg gcagttggttc tggaagcagag tcctcactca ccacgagag cctgcagctc 240
gaatgttgtg cagtttattta ctcgcagcag tataaatact ggcctctcacc ttccgcagga 300
ggccacagc tgtgagacaa a 321

<210> SRQ ID NO 138
<211> LENGTH: 197
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 197

Glu Ile Val Met Thr Gin Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
  1   5  10  15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gin Thr Ile Leu Ser Asn
  20  25 30
Leu Ala Trp Tyr Leu Gin Gly Pro Gly Gin Ala Pro Arg Leu Leu Ile
  35  40  45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Leu Pro Ala Arg Leu Ser Gly
  50  55  60
Ser Gly Ser Gly Thr Gin Phe Thr Leu Thr Ile Ser Ser Leu Gin Ser
  65  70  75  80
Glu Asp Phe Ala Val Tyr Tyr Cys Gin Gin Tyr Asn Asn Trp Pro Leu
  85  90  95
Thr Phe Gly Gly Gly Thr Lys Val Gin Ile Lys
100 105

<210> SRQ ID NO 139
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 18

cagacttt tcagcaac 19

<210> SRQ ID NO 140
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 6

Glu Thr Ile Leu Ser Asn
1   5
<210> SEQ ID NO 141
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 141

ggtgcattc 9

<210> SEQ ID NO 142
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 142

Gly Ala Ser
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<210> SEQ ID NO 143
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 143
cagcagcata ataaotggcc ttcact 27

<210> SEQ ID NO 144
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 144

Gln Gln Tyr Asn Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 145
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 145
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tccgtggag cctctggatt cacctttagg gaccttgaca tgaatggtgctcgctaggtc 120
cggggaggg gctctgagtg gctctgaggt atctggtgaga ctgggtgattac 180
gcaacggcg tgaagggcggt tctacaactata tocagggacat atctaaaaa caacggttgtt 240
tctcataagc gcacccgctgcagcagggccagtctgttta atctctgtgtaa 300
tatggtctagc atagagaacta taaggggcag gacggtgtgg gccaagggc caacgcctc 360
gtcctctca 369

<210> SEQ ID NO 146
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 146

Glu Val Gin Leu Val Gin Ser Gly Gly Gly Leu Val Gin Pro Gly Gly
1  5  10  15
Ser Leu Arg Leu Ser Cys Gly Ala Ser Gly Phe Thr Phe Arg Asp Phe
20  25  30
Asp Met Asn Trp Val Arg Gin Ala Pro Gly Arg Gly Leu Gin Trp Val
35  40  45
Ser Gly Ile Gly Gly Ser Gly Ser Gly Thr Tyr Ala Asp Ser Val
50  55  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Arg Ser Lys Asn Thr Leu Phe
65  70  75  80
Leu Gin Met Ser Ser Leu Arg Ala Gin Thr Ala Val Tyr Tyr Cys
85  90  95
Val Lys Asp Pro Tyr Gly Asp Tyr Arg Asn Tyr Tyr Gly Met Asp Val
100 105 110
Trp Gly Gin Gly Thr Thr Val Thr Val Thr Val Ser Ser
115 120

SEQ ID NO 147
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 147

gtattcaacct ttagggacct tgac

SEQ ID NO 148
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 148

Gly Phe Thr Phe Arg Asp Phe Asp
1  5

SEQ ID NO 149
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 149

attgtgsta gtgggtgtaa caca

SEQ ID NO 150
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 150

Ile Gly Gly Ser Gly Gly Asn Thr
1  5
<210> SEQ ID NO 151
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 151

gtgaagatgcctatgggctgaatagggacttaactggta gggcagtc

<210> SEQ ID NO 152
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 152

Val Lys Asp Pro Tyr Gly Asp Tyr Arg Asn Tyr Gly Met Asp Val
1  5  10  15

<210> SEQ ID NO 153
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 153

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acctcctgca gactcctca actatgaatg gataacaota tttcgatgta
120
taactcctgaga agcagggcga gctctccacaa etctctagat atttcgttct taactcgggcc
180
tccggtgctcc tgctccagtt cgcgggcaat ggtacgaca aggacctttac actggaaatctc
240
agcagagctgg ggcctgcggga tggctgggtt tattactgca tgcagacgcc acaaaactatc
300
accttcgcc aaggcaagc agctggagatt aas
333

<210> SEQ ID NO 154
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 154

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1  5  10  15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20  25  30

Asp Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35  40  45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50  55  60

Asp Arg Phe Arg Gly Ser Gly Ser Asp Lys Asp Phe Thr Leu Lys Ile
65  70  75  80

Ser Arg Val Gly Ala Glu Asp Val Gly Val Tyr Cys Ser Gly Ala
85  90  95

Leu Gln Thr Ile Thr Phe Gly Gin Gly Thr Arg Leu Gln Ile Lys
100 105 110
<210> SEQ ID NO 155
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 155

cagagcttc tacatagtaa tggtacasc tat

<210> SEQ ID NO 156
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 156

Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr
1  5

<210> SEQ ID NO 157
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 157

ttggttct

<210> SEQ ID NO 158
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 158

Leu Gly Ser
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<210> SEQ ID NO 159
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 159

atgcaagctc tacaacctat cacc

<210> SEQ ID NO 160
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 160

Met Gln Ala Leu Gln Thr Ile Thr
1  5

<210> SEQ ID NO 161
<211> LENGTH: 169
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: Synthetic

<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 161

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cagggaagcg gctgaggtg ggctcaact atctctgata gttgggataac cacatatac 180
cgacactcc gcgaaggcgg gttacaactc tccagggaat attcagaaaa cacatgtaat 240
tggcataata cagagctgag agcgagagcc acggcgagttt atactgtgc gaagatcc 300
tattgtgact acaggacact atcaggtgatg gacgtctggg ggcaagggac caggtcacc 360
gtctctca 369

<210> SEQ ID NO: 162
<211> LENGTH: 123
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: Synthetic

