TITLE OF THE INVENTION

[0001] Anti-NK3R Antibodies and Methods of Use

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] Priority is claimed to U.S. Provisional Patent Application No. 63/594,517 filed on 31 October 2023, which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0003] The instant application contains a Sequence Listing which has been electronically submitted in XML format and is hereby incorporated by reference in its entirety. Said XML copy, created on 30 October 2024, is named 27050031WO01SEQL.xml and is 127,438 bytes in size.

TECHNICAL FIELD OF THE INVENTION

[0004] This disclosure generally relates to the fields of medicine and molecular biology. More specifically, this disclosure relates to anti-NK3R antibodies and antigen-binding fragments thereof that are useful in the treatment of a variety of conditions.

BACKGROUND OF THE INVENTION

[0005] Menopause is a natural process of reproductive aging defined as permanent cessation of menstrual periods, determined retrospectively following 12 months of amenorrhea without another obvious pathologic or physiologic cause. One of the most common symptoms of menopause are vasomotor symptoms (VMS), also known as hot flashes or flushes. VMS occur in up to 80% of women during menopause. VMS, typically 2 to 4 minutes in duration, result from an altered thermoregulatory response to hormonal and neuroendocrine changes and manifest as a sudden sensation of heat in the upper chest and face that rapidly becomes generalized, commonly resulting in profuse sweating and occasionally palpitations. Following VMS, women frequently experience chills, shivering, and anxiety.

[0006] While menopausal hormone therapy (MHT) is effective in suppressing VMS due to menopause, many women have contraindications to the use of MHT. Even in those women in which MHT is not contraindicated, there is mounting evidence of increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis associated with MHT. To date, the only nonhormonal treatment for VMS due to menopause with estrogen-

like efficacy is fezolinetant (VEOZAH®), a small molecule neurokinin 3 receptor (NK3R) antagonist that has been approved by the U.S. Food & Drug Administration and the European Medicines Agency (EMA).

[0007] A tachykinin receptor, NK3R (or TACR3) belongs to a family of seven-transmembrane, G-protein coupled receptors that includes the neurokinin 1 receptor (NK1R or TACR1) and neurokinin 2 receptor (NK2R or TACR2). The endogenous ligands of these receptors are the tachykinin peptides: substance P (SP), neurokinin A (NKA), and neurokinin B (NKB). While the tachykinin peptide ligands can each agonize all three neurokinin receptors, there are clear affinity differences such that SP, NKA, and NKB have the highest affinity for NK1R, NK2R, and NK3R, respectively.

[0008] The biology of NK3R and NKB has been informed in recent years by the discovery of human genetic variants which associate with defects in signaling through the hypothalamic-pituitary-gonadal (HPG) axis. Loss-of-function variants in the genes encoding NK3R and NKB result in hypogonadotropic hypogonadism and lack of progression through puberty. Further elucidation of the underlying NK3R/NKB biology has demonstrated NK3R signaling is a critical upstream regulator of signaling through the HPG axis and represents a promising point of pharmacologic intervention for diseases related to reproductive biology and/or sex hormone-related diseases. NK3R activation positively regulates the GnRH pulse frequency which in turn, differentially regulates the circulating levels of Luteinizing hormone (LH) versus Follicle-stimulating hormone (FSH). These gonadotrophins ultimately act on ovaries and testes to promote production of sexual hormones such as testosterone and estradiol.

[0009] Pre-clinical studies using male guinea pigs, dogs and rats demonstrated that certain NK3R antagonists are able to suppress plasma LH and testosterone levels. The essential role for the NKB/NK3R pathway in men and women and its effect on sexual steroid hormones has been largely demonstrated through clinical studies with known NK3R antagonists, such as SJX-653, ESN364 (fezolinetant/VEOZAH®), and MLE4901. These NK3R antagonists have demonstrated the ability to suppress luteinizing hormone and testosterone secretion in healthy men and women with polycystic ovary syndrome. Collectively, these findings support the use of LH and testosterone as predictive biomarkers for therapeutic molecules that modulate the NK3R pathway.

[0010] Given the effects on testosterone and estrogen hormone suppression, these findings also support the use of anti-NK3R antagonists to treat VMS in a non-menopausal context. Outside of menopause, VMS occur in both women and men who undergo endocrine suppression therapy for

hormone-sensitive cancers, such as estrogen and/or progesterone receptor (ER and/or PR) positive breast cancer or prostate cancer. These patients experience substantial, rapid declines in sex hormones. Similarly to estrogen depletion in women, VMS in men is the result of rapid depletion of testosterone, most commonly occurring with prostate cancer-associated androgen deprivation therapy (ADT). Men with castrate sensitive prostate cancer (CSPC) receiving ADT can experience VMS ranging from mild to severe. Similar to menopausal women, few non-hormonal therapies exist to treat VMS associated with ADT in men with CSPC. Effective therapies for VMS in postmenopausal women could be similarly effective in men on ADT for CSPC

[0011] Given the effects on testosterone and estrogen hormone suppression, these findings also support the use of anti-NK3R antagonists to treat hormone-dependent cancers like prostate cancer or estrogen-dependent cancers. The ability to lower testosterone levels in men and estrogen levels in women is beneficial in treating these types of cancers, as these cancers often rely on these hormones for growth and progression. For example, androgen deprivation therapy (ADT) remains a mainstay in prostate cancer treatment, especially in advanced disease.

[0012] A safe and effective alternative to hormone therapy for the treatment of VMS is needed. While fezolinetant is approved for the treatment of VMS, fezolinetant is not without its side effects. In some instances, patients may suffer from nausea, abdominal pain, hot flush, or hepatic transaminase elevation. Fezolinetant is also contraindicated in women with known cirrhosis, severe renal impairment or end-stage renal disease, and concomitant use with CYP1A2 inhibitors such as ciprofloxacin and fluvoxamine.

[0013] Alternative treatments for advanced hormone-sensitive prostate cancer (HSPC) are also needed. While advanced HSPC has traditionally been treated by androgen deprivation therapy (ADT), either by surgical or chemical castration, the most adverse event in men treated with ADT for is VSM. These affect up to 80% of men treated with ADT, and are considered the most distressing aspect of ADT therapy in over one-quarter of those receiving treatment. Testosterone is normally metabolized to produce estrogenic breakdown products and the absence of these during ADT presumably affects the number and sensitivity of KNDy neurons in the thermoregulatory regions of the hypothalamus, thereby producing VMS by a mechanism similar to that seen in menopausal women and in women with breast cancer treated with estrogen deprivation therapies.