<400> SEQUENCE: 162

Glu Val Gin Leu Val Glu Ser Gly Gly Leu Gly Gin Pro Gly Gly
1      5
Ser Leu Arg Leu Ser Cys Gly Ala Ser Gly Phe Met Phe Arg Aam Tyr
20     25
Ala Met Ser Trp Val Arg Gin Ala Pro Gly Lys Gly Leu Glu Trp Val
35     40
Ser Thr Ile Leu Aap Ser Gly Asp Aam Thr Tyr Tyr Ala Aas Aam Aam Ser Val
50     60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Aam Ser Lys Aas Aam Thr Leu Tyr
65     70
Leu Gin Met Aam Ser Leu Arg Ala Glu Aas Thr Ala Val Tyr Tyr Cys
85     95
Ala Lys Aas Pro Tyr Gly Asp Tyr Arg Asp Aam Tyr Aam Gly Met Aap Val
100    110
Trp Gly Gin Gly Thr Thr Val Val Ser Ser
115    120

<210> SEQ ID NO: 163
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: Synthetic

<400> SEQUENCE: 163

gatccagt tgttacacta tgcg 24
<210> SEQ ID NO: 165
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 165

atcttgata gctggatcaca

<210> SEQ ID NO: 166
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 166

Ile Leu Asp Ser Gly Asp Asn Thr
1  5

<210> SEQ ID NO: 167
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 167
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<210> SEQ ID NO: 168
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 168

Ala Lys Asp Pro Tyr G1y Asp Tyr Arg Asp Tyr Gly Met Asp Val
1  5 10 15

<210> SEQ ID NO: 169
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 169
gatattgga tgatcgacg tcgctctcc ctgacgccgc ccaatggcgaa gcccgtctcc
acctctgctc ggtctagctc gacccactca cagataactg gataactgatct tttggattgg
acttctgcgag cccggagcgg ttctctgcta ctgctcttct tttggttct tatactgggcc
tcgggtctc gtcacaggtt cagggctgat gatacggtcg aaagacttttt tctgagatctc
tgctacctg tggacttaga acaaacatc ctgctacgat tcaaatcctc ctgctacgatc
tgccgagc agctgctggg tcaagatag acaaacatc ctgctacgatc

<210> SEQ ID NO: 170
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 170
Asp Ile Val Met Thr Gin Ser Pro Leu Ser Leu Pro Val Thr Pro Gly  
 1  5  10  15
Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gin Ser Leu Leu His Ser  
 20  25  30
Asn Gly Tyr Asn Tyr Leu Asp Thr Tyr Leu Gin Lys Pro Gly Gin Ser  
 35  40  45
Pro Gin Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gin Val Pro  
 50  55  60
Asp Arg Phe Arg Gly Ser Gly Ser Gly Lys Asp Phe Thr Leu Lys Ile  
 65  70  75  80
Ser Arg Val Gin Ala Gin Gin Val Gin Leu Tyr Tyr Cys Met Gin Ala  
 85  90  95
Leu Gin Thr Ile Thr Phe Gly Gin Gin Thr Arg Leu Gin Ile Lys  
100 105 110

<210> SEQ ID NO 171
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 171
cagagctgcc tatactagtaa tgtatacaac tat  
<210> SEQ ID NO 172
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 172
Gln Ser Leu Leu His Ser Asn Gin Tyr Asn Tyr  
1  5  10
<210> SEQ ID NO 173
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 173
tgaggtctc  
<210> SEQ ID NO 174
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 174
Leu Gly Ser  
1
<210> SEQ ID NO 175
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 175

atgcaagctc tacaacatct cac

<210> SEQ ID NO: 176
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 176

Met Gln Ala Leu Gln Thr Ile Thr

<210> SEQ ID NO: 177
<211> LENGTH: 394
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 177

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acctgcaacgt tcctctgggg ctcctacagc ggtcactactt ggctcggat cggccagccc 120
ccagggaggg gactggaggtg gatggtattacttatgttatatgctggtgccac ccagctaac 180
ccctcccctca agaggtgtag cccacatatc ttagacactgt ccagagaaccc gttctccctg 240
aactgagcctctgtgagcgc gcctggtatt tatgtgctgag agatgggaaat 300
tcgagaatttt gagccgccttat gattttcactat cactattacc gcattccagcctg gggggccac 360
gggacacagcc tccactgccctc ctc

<210> SEQ ID NO: 178
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 178

Gln Val Gin Leu Gin Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu

1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Ser Ile Ser Gly Tyr

20 25 30

Tyr Trp Thr Trp Ile Arg Gin Pro Pro Gly Lys Gly Leu Glu Trp Ile

35 40 45

Gly Tyr Ile Tyr Ser Gly Ala Thr Aen Tyr Aen Pro Ser Leu Lys

50 55 60

Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys Aen Gin Phe Ser Leu

65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Cys Ala

85 90 95

Arg Asp Gly Aen Tyr Asp Ile Leu Thr Gly Tyr Aen Tyr His Tyr

100 105 110

Tyr Gly Met Asp Val Thr Gly Gin Gly Thr Thr Val Thr Val Ser Ser

115 120 125

<210> SEQ ID NO: 179
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 179

ggtggtccca tcagtggtta ctac 24

<210> SEQ ID NO 180
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 180

Gly Gly Ser Ile Ser Gly Tyr Tyr
1  5

<210> SEQ ID NO 181
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 181

atctattaca gtttggtgccac c 21

<210> SEQ ID NO 182
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 182

Ile Tyr Tyr Ser Gly Ala Thr
1  5

<210> SEQ ID NO 183
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 183

gcgagagat ggaattacga tattttgact gytstattata actaccacta ttagggcatg 60
gagcgc
66

<210> SEQ ID NO 184
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 184

Ala Arg Asp Gly Aen Tyr Asp Ile Leu Thr Gly Tyr Tyr Aen Tyr His
1  5  10  15

Tyr Tyr Gly Met Asp Val
20
<210> SEQ ID NO: 185
<211> LENGTH: 185
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 185

gscatcaga tgaccaagtc tcctacccct gcgtctgcat ctgtagcagc cagagtcacc
atcactgtc ggagcagctca ggcctgtgctt aattatattg cctcggtttcc gcgaaaccca
gggaaagccc ctcgagccct gcctgatgct gcataccattt tacaatatgg ggtccctatca
aagtctcagc gcgatgtgatc tggcgagcttc tcaactctcata cctcaagcgct ctgagccct
 gagaggtttg cacatttata ctcgcaacag tataaatatt tccctggtgac gtctggccaa
 ggagaccaag gagaaatccaa

<210> SEQ ID NO: 186
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 186

Asp Ile Gin Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
  1  5  10  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Asp Ile Gly Aen Tyr
  20  25  30
Leu Ala Trp Phe Gin Gin Lys Pro Gly Lys Ala Pro Glu Ser Leu Ile
  35  40  45
Tyr Ala Ala Ser Ile Leu Gin Ser Gly Val Pro Ser Lys Phe Ser Gly
  50  55  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
  65  70  75  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin Tyr Asn Thr Phe Pro Trp
  85  90
Thr Phe Gly Gin Gin Thr Lys Val Glu Ile Lys
  100 105

<210> SEQ ID NO: 187
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 187

cggacattg gttaattat

<210> SEQ ID NO: 188
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 188

Gln Asp Ile Gly Aen Tyr
  1  5

<210> SEQ ID NO: 189
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 189

gtcgaatcc

<210> SEQ ID NO 190
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 190

Ala Ala Ser

<210> SEQ ID NO 191
<211> LENGTH: 27
<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 191

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<210> SEQ ID NO 192
<211> LENGTH: 9
<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 192

Gln Gln Tyr Asn Thr Phe Pro Trp Thr

<210> SEQ ID NO 193
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 193

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tctgctgcc cctctggatt caccttcagt gactactaca tgaccttgat cgtcaggtc 120
caggttgggg gcctgagtgt ggtttcatac attaggtgta cttgcaagtac aatatactac 180
gcagactctg tgggggccc gccaccacat tccagggaca aagccaaaca aacactgtat 240
tgcaaatga acaacotsga agcccaggaac aogccctatt actattgtgct cgggtacag 300
gatgggggaa tgtgaactacg ttgtttgagct tactgggccc aaggaactct ggttaccggtc 360
tcota 366

<210> SEQ ID NO 194
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 194
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1     5     10    15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20    25    30
Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp Val
35    40    45
Ser Tyr Ile Ser Asp Thr Gly Ser His Leu Tyr Tyr Ala Asp Ser Val
50    55    60
Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65    70    75    80
Leu Gln Met Asn Asn Leu Arg Ala Gly Thr Ala Val Tyr Cys
85    90
Ala Arg Asp Gln Asp Gly Glu Met Gln Leu Arg Phe Phe Asp Tyr Trp
100   105   110
Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115   120

<210> SEQ ID NO: 195
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 195
gsattaccc tca tgtgacta ctac

<210> SEQ ID NO: 196
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 196
Gly Phe Thr Phe Ser Asp Tyr Tyr
1     5

<210> SEQ ID NO: 197
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 197
attagcata ctg cc gtc tca ctta

<210> SEQ ID NO: 198
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 198
Ile Ser Asp Thr Gly Ser His Leu
1     5

<210> SEQ ID NO: 199
<210> SEQ ID NO: 200
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 200

Ala Arg Asp Gln Asp Gly Met Glu Leu Arg Phe Asp Tyr

1   5

<210> SEQ ID NO: 201
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 201

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ctctctgca ggacgacgca gaccttatgc aactacttg cctgttaaca ccgagaaacct
ccgcacggctc cccggttctcc catcctgtgg gcatccaaaca ggcgaacgttg ccacccgcccc
aggtcctgct gcgtgggtgc ttggacacag ttctctctca ccattagccgattagacgct
agaatccggg cagctatata ctgctagcac cgtaccaacct ggccgcttocc ttcgggagg
ccggacctgg tagtagatccaa a

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<210> SEQ ID NO: 202
<211> LENGTH: 107
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 202

Glu Ile Val Leu Thr Gin Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1   5

Glu Arg Gly Thr Leu Ser Cys Arg Ala Ser Gin Ser Ile Asn Asn Tyr
10  15

Leu Ala Trp Tyr Gin Gin Lys Pro Gly Gin Ala Pro Arg Leu Leu Ile
20  25

Phe Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
30  35

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Ile Gly Pro
40  45

Glu Asp Phe Ala Val Tyr Tyr Cys Gin Gin Arg Thr Asn Trp Pro Leu
50  55

Thr Phe Gly Gly Thre Lys Val Glu Ile Lys
60  65

<210> SEQ ID NO: 203
<211> LENGTH: 18

<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 18

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 21

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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 33

<210> SEQ ID NO: 206
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 24

<210> SEQ ID NO: 207
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 27

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 23

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<212> TYPE: DNA
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<400> SEQUENCE: 20

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<212> TYPE: DNA
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 19

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 17

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 16

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<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 15

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<211> LENGTH: 14
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 14

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<211> LENGTH: 13
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 13

<210> SEQ ID NO: 218
<211> LENGTH: 12
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 12

<210> SEQ ID NO: 219
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<223> OTHER INFORMATION: Synthetic

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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<211> LENGTH: 8
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<211> LENGTH: 6
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Amp Ala Ser
1
<210> SEQ ID NO 207
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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 208
Gln Gln Arg Thr Aen Trp Pro Leu Thr
1
<210> SEQ ID NO 209
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 209

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acctcagta tcctcgtggg gtcatcagat attactaatt gggacttgat cgggcaacc 120
ccaggggaag gactgggaat gagttgatat atctattata gttggagac caagtacaa 180
ccctcttttt agagcagat cacatataa ctgtacagtt ccaagaacc gttctctctg 240
aacagctcat ctcgagagcc gctcggatct aactgtgagag agattgggat 300
gtacagcag ctgctcccc ttaaccctc cactaaggtg tygaagtttgt gggccacagg 360
accaaggtca cctgtctctc a 381