[0014] Antibodies possess several characteristics that can provide a safer and longer-acting treatment for VMS associated with menopause as compared to small molecules like fezolinetant. As antibodies are almost exclusively delivered intravenously or subcutaneously and are highly

specific with a degradation pathway independent of the liver, there are fewer concerns regarding hepatotoxicity compared to small molecules. Further, antibodies generally have a longer half-life compared to small molecules, allowing for less frequent dosing, which may improve patient compliance and convenience. While there are challenges to using antibodies and other large molecule therapeutics in treating disorders involving the central nervous system, the neurons that express NK3R are largely located in the arcuate nucleus and infundibular nucleus of the hypothalamus, which is not protected by the blood-brain barrier. Accordingly, therapeutic antibodies that act as anti-NK3R antagonists can be used to treat VMS, castrate-sensitive prostate cancer, estrogen-dependent cancer, and possibly other sex hormone-related disorders related to NK3R and its role in HPG signaling.

BRIEF SUMMARY OF THE INVENTION

[0015] The present disclosure relates to methods, compositions of matter, and articles of manufacture that may be used in the treatment of sex hormone-related disorders and the amelioration of symptoms thereof, such as vasomotor symptoms associated with menopause and other conditions, and hormone-dependent cancers (e.g., prostate, breast, ovarian, and uterine). To that end, provided herein are recombinantly produced antibodies that specifically bind to and antagonize NK3R. In particular, anti-NK3R antibodies annotated by non-consecutive internal designation numbers 20810-27933 are disclosed herein and are set forth in SEQ ID NOs: 1-119. Amino acid sequences of the heavy chain variable regions of these antibodies are set forth in SEQ ID NOs 1, 5, 9, 13, 17, 25, 31, 42, 50, 54, 59, 67, 71, 73, 77, 82, 88, 90, 93, 99, 102, 104, 106, 108, 110, 112, and 116-119 while amino acid sequences of the light chain variable regions of these antibodies are set forth in SEQ ID NOs 2, 6, 10, 14, 26, 32, 51, 56, 60, 68, 74, 79, 83, 86, 94, 96, 98, 100, and 113. Amino acid sequences of the complete heavy chains of these antibodies are set forth in SEQ ID NOs 3, 7, 11, 15, 18, 29, 33, 35, 44, 52, 55, 58, 61, 63, 65, 66, 69, 72, 75, 78, 81, 84, 89, 91, 103, 105, 109, and 111, while amino acid sequences of the complete light chains of these antibodies are set forth in SEQ ID NOs 4, 8, 12, 16, 30, 34, 53, 57, 62, 64, 70, 76, 80, 85, 87, 92, 95, 97, 101, 107, 114 and 115.

[0016] In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof (e.g., mAbs 26105, 26106, 27860, or 27870) comprises (a) a heavy chain variable region comprising residues 31-35 for CDR-H1, residues 50-66 for CDR-H2, and residues 99-114 for CDR-H3; and (b) a light chain variable region comprising residues 24-34 for CDR-L1, residues

50-56 for CDR-L2, and residues 89-97 for CDR-L3; wherein the CDR numbering is according to Kabat. In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof (e.g., mAbs 25125, 25129) comprises (a) a heavy chain variable region comprising residues 31-35 for CDR-H1, residues 50-68 for CDR-H2, and residues 101-117 for CDR-H3; and (b) a light chain variable region comprising residues 24-34 for CDR-L1, residues 50-56 for CDR-L2, and residues 89-97 for CDR-L3; wherein the CDR numbering is according to Kabat. In some embodiments, the six CDRs of the anti-NK3R antibody or antigen-binding fragment thereof are defined by reference to SEQ ID NOs (e.g., SEQ ID NOs: 19-24, 36-41, and 45-49).

[0017] In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof comprises a heavy chain variable region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to one of the heavy chain variable region sequences explicitly disclosed herein and a light chain variable region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to one of the light chain variable region sequences explicitly disclosed herein (e.g., a heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region set forth as SEQ ID NO: 51; or a heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region set forth as SEQ ID NO: 26; or a heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable region set forth as SEQ ID NO: 10).

[0018] In some embodiments, the anti-NK3R antibody further comprises a heavy chain constant region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a heavy chain constant region of an anti-NK3R antibody disclosed herein and further comprises a light chain constant region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a light chain constant region of an anti-NK3R antibody disclosed herein. In particular embodiments, the anti-NK3R antibody further comprises a heavy chain constant region having an amino acid sequence forth as SEQ ID NO: 43 and a light chain constant region set forth as SEQ ID NO: 28 or a heavy chain constant region set forth as SEQ ID NO: 27 and a light chain constant region set forth as SEQ ID NO: 28. In some embodiments, the heavy chain constant region further comprises a C-terminal lysine residue.

[0019] In some embodiments, the anti-NK3R antibody comprises a heavy chain having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a heavy chain disclosed herein and a light having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a light chain disclosed herein (e.g., a heavy chain set forth as SEQ ID NO:

52 and a light chain set forth as SEQ ID NO: 53; or a heavy chain set forth as SEQ ID NO: 81 and a light chain set forth as SEQ ID NO: 53; or a heavy chain set forth as SEQ ID NO: 35 and a light chain set forth as SEQ ID NO: 30; or a heavy chain set forth as SEQ ID NO: 29 and a light chain set forth as SEQ ID NO: 30; or a heavy chain set forth as SEQ ID NO: 44 and a light chain set forth as SEQ ID NO: 12; or a heavy chain set forth as SEQ ID NO: 65 and a light chain set forth as SEQ ID NO: 12).

[0020] In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof is a Fab fragment, Fab′ fragment, $F(ab')_2$ fragment, Fab′-SH fragment, Fv fragment, linear antibody, or single-chain antibody. In other embodiments, the antibody is a full-length antibody. In yet other embodiments, the heavy chain variable region is fused to a heavy chain constant region and the light chain variable region is fused to a light chain constant region. In still yet other embodiments, the heavy chain constant region is selected from the group consisting of IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, and IgM.

[0021] In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof is an Fc variant that comprises an Fc silencing mutation. In some embodiments, the Fc silencing mutation comprises one or more amino acid substitutions to block antibody binding to FcγRI, FcγRII, or FcγRIIIa. In particular embodiments, the Fc variant comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 252, 254, and 256, wherein the Fc variant further comprises an amino acid deletion at position 447, and wherein amino acid numbering is according to the EU index. Examples of such embodiments of these FC variants include L234S, L235T, G236R, wherein K447 is deleted and L234S, L235T, G236R, M252Y, S254T, and T256E, wherein K447 is deleted.