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 210

Gln Val Gin Leu Gin Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu  
1    5    10    15
Thr Leu Ser Leu Thr Tyr Val Ser Gly Gly Phe Ile Ser Asn Tyr  
20   25   30
Tyr Trp Ser Trp Ile Arg Gin Pro Pro Gly Lys Gly Leu Glu Trp Ile  
35   40   45
Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Lys Tyr Asn Pro Ser Leu Lys  
50   55   60
Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gin Phe Ser Leu  
65   70   75   80
Lys Leu Ser Ser Ser Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala  
85   90   95
Arg Asp Gly Val Val Ala Ala Gly Pro Pro Tyr His Tyr His Tyr  
100 105 110
Gly Leu Asp Val Trp Gly Gly Thr Val Thr Val Ser Ser  
115 120 125

<210> SEQ ID NO 211
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 211
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<210> SEQ ID NO 212
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 212

Gly Gly Phe Ile Ser Asn Tyr Tyr  
1    5

<210> SEQ ID NO 213
<211> LENGTH: 21

<210> SEQ ID NO 214
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 213
gcgagcagc tcagggcttgc caggtctgcgg caggtctgcgg caggtctgcgg 24
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<210> SEQ ID NO 214
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 214

Ile Tyr Tyr Ser Gly Ser Thr
1 5

<210> SEQ ID NO 215
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 215
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gtc

63

<210> SEQ ID NO 216
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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 216

Ala Arg Asp Gly Val Val Ala Ala Ala Gly Pro Pro Tyr His Tyr His
1 5 10 15
Tyr Gly Leu Asp Val
20

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<212> TYPE: DNA
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 217
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60
atcaacctca gtgcagcgca gaattttta tacacctca gcataagaa ctctttagct

120
tgtggcacg aggaaaccag acagccctct gcgtgctgca tttactgggc atetaccogg

180
gaatccgaggg tctctgaccg atccagtgcc agcggctctg ggcagagttt cattttcacc

240
atcagcagc tcgcagtgta agatgtggca gttttattact tgcagcata ttatatgtgt

300
cggggagt tggccaggg gcacaaaggt gcacaaaa

339

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**SEQ ID NO 219**

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Gln Gln Tyr Tyr Ser Ser Pro Trp Thr
1 5

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30
Tyr Met Thr Trp Ile Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45
Ser Tyr Ile Ser Ser Thr Gly Asn Arg Tyr Gly Asp Ser Val
50 55 60
Lys Gly Arg Phe Ala Ile Ser Arg Asp Ala Lys Asn Leu Leu Phe
65 70 75 80
Leu Gln Met Asn Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Glu Asn Asn Trp Asn Pro Tyr Phe Phe Tyr Tyr Gly Met Asp
100 105 110
Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
 115  120

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<212> TYPE: PRT
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     1    5

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aggtttcagcg gcagttggaac tggagcaagat ttcactctca ccatcacacag cttgcagcatct 240
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Leu Ala Trp Tyr Gin Gin Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Ser Ala Ser Thr Leu Gin Ser Ser Val Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
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Glu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin Ala Asn Ser Phe Pro Leu
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<210> SEQ ID NO 239
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Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35     40      45
 Ala Val Ile Tyr Tyr Gly Ser Asn Asp Tyr Tyr Val Asp Ser Val
50     55      60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65     70      75      80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Val Thr Val Ser Ser
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<210> SEQ ID NO: 243
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<210> SEQ ID NO: 244
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<212> TYPE: PRT
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<400> SEQUENCE: 246
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<210> SEQ ID NO: 247
### US 9,447,173 B2

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ggctgccttg tcgaggccgc ttcacccgct tccagacgca aagccacgaa atccctgtat 240
tctaaatgct acacctgctag agcctggagc acgctctgctc tttttgtaga aagaacgcgc 300
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Ala Met His Trp Val Arg Gln Ala Asp Pro Gly Lys Gly Leu Gln Trp Val 35 40 45
Ser Gly Val Ser Trp Ser Gly Ser Thr Val Gly Tyr Ala Asp Ser Val 50 55 60
Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Gln Lys Ser Leu Tyr 65 70 75 80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys 90 95
Val Lys Asp Ala Tyr Lys Tyr Asn Tyr Tyr Tyr Gly Leu Asp Val 100 105 110
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**<210> SEQ ID NO 267**

**<211> LENGTH: 18**

**<212> TYPE: DNA**

**<213> ORGANISM: Artificial Sequence**

**<220> FEATURE:**

**<223> OTHER INFORMATION: Synthetic**

**<400> SEQUENCE: 267**

cagacttt tcaacaac

**<210> SEQ ID NO 268**

**<211> LENGTH: 6**

**<212> TYPE: PRT**

**<213> ORGANISM: Artificial Sequence**

**<220> FEATURE:**

**<223> OTHER INFORMATION: Synthetic**

**<400> SEQUENCE: 268**

Gln Thr Ile Leu Ser Asn

**<210> SEQ ID NO 269**

**<211> LENGTH: 9**

**<212> TYPE: DNA**

**<213> ORGANISM: Artificial Sequence**

**<220> FEATURE:**

**<223> OTHER INFORMATION: Synthetic**

**<400> SEQUENCE: 269**

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**<210> SEQ ID NO 270**

**<211> LENGTH: 3**

**<212> TYPE: PRT**

**<213> ORGANISM: Artificial Sequence**

**<220> FEATURE:**

**<223> OTHER INFORMATION: Synthetic**

**<400> SEQUENCE: 270**

Gly Ala Ser

**<210> SEQ ID NO 271**

**<211> LENGTH: 27**

**<212> TYPE: DNA**

**<213> ORGANISM: Artificial Sequence**

**<220> FEATURE:**

**<223> OTHER INFORMATION: Synthetic**
cagcagata ataactgggc cctcact

Gln Gln Tyr Asn Asn Trp Pro Leu Thr
1      5

Gaagtgcag tcgctgagtc tgggagagcc tggtagcagc ctgagggcct cctgagcctc
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Tccctctgag ccctctgagg gacctctgat gagctgcaac tggactggttg ctggcaagct
120
Ccagggagag gcctggagtg gggctgaggt gttgagtagt tggtagatcc ctggaggtat
180
Gcggagcctc tgaagggcgcg attccactgc tccagagcag aagccagacg aatcctgtat
240
Ctcaaatgac acgtgagag wgctggagac agggcttggt attacggttg aaagaagcgc
300
Tataatctca actactacta ctagtttttg gacgcttggg gccaagggcag cacgctcacc
360
Gtcctcctca
369
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 275

gatttcacct tgatgatta tgcc

24

<210> SEQ ID NO 276
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 276

Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> SEQ ID NO 277
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 277

gttggtggga gggtgtagtac cgta

24

<210> SEQ ID NO 278
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 278

Val Ser Trp Ser Gln Ser Thr Val
1 5

<210> SEQ ID NO 279
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 279

gaaaaacag cgtataaatt caactactac tactacggt tgtacgtc

48

<210> SEQ ID NO 280
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 280

Val Lys Asp Ala Tyr Lys Lys Phe Asn Tyr Tyr Tyr Tyr Gln Leu Asp Val
1 5 10 15

<210> SEQ ID NO 281
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 281
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cctcctgca gcggcagctc gactatctct acgcaacctg ccgaaacctc 120
ggcagagct gcagatctct cattctaggt gcatccacca ggccacatgg ttcctcagc 180
gagttctgct ctgaggtggt tcggacagaag ttccattcct caatacagcag cttggcagct 240
gsagtttnga cggatttactt ctgctcgacg tatataact gcctctocac tttrggcgsa 300
gggaccaaggg tggagaccaaa a 321

<210> SEQ ID NO 282
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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Glu Ile Val Met Thr Gin Ser Pro Ala Thr Leu Ser Val Ser Pro Gly 1 5 10 15
Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gin Thr Ile Leu Ser Asn 20 25 30
Leu Ala Trp Tyr Leu Glu Lys Pro Gly Gin Ala Pro Arg Leu Leu Ile 35 40 45
Tyr Gly Ala Ser Thr Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly 40 45 50
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gin Ser 50 55 60
Glu Asp Phe Ala Val Tyr Tyr Cys Gin Glu Tyr Asn Asn Trp Pro Leu 65 70 75 80
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys 85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys 100 105

<210> SEQ ID NO 283
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 283
cagactaccc tccgacac 18

<210> SEQ ID NO 284
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 284
Gln Thr Ile Leu Ser Asn 1 5

<210> SEQ ID NO 285
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 285
Gln Thr Ile Leu Ser Asn 1 5
<210> SEQ ID NO 286
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 286

Gly Ala Ser

1

<210> SEQ ID NO 287
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 287
cagcgctata ataactg gccct ttcact

27

<210> SEQ ID NO 288
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 288

Gln Gln Tyr Arg Arg Trp Pro Leu Thr

1 5

<210> SEQ ID NO 289
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 289
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tctgtgaaag cttcggcgcga ccccttcacc ggtccctata taaactggtt gcgcagcgc

120
tccggacag ggcctgagtg gageggaag atcaatacta acagtgtrgg cacatctt

180
tcagcagctt ttctgcctcg ggcctctctg accagggaca cgcctccata cacgctcagt

240
tagaggctgca gcagcgtgag agctgagacc acggcgcgtt attactgtgc agaaattggtt

300
tagcatttt tgcactaatc tgcatttttt gcataatggg gccaagggac aatgcgtcacc

360
gtcttcca

369

<210> SEQ ID NO 290
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 290

Gln Val Glu Leu Glu Gin Ser Gly Ala Glu Val Lys Pro Gly Ala

1 5 10 15

Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Gly Tyr
Tyr Ile Asn Trp Val Arg Gin Ala Pro Gly Gin Gly Leu Glu Trp Net
Gly Trp Ile Asn Thr Asn Ser Gly Gly Thr Tyr Phe Ser Gin Lys Phe
Gln Val Arg Val Ile Leu Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
Met Glu Leu Ser Arg Leu Arg Ser Asp Thr Ala Val Tyr Tyr Cys
Ala Arg Met Phe Tyr Asp Ile Leu Thr Asn Ser Asp Ile Phe Asp Ile
Trp Gly Gin Gly Thr Met Val Thr Val Ser Ser

<210> SEQ ID NO 291
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 291
gggracacct tcaaggcgtca ccat

<210> SEQ ID NO 292
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 292
Gly Asp Thr Phe Thr Gly Tyr Tyr

<210> SEQ ID NO 293
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 293
atcatacta acagtggggtg caca

<210> SEQ ID NO 294
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 294
Ile Asn Thr Asn Ser Gly Gly Thr

<210> SEQ ID NO 295
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 295
ggcagaatgt tttagatat tttgactaat tctgatat ttgatatatt 48

<210> SEQ ID NO 296
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 296

Ala Arg Met Phe Tyr Asp Ile Leu Thr Asn Ser Asp Ile Phe Asp Ile
1    5     10    15

<210> SEQ ID NO 297
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 297

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acacttgcc ggccaggtgaa ggcataaga aatgatttag gctggtatca gcagaaacca 120
gggagagccc ctaagtgtgcat ctctatgtgat gcacccaggt gcacaggttg accctca 180
aggttacagg gcagttgtgatc tgggacagaa ttctactctca caatcagcg gctcagcct 240
ggaattttgt caatctatcatctgctacaa ctagagaaaaatt acatgtcacac ttttxgcccag 300
ggcagactcg tggagatcacc ata 321

<210> SEQ ID NO 298
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 298

Asp Ile Gln Met Thr Gin Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1    5     10    15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gin Asp Ile Arg Asn Asp
20   25   30
Leu Gly Trp Tyr Gin Gin Ser Pro Gly Lys Ala Pro Lys Cys Leu Ile
35   40   45
Tyr Gly Ala Ser Leu Gin Ser Gly Val Pro Ser Arg Phe Ser Gly
50   55   60
Ser Gly Ser Gly Thr Gin Phe Thr Leu Thr Ile Ser Ser Leu Gin Pro
65   70   75   80
Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gin His Lys Asn Tyr Met Tyr
85   90
Thr Phe Gly Gin Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 299
<211> LENGTH: 19
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 299
cagacataa gaatgat

<210> SEQ ID NO: 300
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 300

Gln Asp Ile Arg Aen Asp
1  5

<210> SEQ ID NO: 301
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 301
gtgcatcc

<210> SEQ ID NO: 302
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 302

Gly Ala Ser
1

<210> SEQ ID NO: 303
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 303
cGacaGataa asaattacat gtaacat