[0022] In some embodiments, the antibody or antigen-binding fragment thereof is formulated as a pharmaceutical composition. In some embodiments, the pharmaceutical composition may comprise one or more pharmaceutically acceptable carriers, diluents, or excipients.

[0023] The instant disclosure also encompasses isolated nucleic acids encoding part or all of the anti-NK3R antibodies and antigen-binding fragments thereof disclosed herein. In some embodiments, the foregoing nucleic acids may be incorporated into an expression vector. In some embodiments, the foregoing nucleic acids may be incorporated into a host cell or incorporated into an expression vector and then into a host cell. The instant disclosure also includes methods of manufacturing the anti-NK3R antibodies and antigen-binding fragments thereof disclosed herein using the aforementioned nucleic acids, expression vectors, and host cells. In particular

embodiments, the methods comprise cultivating a host cell under conditions such that the antibody is expressed and recovered.

[0024] The instant disclosure also encompasses articles of manufacture useful for treating a contemplated sex hormone-related disorder comprising a receptacle comprising an anti-NK3R antibody or antigen-binding fragment thereof, or pharmaceutical composition comprising the same, as well as instructional materials for using the same to treat the disorder.

[0025] The instant disclosure also encompasses methods of treating a contemplated sex hormone-related disorder comprising administering to a subject a therapeutically effective amount of an anti-NK3R antibody or antigen-binding fragment thereof. In some embodiments, the antibody or antigen-binding fragment thereof may be formulated as a pharmaceutical composition prior to administration.

[0026] The foregoing is a summary and thus contains, by necessity, simplifications, generalizations, and omissions of detail; consequently, those skilled in the art will appreciate that the summary is illustrative only and is not intended to be in any way limiting. Other aspects, features, and advantages of the subject matter described herein will become apparent in the teachings set forth herein. The summary is provided to introduce a selection of concepts in a simplified form that are further described below in the Detailed Description of the Invention. This summary is not intended to identify key features or essential features of the claimed subject matter, nor is it intended to be used as an aid in determining the scope of the claimed subject matter.

BRIEF SUMMARY OF THE SEVERAL VIEWS OF THE DRAWINGS

[0027] Figure 1 shows the number of antibodies isolated from rodents immunized with the antigen. Dark squares represent shared heavy chain clusters and light squares represent light chain clusters. Clonal clusters are defined by chain sequences sharing the same V-gene, J-gene and CDR3 length. Each line represents a unique antibody pair.

[0028] Figure 2 shows the relative potency of chimeric antibodies as measured against human NK3R cell line using the calcium mobilization assays in response to the human NK3R ligand, senktide. Data presented as percentage inhibition of the maximum response in the absence of antibody, with mean ± SD shown.

[0029] Figure 3 shows the relative potency of humanized antibodies derived from mAb 20811 as measured against human NK3R cell line using the calcium mobilization assays in response to

the human NK3R ligand, senktide. Each data point represents an independent experiment. The solid line represents the average IC_{50} for the humanized antibody.

[0030] Figure 4 shows the relative potency of humanized antibodies derived from mAb 20813 as measured against human NK3R cell line using the calcium mobilization assays in response to the human NK3R ligand, senktide. Each data point represents an independent experiment. The solid line represents the average IC_{50} for the humanized antibody.

[0031] Figure 5 shows the relative potency of humanized antibodies derived from mAb 27858 as measured against human NK3R cell line using the calcium mobilization assays in response to the human NK3R ligand senktide. Each data point represents an independent experiment. The solid line represents the average IC_{50} for the humanized antibody.

[0032] Figure 6 shows the relative potency of optimized antibodies as measured against human NK3R cell line using the calcium mobilization assays in response to the human NK3R ligand, NKB. Data presented as mean ± SD.

[0033] Figure 7 shows the plasma testosterone concentration in male Sprague Dawley rats that were jugular cannulated and administered anti-NK3R antibody, mAb 20811, fezolinetant, or isotype control via IV administration. Data represents mean ± SD.

[0034] Figure 8 shows the serum luteinizing hormone response in female ovariectomized rats that were administered with mAb 26106 or isotype control via IV. Data represents mean ± SD.

DETAILED DESCRIPTION OF THE INVENTION

[0035] While the present inventions may be embodied in many different forms, disclosed herein are specific illustrative embodiments thereof that exemplify the principles of inventions described herein. It should be emphasized that the inventions described herein are not limited to the specific embodiments illustrated. Moreover, any section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0036] Unless otherwise defined herein, scientific, and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. More specifically, as used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a protein” includes a plurality of proteins; reference to “a cell” includes mixtures of cells, and the like. In

addition, ranges provided in the specification and appended claims include both end points and all points between the end points. Therefore, a range of 1.0 to 2.0 includes 1.0, 2.0, and all points between 1.0 and 2.0.

[0037] Generally, nomenclature used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well-known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art, or as described herein. The nomenclature used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well-known and commonly used in the art.

[0038] Exemplary Embodiments of the Invention

[0039] In some embodiments, the inventions disclosed herein encompass an antibody or antigen-binding fragment thereof that specifically binds NK3R, wherein the antibody or antigen-binding fragment thereof comprises three CDRs of a heavy chain variable region of one of the heavy chain variable region sequences set forth in one of SEQ ID NOs: 1, 5, 9, 13, 17, 25, 31, 42, 50, 54, 59, 67, 71, 73, 77, 82, 88, 90, 93, 99, 102, 104, 106, 108, 110, 112, and 116-119 and comprises three CDRs of a light chain variable region having an amino acid sequence identical to one of the corresponding light chain variable region sequences set forth in one of SEQ ID NOs: 1 NOs: 2, 6, 10, 14, 26, 32, 51, 56, 60, 68, 74, 79, 83, 86, 94, 96, 98, 100, and 113. As used herein, the term "corresponding" refers to a pair of heavy and light chain variable regions (or pair of heavy and light chains) that are identified by the same internal reference number. For example, the inventions disclosed herein encompass an antibody or antigen-binding fragment thereof that specifically binds NK3R, wherein the antibody or antigen-binding fragment thereof comprise three CDRs of a heavy chain variable region set forth as SEQ ID NO: 50 (i.e., mAb 26106 VH) and three CDRs of a light chain variable region set forth as SEQ ID NO: 51 (i.e., mAb 26106 VL).

[0040] In particular embodiments, the inventions disclosed herein encompass an antibody or antigen-binding fragment thereof, wherein the antibody or fragment thereof comprises: (a) CDR-

H1 comprising residues 31-35, CDR-H2 comprising residues 50-66, and CDR-H3 comprising residues 99-114 of the heavy chain variable region (V_H); and (b) CDR-L1 comprising residues 24-34, CDR-L2 comprising residues 50-56, and CDR-L3 comprising residues 89-97 of the light chain variable region (V_L), wherein the CDR numbering is according to Kabat. In another particular embodiment, the inventions disclosed herein encompass an antibody or antigen-binding fragment thereof, wherein the antibody or fragment thereof comprises: (a) CDR-H1 comprising residues 31-35, CDR-H2 comprising residues 50-68, and CDR-H3 comprising residues 101-117 of the V_H; and (b) CDR-L1 comprising residues 24-34, CDR-L2 comprising residues 50-56, and CDR-L3 comprising residues 89-97 of the light chain variable region (V_L), wherein the CDR numbering is according to Kabat. In some embodiments, the six CDRs of the anti-NK3R antibody or antigen-binding fragment thereof are defined by reference to SEQ ID NOs. (e.g., SEQ ID NOs: 19-24, 36-41, and 45-49).

[0041] In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof comprises a heavy chain variable region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to one of the heavy chain variable region sequences disclosed herein (i.e., SEQ ID NOs: 1, 5, 9, 13, 17, 25, 31, 42, 50, 54, 59, 67, 71, 73, 77, 82, 88, 90, 93, 99, 102, 104, 106, 108, 110, 112, and 116-119) and a corresponding light chain variable region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to one of the light chain variable region sequences disclosed herein (i.e., 2, 6, 10, 14, 26, 32, 51, 56, 60, 68, 74, 79, 83, 86, 94, 96, 98, 100, and 113).

[0042] In some embodiments, the anti-NK3R antibody further comprises a heavy chain constant region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a heavy chain constant region of an anti-NK3R antibody disclosed herein and further comprises a light chain constant region having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a light chain constant region of an anti-NK3R antibody disclosed herein. In particular embodiments, the anti-NK3R antibody further comprises a heavy chain constant region having an amino acid sequence forth as SEQ ID NO: 43 and a light chain constant region set forth as SEQ ID NO: 28 or a heavy chain constant region set forth as SEQ ID NO: 27 and a light chain constant region set forth as SEQ ID NO: 28. In particular embodiments, the heavy chain constant region further comprises a C-terminal lysine residue.

[0043] In some embodiments, the anti-NK3R antibody comprises a heavy chain having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a heavy chain

disclosed in one of the sequences disclosed herein (i.e., SEQ ID NOs: 3, 7, 11, 15, 18, 29, 33, 35, 44, 52, 55, 58, 61, 63, 65, 66, 69, 72, 75, 78, 81, 84, 89, 91, 103, 105, 109, and 111) and a light chain having an amino acid sequence that is at least 90%, 95%, 98%, 99%, or 100% identical to a corresponding light chain disclosed herein (i.e., SEQ ID NOs: 4, 8, 12, 16, 30, 34, 53, 57, 62, 64, 70, 76, 80, 85, 87, 92, 95, 97, 101, 107, 114 and 115). In particular embodiments, the anti-NK3R antibody comprises a heavy chain set forth as SEQ ID NO: 52 and a light chain set forth as SEQ ID NO: 53; or a heavy chain set forth as SEQ ID NO: 81 and a light chain set forth as SEQ ID NO: 53; or a heavy chain set forth as SEQ ID NO: 35 and a light chain set forth as SEQ ID NO: 30; or a heavy chain set forth as SEQ ID NO: 29 and a light chain set forth as SEQ ID NO: 30; or a heavy chain set forth as SEQ ID NO: 44 and a light chain set forth as SEQ ID NO: 12; or a heavy chain set forth as SEQ ID NO: 65 and a light chain set forth as SEQ ID NO: 12.

[0044] In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof is a Fab fragment, Fab′ fragment, $F(ab')_2$ fragment, Fab′-SH fragment, Fv fragment, linear antibody, or single-chain antibody. In other embodiments, the antibody is a full-length antibody. In yet other embodiments, the heavy chain variable region is fused to a heavy chain constant region and the light chain variable region is fused to a light chain constant region. In still yet other embodiments, the heavy chain constant region is selected from the group consisting of IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, and IgM.

[0045] In some embodiments, the anti-NK3R antibody or antigen-binding fragment thereof is an Fc variant that comprises an Fc silencing mutation. In some embodiments, the Fc silencing mutation comprises one or more amino acid substitutions to reduce antibody binding to FcγRI, FcγRII, or FcγRIIIa. In particular embodiments, the Fc variant comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 252, 254, and 256, wherein the Fc variant further comprises an amino acid deletion at position 447, and wherein amino acid numbering is according to the EU index. Examples of such embodiments of these FC variants include L234S, L235T, G236R, wherein K447 is deleted and L234S, L235T, G236R, M252Y, S254T, and T256E, wherein K447 is deleted.

[0046] In some embodiments, the inventions disclosed herein encompass a pharmaceutical composition comprising an antibody or antigen-binding fragment thereof described in the preceding paragraphs of this section and one or more pharmaceutically acceptable carriers, diluents, or excipients. In particular embodiments, the pharmaceutical composition comprises at least one additional antibody that binds to NK3R.

[0047] In some embodiments, the inventions disclosed herein encompass a nucleic acid encoding a heavy chain variable region having an amino acid sequence that is identical to a heavy chain variable region described herein. In particular embodiments, the inventions disclosed herein encompass a nucleic acid encoding a light chain variable region having an amino acid sequence that is identical to a light chain variable region described herein. In particular embodiments, the inventions disclosed herein encompass a nucleic acid encoding a heavy chain having an amino acid sequence that is identical to a heavy chain described herein or a nucleic acid encoding a light chain having an amino acid sequence that is identical to the light chain described herein.

[0048] In some embodiments, the inventions disclosed herein encompass an expression vector comprising at least one of (a) a nucleic acid encoding an antibody or antigen-binding fragment thereof comprising a heavy chain variable region having an amino acid sequence that is identical to a heavy chain variable region described herein; and (b) a nucleic acid encoding an antibody or antigen-binding fragment thereof comprising a light chain variable region having an amino acid sequence that is identical to a light chain variable region described herein. In particular embodiments, the inventions disclosed herein encompass a vector comprising both (a) and (b), wherein both (a) and (b) are corresponding parts of a heavy and light chain or antigen-binding fragment thereof.

[0049] In some embodiments, the inventions disclosed herein encompass a host cell comprising one or more nucleic acids described in the preceding paragraphs of this section or one or more expression vectors described in the preceding paragraphs of this section.