<210> SEQ ID NO: 304
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 304

Leu Gln His Lye Aen Tyr Met Tyr Thr
1  5

<210> SEQ ID NO: 305
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 305
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acgctgctg tctatggtgg gtccocactg gattaactg ggagctgtat cgcagccc
ccagggaag ggctgaggtg gattgggsaa atcaatcata gtgggacoac caactacagc 180
cgctctctca agaagtcgag caaccctcctg atgatagacctg caaagaactct gtttctctcg 240
aaagtggagcat ctctggcagcc cgcccacaccg gcgttggaat acgtctgcag gctgataatc 300
aatttttgtga tggtgggcggag ggacctctg gtcacgctct ctct 345

<210> SEQ ID NO 306
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 306
Gln Val Gln Leu Gln Glu Gly Ala Gly Leu Leu Lys Pro Ser Glu
1   5   10   15
Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Leu Ser Asp Tyr
20  25  30
Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35  40  45
Gly Glu Ile Asn His Ser Gly Asp Thr Asn Tyr Asp Pro Ser Leu Lys
50  55  60
Ser Arg Leu Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65  70  75  80
Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Cys Ala
85  90
Ser Leu Tyr Phe Asn Phe Trp Met Trp Gly Arg Gly Ala Leu Val Thr
100 105 110
Val Ser Ser
115

<210> SEQ ID NO 307
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 307
gtggtgccct tcagtgatata ctac 24

<210> SEQ ID NO 308
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 308
Gly Gly Ser Leu Ser Asp Tyr Tyr
1   5

<210> SEQ ID NO 309
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 309
atcaatcata gtgggacoac c 21
<210> SEQ ID NO 310
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 310

Ile Arg His Ser Gly Arg Thr
1  5

<210> SEQ ID NO 311
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 311
gccagctctgt atttcaatttt ttggatg 27

<210> SEQ ID NO 312
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 312

Ala Ser Leu Tyr Phe Arg Arg Phe Trp Met
1  5

<210> SEQ ID NO 313
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 313
gatattggga tggccacaga tacactctcc tacactcttcg ttcttggaaca gocgggcttaa 60
acccctctcg ggtctgctgta aagctgctgta tacagtgtgta gaaacactga cttggtggtgg 120
ttcagcggga ggcggcagcc aacggccacttt ttaggattttat ctaaccggcttc 180
ttctgtgctc cagacagatt aagtgcaagtt ggagcaggga cagatttaac acctggaaatc 240
gagcgagggg aagctgagga tgtcgggaatt tattactgca tgcggactcac acaatcttccgg 300
ttcacttggc ggcgggggag cacggtgagat atcaaa 336

<210> SEQ ID NO 314
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 314

Asp Ile Val Met Thr Gin Thr Pro Leu Ser Ser Pro Val Ile Leu Gly
1  5  10  15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gin Ser Leu Val Tyr Ser
20  25  30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gin Gin Gin Arg Pro Gly Gin Pro
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<210> SEQ ID NO 315
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 315

caaagctcgtatacaagtga tgcaaacacc tac

<210> SEQ ID NO 316
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 316

Gln  Ser  Leu  Val  Tyr  Ser  Asp  Gly  Asn  Thr  Tyr
   1    5     10

<210> SEQ ID NO 317
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 317

aagatttct

<210> SEQ ID NO 318
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 318

Lys  Ile  Ser
   1

<210> SEQ ID NO 319
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 319

atgcacaact cacaatttcc gtcacat

<210> SEQ ID NO 320
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> SEQUENCE: 320
Met Gln Thr Thr Gln Phe Pro Leu Thr
1 1 5

<210> SEQ ID NO 321
<211> LENGTH: 369
<212> ORGANISM: Artificial Sequence
<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 321
ccagtgcagt tgagagactc tgggcttgag gtaggaagtc ctgggacotc agtgaggatc 60
tctctgcaagg ctctggcgca acatctccac ggtcaactata tgaactgggt gcgcagggcc 120
cctggcacaag ggtctggaag gatgaggatg atcaataacta acagttggtg caaatacttt 180
tccagagat tcagggcag ggtcaacotg aacaggagcag ctgctctacag aacagctc 240
tgcagagttga gcagagctag atctggaag acagcaggttt atctagttgc gagaagttt 300
tgaaggttct tgaacgggttc tgaatggtaa gatatttgag gcagaaggac aatgtctc 360
gtcctctca 369

<210> SEQ ID NO 322
<211> LENGTH: 123
<212> ORGANISM: Artificial Sequence
<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 322
Gln Val Gln Leu Glu Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Thr
1 5 10 15
Ser Val Arg Ile Ser Cys Ala Ser Gly Asp Ile Phe Thr Gly Tyr
20 25 30
Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Ile Asn Thr Asn Ser Gly Gly Thr Tyr Phe Ser Gln Arg Phe
50 55 60
Gln Gly Arg Val Thr Leu Thr Arg Ser Gly Ser Asp Thr Ser Asp Thr Ala Tyr
65 70 75 80
Met Glu Leu Ser Arg Leu Arg Ser Asp Thr Ala Val Tyr Cys
85 90 95
Ala Arg Met Phe Tyr Asp Ile Leu Thr Gly Ser Asp Val Phe Asp Ile
100 105 110
Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
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<210> SEQ ID NO 323
<211> LENGTH: 24
<212> ORGANISM: Artificial Sequence
<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 323
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<210> SEQ ID NO 324
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
<400> SEQUENCE: 324

Gly Asp Ile Phe Thr Gly Tyr Tyr
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atcaatcata acagtggtgg caca

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<220> FEATURE:
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Ala Arg Met Phe Tyr Asp Ile Leu Thr Gly Ser Asp Val Phe Asp Ile
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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atcactgccc gggcaagcga ggacataaga aatgattag gctggtatac cgagaacaa

gggggagccc ctaaggctgc gatctatggg gccacagctg gtcgctgcttt ctcattcct

aggtcagcgg gcagtggtac ggagccagag ttgactccca caactacgac gctcgagct

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<212> TYPE: PRT
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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1  5  10  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Cys Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Cys Leu Gln His Lys Asn Tyr Met Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Gln Ile Lys
100 105