[0050] In some embodiments, the inventions disclosed herein encompass a process for producing an antibody or antigen-binding fragment thereof described in the preceding paragraphs of this section comprising (a) cultivating the host cell described in the preceding paragraphs under conditions such that the antibody or antigen-binding fragment thereof is expressed; and (b) recovering the expressed antibody or antigen-binding fragment thereof.

[0051] In some embodiments, the inventions disclosed herein encompass an article of manufacture useful for treating a sex hormone-related disorder comprising a receptacle comprising the antibody or antigen-binding fragment thereof described in the preceding paragraphs of this section, or a pharmaceutical composition comprising the same and instructional materials for using the same to treat the sex hormone-related disorder. In particular embodiments, the sex hormone-related disorder comprises moderate to severe vasomotor symptoms (VMS). In other

embodiments, the sex hormone-related disorder is prostate cancer. In yet other embodiments, the sex hormone-related disorder is an estrogen-dependent cancer.

[0052] In some embodiments, the inventions disclosed herein encompass a method of treating a sex hormone-related disorder comprising administering to a subject a therapeutically effective amount of the antibody or antigen-binding fragment thereof described in the preceding paragraphs of this section or a pharmaceutical composition comprising the same. In particular embodiments, the sex hormone-related disorder comprises moderate to severe vasomotor symptoms (VMS). In particular embodiments, the moderate to severe vasomotor symptom is caused by peri-menopause, menopause, or post-menopause. In particular embodiments, the moderate to severe vasomotor symptom is caused by endocrine therapy for a hormone-sensitive tumor. In particular embodiments, the frequency and severity of the moderate to severe vasomotor symptom is reduced compared to a placebo or no treatment. In particular embodiments, the moderate to severe vasomotor symptom is a hot flash. In particular embodiments, the patient has a serum estradiol level of $\leq$50 pg/mL. In particular embodiments, the patient has at least about 7 moderate to severe hot flushes per day. In particular embodiments, the patient has at least about 50 moderate to severe hot flushes per week. In particular embodiments, the frequency and severity of moderate to severe vasomotor symptoms associated with menopause is reduced when compared with placebo treatment at 4 weeks. In particular embodiments, the frequency and severity of moderate to severe vasomotor symptoms associated with menopause is reduced when compared with placebo treatment at 12 weeks. In particular embodiments, the levels of luteinizing hormone (LH) in the patient are each reduced by at least 70% compared to baseline levels of LH. In particular embodiments, the reduction in levels of LH is reversible.

[0053] In some embodiments, the sex hormone-related disorder is prostate cancer. In particular embodiments, the prostate cancer is a hormone responsive prostate cancer. In particular embodiments, the effective amount of the anti-NK3R antibody or antigen-binding fragment thereof reversibly lowers the patient's serum testosterone to a concentration lower than or equal to 20 ng/dL. In particular embodiments, the patient is a lower risk patient, an intermediate risk patient, or a high-risk patient. In particular embodiments, the patient is not undergoing androgen deprivation therapy (ADT). In particular embodiments, the patient is undergoing androgen deprivation therapy and the anti-NK3R antibody or antigen-binding fragment thereof is administered in combination with the ADT. In particular embodiments, the androgen deprivation therapy comprises administration of a gonadotropin releasing hormone (GnRH) agonist, a GnRH

antagonist, a histamine H2 receptor antagonist, a non-steroidal antiandrogen (NSAA), or an androgen receptor antagonist. The method of claim 57, wherein the androgen deprivation therapy comprises leuprolide, elagolix, linzagolix, relugolix, goserelin, triptorelin, buserelin, deslorelin, fertirelin, gonadorelin, histrelin, lecirelin, nafarelin, peforelin, triptorelin, abarelix, cetrorelix, degarelix, ganirelix, flutamide, nilutamide, bicalutamide, topilutamide, apalutamide, enzalutamide, darolutamide, cimetidine, proxalutamide, seviteronel, cioteronel, inocoterone acetate, RU-58841, dimethylcurcumin, AZ3514, arv-110, MTX-23, ARD-61, UT-34, FL442, MK-4541, LY2452473, GTx-024/Enobosarm, or GSK2881078. In particular embodiments, the anti-NK3R antibody is administered in combination with radiation treatment. In particular embodiments, the levels of testosterone in the patient are each reduced by at least 70% compared to baseline levels of testosterone. In particular embodiments, the reduction in levels of testosterone is reversible. In particular embodiments, the patient has undergone prostatectomy. In particular embodiments, the patient is suffering from non-metastatic prostate cancer.

[0054] In some embodiments, the sex hormone-related disorder is an estrogen-dependent cancer. In particular embodiments, the estrogen-dependent cancer is selected from the group consisting of breast cancer, ovarian cancer, endometrial cancer, and uterine cancer.

[0055] In some embodiments of the methods of treating a sex hormone-related disorder disclosed herein, the antibody or antigen-binding fragment thereof is administered via intravenous or subcutaneous injection. In some embodiments, the antibody or antigen-binding fragment thereof is administered via injection and the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or antigen-binding fragment thereof. In some embodiments, the antibody or antigen-binding fragment thereof is a disease modifying drug. In some embodiments, the antibody or antigen-binding fragment thereof is administered at least twice with at least one interval of 1 to 6 months. In some embodiments, the antibody or antigen-binding fragment thereof is administered at least twice with at least one interval of around 3 months.

[0056] In some embodiments of the methods of treating a sex hormone-related disorder disclosed herein, each dose of the antibody or antigen-binding fragment thereof is between about 20 mg and about 1800 mg; or each dose of the antibody or antigen-binding fragment thereof is about 75 mg, about 100 mg, about 150 mg, about 300 mg, or about 600 mg; or the dose of the antibody or antigen-binding fragment thereof is about 75 mg; or the dose of the antibody or antigen-binding fragment thereof is about 100 mg; or the dose of the antibody or antigen-binding fragment thereof is about 150 mg; or the dose of the antibody or antigen-binding fragment thereof

is about 300 mg; or the dose of the antibody or antigen-binding fragment thereof is about 600 mg; or the dose of the antibody or antigen-binding fragment thereof is between about 0.45 mg/kg and about 12 mg/kg.

[0057] In some embodiments of the methods of treating a sex hormone-related disorder disclosed herein, the antibody or antigen-binding fragment thereof is administered via injection and the minimum blood serum concentration reached by the antibody or antigen-binding fragment thereof between any two injections (Cmin) is at least between about 0.9 μg/mL and 250 μg/mL; or the maximum blood serum concentration reached by the antibody or antigen-binding fragment thereof after administration of an injection and prior to administration of a subsequent injection (Cmax) is at least between about 1.5 μg/mL and 275 μg/mL; or blood serum concentrations of the antibody or antigen-binding fragment thereof during treatment range between about 1.5 μg/mL and about 550 μg/mL; or the area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [$AUC_{0\text{-}inf}$]) injection may be at least around 75,000 ng*day/mL to at least around 10,500,000 ng*day/mL.

[0058] In some embodiments, the methods of treating a sex hormone-related disorder disclosed herein comprise an induction phase and a maintenance phase. In some embodiments, the induction dose of the antibody or antigen-binding fragment thereof is between about 20 mg and about 1000 mg or the maintenance dose of the antibody or antigen-binding fragment thereof is between about 20 mg and about 600 mg or the antibody or antigen-binding fragment thereof is administered via injection and the interval between two or more induction phase injections is between about 2 weeks and about 24 weeks, and the interval between two or more maintenance phase injections is between about 2 weeks and about 52 weeks.

[0059] In some embodiments of the methods of treating a sex hormone-related disorder disclosed herein, the first injection of the antibody or antigen-binding fragment thereof can be a loading dose, wherein the loading dose of the antibody or antigen-binding fragment thereof is up to three times the mass of the treatment dose or the loading dose of the antibody or antigen-binding fragment thereof is between about 100 mg and about 600 mg. In such embodiments, the second and additional injections of the antibody or antigen-binding fragment thereof can be treatment doses of at least 5 treatment injections, wherein the treatment dose of the antibody or antigen-binding fragment is between about 50 mg and about 300 mg.

[0060] In some embodiments of the methods of treating a sex hormone-related disorder disclosed herein, administration of the anti-NK3R antibody, or antigen-binding fragment thereof

results in the decrease in serum levels of at least one biomarker selected from the group consisting of: gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, or testosterone; or the administration of the anti-NK3R antibody, or antigen-binding fragment thereof results in the decrease in serum levels of at least one biomarker selected from the group consisting of: gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, or testosterone, and wherein the decrease is maintained for at least 12 weeks or at least 24 weeks following the final dose.

[0061] In some embodiments of the methods of treating a sex hormone-related disorder disclosed herein, the method further comprises administering one or more additional therapeutic agents selected from the group consisting of a selective estrogen receptor modulator (SERM), a gonadotropin-releasing hormone (GnRH) agonist, a gonadotropin-releasing hormone (GnRH) antagonist, nonsteroidal anti-androgen, kappa opioid agonist, selective estrogen receptor degrader (SERD).

[0062] In some embodiments, the inventions disclosed herein encompass an antibody or antigen-binding fragment thereof described in the preceding paragraphs of this section or a pharmaceutical composition comprising the same for use in the treatment of a sex hormone-related disorder.

[0063] In some embodiments, the inventions disclosed herein encompass an antibody or antigen-binding fragment thereof described in the preceding paragraphs of this section or a pharmaceutical composition comprising the same for use in the manufacture of a medicament for the treatment of a sex hormone-related disorder.

[0064] Anti-NK3R antibodies

[0065] The present disclosure is directed to anti-NK3R antibodies and their use in the diagnosis, theragnosis, treatment and/or prophylaxis of a sex hormone-related disorder and symptoms thereof. As used herein, the term "antibody" or "immunoglobulin" are used interchangeably and in the broadest sense and cover both intact molecules and immunologically-reactive fragments thereof. These terms cover, for example, synthetic antibodies, monoclonal antibodies, recombinantly produced antibodies, intrabodies, monovalent antibodies, human antibodies, humanized antibodies, chimeric antibodies, CDR-grafted antibodies, primatized antibodies, Fab fragments, F(ab') fragments, $F(ab')_2$ fragments, F(ab)c fragments, single-chain

FvFcs (scFvFc), single-chain Fvs (scFv), anti-idiotypic (anti-Id) antibodies, and any other immunologically-reactive/antigen-binding fragments thereof.

[0066] As used herein, the term "anti-NK3R antibody(ies)" describes antibodies that specifically recognize, bind to, or otherwise associate with an NK3R molecule present on a cell (e.g., hypothalamic KNDy neurons). As used herein terms, "specifically recognize," "bind," and "binds" are intended to mean, unless indicated otherwise, the ability of a protein or molecule to form a chemical bond or attractive interaction with another protein or molecule, which results in proximity of the two proteins or molecules as determined by common methods known in the art.

[0067] Human antibodies are grouped into five distinct classes that can be distinguished biochemically and depending on the amino acid sequence of the constant domain of their heavy chains, can readily be assigned to the appropriate class. For historical reasons, the major classes of intact antibodies are termed IgA, IgD, IgE, IgG, and IgM. In humans, the IgG and IgA classes may be further divided into recognized subclasses (isotypes), i.e., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2 depending on structure and certain biochemical properties. It will be appreciated that the IgG isotypes in humans are named in order of their abundance in serum with IgG1 being the most abundant.

[0068] While all five classes of antibodies (i.e., IgA, IgD, IgE, IgG, and IgM) and all isotypes (i.e., IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2), as well as variations thereof, are within the scope of the present disclosure, preferred embodiments belonging to the IgG class are discussed in some detail solely for the purposes of illustration. It will be understood that such disclosure is, however, merely demonstrative of exemplary compositions and methods and is not in any way limiting.

[0069] In this respect, human IgG immunoglobulins comprise two identical light polypeptide chains of molecular weight approximately 23,000 Daltons, and two identical heavy chains of molecular weight 53,000-70,000 depending on the isotype. Heavy-chain constant domains that correspond to the different classes of antibodies are denoted by the corresponding lower case Greek letter α, δ, ε, γ, and μ, respectively. The light chains of the antibodies from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains. Those skilled in the art will appreciate that the subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0070] The four chains are joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" and continuing through the

variable region to the dual ends of the "Y." Each light chain is linked to a heavy chain by one covalent disulfide bond while two disulfide linkages in the hinge region join the heavy chains. The respective heavy and light chains also have regularly spaced intrachain disulfide bridges the number of which may vary based on the isotype of IgG.

[0071] Each heavy chain has at one end a variable region (V_H) followed by a number of constant regions. Each light chain has a variable region at one end (V_L) and a constant region at its other end; the constant region of the light chain is aligned with the first constant region of the heavy chain, and the light chain variable region is aligned with the variable region of the heavy chain. The variable regions of both the light (V_L) and heavy (V_H) chain portions determine antigen recognition and specificity. Conversely, the constant regions of the light chain (C_L) and the heavy chain (C_H1, C_H2 or C_H3) confer and regulate important biological properties such as secretion, transplacental mobility, circulation half-life, complement binding, and the like. By convention, the numbering of the constant region regions increases as they become more distal from the antigen binding site or amino-terminus of the antibody. Thus, the amino or N-terminus of the antibody comprises the variable region and the carboxy or C-terminus comprises the constant region. Thus, the C_H3 and C_L regions actually comprise the carboxy-terminus of the heavy and light chain, respectively.