<210> SEQ ID NO: 331
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<400> SEQUENCE: 331
caggacataa gaatgat

<210> SEQ ID NO: 332
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Gln Asp Ile Arg Asn Asp
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<210> SEQ ID NO: 333
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Gly Ala Ser
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<212> TYPE: DNA
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<220> FEATURE:
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<400> SEQUENCE: 335
cacaacata asaatcactgtcact
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<210> SEQ ID NO 336
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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: Synthetic

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384

<210> SEQ ID NO 338
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<400> SEQUENCE: 338
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Asn Tyr
20 25 30
Glu Met Asn Trp Val Arg Gin Ala Pro Gly Lys Gly Leu Gin Trp Val
35 40 45
Ser Tyr Ile Ser Thr Ser Gly Ile Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60
Gln Gly Arg Phe Thr Ile Ser Arg Asp Ala Asp Leu Asn Ser Leu Tyr

10
65  70  75  80
Leu Gln Leu Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85  90  95
Ala Arg Gly Tyr Cys Thr Asn Gly Val Cys Tyr Pro His Tyr Tyr
100 105 110
Ser Asp Met Asp Val Trp Gly Gin Gly Thr Thr Val Thr Val Ser Ser
115 120 125

SEQ ID NO 339
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 339
gattacca tcaatctatg taaga

SEQ ID NO 340
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 340
Gly Phe Thr Ile Ser Asn Tyr Glu
1  5

SEQ ID NO 341
LENGTH: 24
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 341
ataggtacag agtgatattc cata

SEQ ID NO 342
LENGTH: 8
TYPE: PRT
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 342
Ile Ser Thr Ser Gly Ile Thr Ile
1  5

SEQ ID NO 343
LENGTH: 63
TYPE: DNA
ORGANISM: Artificial Sequence
FEATURE:
OTHER INFORMATION: Synthetic

SEQUENCE: 343
gogogogogat atgtacaaa tggtgtarge tacccctatt cactactactc gatargga
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gtc
63

SEQ ID NO 344
LENGTH: 21
TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 344

Ala Arg Gly Tyr Cys Thr Asn Gly Val Cys Tyr Pro His Tyr Tyr Tyr  
  1  5  10  15
Ser Asp Met Asp Val  
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<210> SEQ ID NO: 345
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 345
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tataactggcc gggagcactg agcattacgacctatattac attgtttgcatcgcctgcgtgagtatg  
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gggagctggcc ctaaactctctggtatata ttattacagctgtctctcttacacaggtctctgtg  
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gagggtccgt gcgcgagactgtgagagact gttcatctctctcacatcaggtctctctct  
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<210> SEQ ID NO: 346
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<212> TYPE: PRT
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<400> SEQUENCE: 346

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  1  5  10  15
Asp Arg Leu Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Thr Tyr  
 20  25  30
Leu Asn Trp Phe Gln Gln Gly Val Gly Asn Ala Pro Lys Leu Leu Ile  
 35  40  45
Tyr Ser Thr Ser Leu Gln Ser Val Pro Ala Arg Phe Ser Gly  
 50  55  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
 65  70  75  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gin Gin Ser Tyr Ser Ser Pro Pro  
 85  90  95
Thr Phe Gly Gin Gly Thr Lys Val Gin Ile Lys  
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<210> SEQ ID NO: 347
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE: 
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 347
cagactcata gcacactat  
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<210> SEQ ID NO: 348
Gln Thr Ile Ser Thr Tyr
1 5

cttacatcc
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Ser Thr Ser
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ciaacaggtt acagtagtcc tccgaag
27

Gln Gln Ser Tyr Ser Ser Pro Pro Thr
1 5

Met His Arg Pro Arg Arg Gly Thr Arg Pro Pro Pro Leu Ala Leu
1 5 10 15

Leu Ala Ala Leu Leu Leu Ala Ala Arg Gly Ala Asp Ala Asn Ile Thr
20 25 30

Glu Glu Phe Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu
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Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
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Gly Gly Tyr Glu Gly Val Asp Glu Ile Phe Tyr Ala Gln Lys Phe
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Gln His Arg Leu Thr Val Ile Ala Asp Thr Ala Thr Asp Thr Val Tyr
65    70     75     80
Met Glu Leu Gly Arg Leu Thr Ser Asp Asp Thr Ala Val Tyr Phe Cys
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Gly Thr Leu Gly Val Thr Val Thr Glu Ala Gly Leu Gly Ile Asp Asp
100   105    110
Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ala Ser Thr Lys
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Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
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Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
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SEQ ID NO: 358
LENGTH: 215
TFFP: PRT
ORGANISM: Artificial Sequence
FEATURE: OTHER INFORMATION: Synthetic
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| SEQ ID NO | 360 |
| LENGTH | 213 |
| TYPE | PRT |
| ORGANISM | Artificial Sequence |
| FEATURE | |
| OTHER INFORMATION | Synthetic Palivizumab HC |

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What is claimed is:

1. An isolated human antibody or antigen-binding fragment thereof that binds specifically to RSV-F, wherein the antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) amino acid sequences selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338; and comprises three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) amino acid sequences selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

2. The isolated human antibody or antigen-binding fragment of claim 1, comprising:
   (a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340;
   (b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 252, 278, 294, 310, 326 and 342;
   (c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 252, 248, 264, 280, 296, 312, 328, and 344;
   (d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348;
   (e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350; and
   (f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16,
3. An isolated antibody or antigen-binding fragment thereof that competes for specific binding to RSV-F with an antibody or antigen-binding fragment comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, wherein the antibody that competes for specific binding to RSV-F interacts with an epitope comprising an amino acid sequence ranging from about position 161 to about position 188 of SEQ ID NO:354, or interacts with the serine at position 173 of SEQ ID NO: 354, and/or the threonine at position 174 of SEQ ID NO: 354.

4. An isolated antibody or antigen-binding fragment thereof that binds the same epitope on RSV-F that is recognized by an antibody comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, wherein the epitope comprises an amino acid sequence ranging from about position 161 to about position 188 of SEQ ID NO:354.