[0072] Portions of the variable regions of both the heavy chain and light chain differ extensively in sequence among immunoglobulins and these hypervariable sites largely define the binding and specificity of a particular antibody. These hypervariable sites manifest themselves in three segments, known as complementarity determining regions (CDRs). The more highly conserved portions of variable regions flanking the CDRs are termed framework regions (FRs). More specifically, in naturally occurring monomeric IgG antibodies, the six CDRs present on each arm of the antibody are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen-binding site as the antibody assumes its three-dimensional configuration *in vivo* or *in vitro*. CDRs encompass amino acid residues identified using any sequence or structure-based method or nomenclature system known in the art and as described below.

[0073] By way of example, CDRs may be defined using the nomenclature described by Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.), specifically, residues 31-35 (CDR-H1), 50-66 (CDR-H2), and 99-114 (CDR-H3) in the heavy chain variable region and residues 24-34 (CDR-L1), 50-56 (CDR-L2), and 89-97 (CDR-L3) in the

light chain variable region. By way of another example, CDRs may be defined using the nomenclature described by Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.), specifically, residues 31-35 (CDR-H1), 50-68 (CDR-H2), and 101-117 (CDR-H3) in the heavy chain variable region and residues 24-34 (CDR-L1), 50-56 (CDR-L2), and 89-97 (CDR-L3) in the light chain variable region.

[0074] CDRs vary considerably from antibody to antibody (and by definition will not exhibit homology with the Kabat consensus sequences). Maximal alignment of framework residues frequently requires the insertion of spacer residues in the numbering system, to be used for the Fv region. In addition, the identity of certain individual residues at any given Kabat site number may vary from antibody chain to antibody chain due to interspecies or allelic divergence.

[0075] One skilled in the art could readily define, identify derive and/or enumerate the CDRs as defined by Kabat et al. for each respective antibody heavy and light chain sequence set forth herein. Accordingly, each of the subject CDRs and antibodies comprising CDRs defined by all such nomenclature are expressly included within the scope of the instant disclosure.

[0076] The framework regions comprise the remainder of the heavy and light chain variable regions and are thus comprised of a non-contiguous sequence between about 100-120 amino acids in length. For example, using the nomenclature of Kabat et al., framework region 1 corresponds to the region of the variable region encompassing amino acids 1-30; framework region 2 corresponds to the region of the variable region encompassing amino acids 36-49; framework region 3 corresponds to the region of the variable region encompassing amino acids 66-94, and framework region 4 corresponds to the region of the variable region from amino acids 103 to the end of the variable region.

[0077] The framework regions show less inter-molecular variability in amino acid sequence and largely adopt a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β-sheet structure. Thus, these framework regions act to form a scaffold that provides for positioning the six CDRs in correct orientation by inter-chain, non-covalent interactions. The antigen-binding site formed by the positioned CDRs defines a surface complementary to the epitope on the immunoreactive antigen. This complementary surface promotes the non-covalent binding of the antibody to the immunoreactive antigen epitope.

[0078] All or part of the heavy and light chain variable regions may be recombined or engineered using standard recombinant and expression techniques to provide improve one or more properties of the resultant antibody. That is, the heavy or light chain variable region from a first

antibody (or any portion thereof) may be mixed and matched with any selected portion of the heavy or light chain variable region from a second antibody. For example, in one embodiment, the entire light chain variable region comprising the three light chain CDRs of a first antibody may be paired with the entire heavy chain variable region comprising the three heavy chain CDRs of a second antibody. Moreover, in other embodiments, individual heavy and light chain CDRs derived from various antibodies may be mixed and matched to provide the desired antibody having optimized characteristics. Thus, an exemplary antibody may comprise three light chain CDRs from a first antibody, two heavy chain CDRs derived from a second antibody and a third heavy chain CDR from a third antibody.

[0079] With the aforementioned structural considerations in mind, those skilled in the art will appreciate that the antibodies in accordance with the invention disclosed herein may comprise any one of a number of functional embodiments. In this respect, compatible antibodies may comprise any immunoreactive antibody (as the term is defined herein) that provides the desired physiological response in a subject. While any of the disclosed antibodies may be used in conjunction with the present teachings, certain embodiments of the invention will comprise chimeric, humanized, or human monoclonal antibodies or immunoreactive fragments thereof. Moreover, it will be understood that such configurations are not mutually exclusive and that compatible individual antibodies may comprise one or more of the functional aspects disclosed herein. For example, a compatible antibody may comprise a single chain diabody with humanized variable regions or a fully human full-length antibody with Fc modifications that alter the glycosylation pattern to modulate serum half-life. Other exemplary embodiments are readily apparent to those skilled in the art and may easily be discernable as being within the scope of the invention.

[0080] Antibodies produced by naive libraries (either natural or synthetic) can be of moderate affinity (K_a of about 10^6 to 10^7 M^{-1}), but affinity maturation can also be mimicked *in vitro* by constructing and reselecting from secondary libraries as described in the art. For example, mutations can be introduced at random *in vitro* by using error-prone polymerase.

[0081] Additionally, affinity maturation can be performed by randomly mutating one or more CDRs, e.g., using PCR with primers carrying random sequence spanning the CDR of interest, in selected individual Fv clones and screening for higher affinity clones. Another approach is to recombine the V_H or V_L regions selected by phage display with repertoires of naturally occurring variable region variants obtained from unimmunized donors and screen for higher affinity in

several rounds of chain reshuffling. This technique allows the production of antibodies and antibody fragments with a dissociation constant K_d (k_{off}/k_{on}) of about 10^{-9} M or less.

[0082] Regardless of the type of antibody (e.g., chimeric, humanized, etc.), those skilled in the art will appreciate that immunoreactive or antigen-binding fragments of the same may also be used. In the broadest sense, an antibody fragment comprises at least a portion of an intact antibody (e.g., a naturally occurring immunoglobulin). More particularly the term "fragment" refers to a part or portion of an antibody or antibody chain comprising fewer amino acid residues than an intact or complete antibody or antibody chain. As used herein, the term "antigen-binding fragment" refers to a polypeptide fragment of an immunoglobulin or antibody that binds antigen or competes with intact antibody (i.e., with the intact antibody from which they were derived) for antigen binding (i.e., specific binding). As used herein, antigen-binding fragments included an antibody light chain (V_L), an antibody heavy chain (V_H), a single chain antibody (scFv), a $F(ab')_2$ fragment, a Fab fragment, an Fd fragment, an Fv fragment, single region antibody fragments, linear antibodies, and single-chain antibody molecules.