5. The isolated antibody of claim 1, wherein the antibody does not cross-compete for binding to RSV-F with palivizumab, or AM-22.

6. The isolated human antibody of claim 1, wherein the antibody does not bind to an epitope on RSV-F ranging from amino acid residue 255 to amino acid residue 276 of SEQ ID NO: 354.

7. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody is a human recombinant monoclonal antibody.

8. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354.

9. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

10. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region (HCVR) amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338.

11. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment comprises a light chain variable region (LCVR) amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.


13. The isolated antibody or antigen-binding fragment thereof of claim 12, comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

14. The isolated antibody or antigen-binding fragment thereof of claim 13, comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282.

15. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates the ability to significantly reduce the lung viral load in a mouse model of RSV infection when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg.

16. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates a 1-2 logs greater reduction of nasal and/or lung viral titers as compared to palivizumab in a cotton rat model of RSV infection when administered at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg.

17. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED₅₀ of about 0.15 mg/kg or less when administered in a mouse model of RSV subtype A infection.

18. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED₅₀ of about 0.62 mg/kg or less when administered in a cotton rat model of RSV subtype A infection.

19. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED₅₀ of about 2.5 mg/kg or less when administered in a cotton rat model of RSV subtype B infection.

20. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED₅₀ that is about 2 to 3 fold lower than the ED₅₀ for palivizumab or motavizumab.

21. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype A laboratory strains of RSV that is about a 15 to 17 fold improvement over palivizumab, or demonstrates a neutralization potency against one or more subtype A clinical strains of RSV that is about 10 to 22 fold improvement over palivizumab.

22. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2 to 5 fold improvement over palivizumab.

23. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype A laboratory strains or subtype A clinical strains of RSV that is about 0.5 to 2 fold improvement over AM-22.

24. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about 2.5 to 17 fold improvement over AM-22.

25. The isolated antibody or an antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding
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fragment thereof binds specifically to RSV-F with a K_D ranging from 1.0x10^{-7} M to 6.0x10^{-10} M, as measured by surface plasmon resonance.

26. The isolated antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof has one or more of the following characteristics:

(a) is capable of neutralizing respiratory syncytial virus subtype A and subtype B strains in vitro;
(b) demonstrates the ability to significantly reduce the nasal and/or lung viral load in vivo in an animal model of RSV infection;
(c) interacts with at least one amino acid residue within SEQ ID NO: 355 or 356; or
(d) inhibits fusion of the virus to the cell.

27. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment of claim 1.

28. An expression vector comprising the nucleic acid molecule of claim 27.

29. A host cell comprising the expression vector of claim 28.

30. A method for preventing or treating a respiratory syncytial virus (RSV) infection, or at least one symptom associated with the RSV infection, the method comprising administering an antibody or antigen-binding fragment of claim 1, or a composition comprising an antibody or antigen-binding fragment of claim 1, to a patient in need thereof, such that the RSV infection is prevented, or at least one symptom associated with the infection is alleviated or reduced in number or severity.

31. The method of claim 30, wherein the administering results in prevention of recurrent wheezing in the patient.

32. The method of claim 30, wherein the administering results in prevention of RSV-associated asthma in a child.

33. The method of claim 30, wherein the RSV infection is caused by a subtype A or a subtype B respiratory syncytial virus.

34. The method of claim 30, wherein the patient in need thereof is a patient at high risk of acquiring an RSV infection, or a patient who may experience a more severe form of the RSV infection due to an underlying or pre-existing medical condition.

35. The method of claim 34, wherein the patient is a pre-term infant, a full term infant, a child greater than or equal to one year of age with or without an underlying medical condition (e.g. congenital heart disease, chronic lung disease, cystic fibrosis, immunodeficiency, a neuromuscular disorder), an institutionalized or hospitalized patient, or an elderly adult (greater than 65 years of age) with or without an underlying medical condition such as congestive heart failure or chronic obstructive pulmonary disease.

36. The method of claim 34, wherein the patient suffers from a condition resulting from a compromised pulmonary, cardiovascular, neuromuscular, or immune system.

37. The method of claim 36, wherein the condition is selected from the group consisting of an abnormality of the airway, a chronic lung disease, a chronic heart disease, a neuromuscular disease that compromises the handling of respiratory secretions and immunosuppression.

38. The method of claim 37, wherein the chronic lung disease is chronic obstructive pulmonary disease (COPD), cystic fibrosis, or bronchopulmonary dysplasia.

39. The method of claim 37, wherein the chronic heart disease is congestive heart failure (CHF), or congenital heart disease.

40. The method of claim 37, wherein the immunosuppression is a result of severe combined immunodeficiency or severe acquired immunodeficiency, or is a result of any other infectious disease or cancerous condition that leads to immunosuppression, or is a result of treatment with immunosuppressant drug therapy or radiation therapy.

41. The method of claim 30, wherein the at least one symptom is selected from the group consisting of fever, nasal congestion, cough, decreased appetite, hypoxia, breathing difficulties (rapid breathing or shortness of breath), wheezing, apnea, dehydration, poor feeding and altered mental status.

42. The method of claim 30, wherein the patient in need thereof is administered the antibody or antigen-binding fragment thereof prophylactically, or therapeutically.

43. The method of claim 30, wherein the antibody or antigen-binding fragment thereof is administered via a route selected from the group consisting of intravenously, intramuscularly, and subcutaneously.

44. The method of claim 30, wherein the antibody or antigen-binding fragment is administered to the patient in combination with a second therapeutic agent.

45. The method of claim 44, wherein the second therapeutic agent is selected from the group consisting of an antiviral agent; a vaccine specific for RSV, a vaccine specific for influenza virus, or a vaccine specific for metapneumovirus (MPV); an siRNA specific for an RSV antigen or a metapneumovirus (MPV) antigen; a second antibody specific for an RSV antigen or a metapneumovirus (MPV) antigen; an anti-IL4R antibody, an antibody specific for an influenza virus antigen, an anti-RSV-G antibody and a NSAID.

46. A pharmaceutical composition comprising any one or more of the isolated antibodies or antigen binding fragments thereof of claim 1 and a pharmaceutically acceptable carrier.

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