[0083] Those skilled in the art will also appreciate that antibody fragments can be obtained via chemical or enzymatic treatment of an intact or complete antibody (e.g., antibody or antibody chain) or by recombinant means. In this regard, while various antibody fragments are defined in terms of the digestion of an intact antibody, one skilled in the art will appreciate that such fragments may be synthesized *de novo* either chemically or by using recombinant DNA methodology.

[0084] By way of example, papain digestion of antibodies produces two identical antigen-binding fragments, called Fab fragments, each with a single antigen-binding site, and a residual Fc fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen-binding sites and is still capable of cross-linking antigen. The Fab fragment also contains the constant region of the light chain and the first constant region (C_H1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy-chain C_H1 region including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant regions bear at least one free thiol group. $F(ab')_2$ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0085] By way of further example, an Fv fragment is an antibody fragment that contains a complete antigen recognition and binding site. This region is made up of a dimer of one heavy and one light chain variable region in tight association, which can be covalent in nature, for example in scFv. It is in this configuration that the three CDRs of each variable region interact to define an antigen binding site on the surface of the V_H-V_L dimer. Collectively, the six CDRs or a subset thereof confer antigen binding specificity to the antibody. However, even a single variable region (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although usually at a lower affinity than the entire binding site.

[0086] In some embodiments an anti-NK3R antibody fragment, for example, is one that comprises the Fc region, retains at least one of the biological functions normally associated with the Fc region when present in an intact antibody, such as FcRn binding, antibody half-life modulation, ADCC function and complement binding. In one embodiment, an antibody fragment is a monovalent antibody that has an *in vivo* half-life substantially similar to an intact antibody. For example, such an antibody fragment may comprise on antigen binding arm linked to an Fc sequence capable of conferring *in vivo* stability to the fragment.

[0087] In addition to various modifications, substitutions, additions, or deletions to the variable or binding regions of anti-NK3R antibodies disclosed herein, those skilled in the art will appreciate that selected embodiments may also comprise substitutions or modifications of the constant region (i.e., the Fc region). More particularly, it is contemplated that anti-NK3R antibodies disclosed herein may contain one or more additional amino acid residue substitutions, mutations and/or modifications, which result in a compound with preferred characteristics including, but not limited to: altered pharmacokinetics, increased serum half-life, increase binding affinity, reduced immunogenicity, increased production, altered Fc ligand binding, reduced ADCC or CDC activity, altered glycosylation and/or disulfide bonds, and modified binding specificity.

[0088] As used herein, the term "Fc region" defines a C-terminal region of an immunoglobulin heavy chain, including native sequence Fc regions and variant Fc regions. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The C-terminal lysine (residue 447 according to the EU numbering system) of the Fc region may be removed, for example, during production or purification of the antibody, or by recombinantly engineering the nucleic acid encoding a heavy chain of the antibody. Accordingly, a composition of intact antibodies may comprise antibody

populations with all K447 residues removed, antibody populations with no K447 residues removed, and antibody populations having a mixture of antibodies with and without the K447 residue. A functional Fc region possesses an effector function of a native sequence Fc region. Exemplary effector functions include C1q binding; CDC; Fc receptor binding; ADCC; phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding region (e.g., an antibody variable region) and can be assessed using various assays as disclosed, for example, in definitions herein.

[0089] As used herein, the term "Fc receptor" or FcR, describes a receptor that binds to the Fc region of an antibody. In some embodiments, an FcR is a native human FcR. In some embodiments, an FcR is one that binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, Fc.RII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of those receptors. Fcγll receptors include FcγRIIA (an activating receptor) and FcγRIIB (an inhibiting receptor), which have similar amino acid sequences that differ primarily in the cytoplasmic regions thereof. Activating receptor FcγRIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic region. Inhibiting receptor FcyRIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic region. Methods of measuring binding to FcRn are known in the art.

[0090] As used herein, "complement dependent cytotoxicity" or CDC refers to the lysing of a target cell in the presence of complement. The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule, an antibody for example, complexed with a cognate antigen. To assess complement activation, a CDC assay may be performed.

[0091] "Antibody-dependent cell-mediated cytotoxicity" or ADCC refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enables these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. Lysis of the target cell is extracellular, requires direct cell-to-cell contact, and does not involve complement.

[0092] Variants of anti-NK3R antibodies disclosed herein that have altered FcR binding affinity or ADCC activity are those that have either enhanced or diminished FcR binding activity and/or ADCC activity compared to a parent or unmodified antibody comprising a native sequence

Fc region. A variant antibody that displays increased binding to an FcR binds at least one FcR with better affinity than the parent or unmodified antibody or to a antibody comprising a native sequence Fc region. A variant antibody that displays decreased binding to an FcR, binds at least one FcR with worse affinity than the parent or unmodified antibody or to a antibody comprising a native sequence Fc region. Such variants which display decreased binding to an FcR may possess little or no appreciable binding to an FcR, e.g., 0-20% binding to the FcR compared to a native sequence IgG Fc region, e.g., as determined by techniques well known in the art.

[0093] Although antibodies with increased tumor-destroying functions of Fcs are desirable for tumor targeting, those with benign immune-silenced Fc's are advantageous over native Fcs when ADCC and/or CDC would be detrimental to a patient. Methods of altering Fcs in order to achieve such an objective are known in the art. Some examples include, but are not limited to, mutating residues that are responsible for FcγR or C1q binding or using IgG2 or IgG4, rather than IgG1, Fc. Other examples contemplated in accordance with the inventions disclosed herein include IgG1 variants comprising STR (L234S/L235T/G236R), LALA (L234A/L235A), and LAGA (L234A/G237A) mutations.

[0094] As to FcRn, anti-NK3R antibodies disclosed herein can also encompass Fc variants with modifications to the constant region that provide half-lives (e.g., serum half-lives) in a mammal, preferably a human, of greater than 5 days, greater than 10 days, greater than 15 days, preferably greater than 20 days, greater than 25 days, greater than 30 days, greater than 35 days, greater than 40 days, greater than 45 days, greater than 2 months, greater than 3 months, greater than 4 months, or greater than 5 months. The increased half-lives of the antibodies (or Fc containing molecules) of the present invention in a mammal, preferably a human, results in a higher serum titer of antibodies or antibody fragments in the mammal, and thus, reduces the frequency of the administration of antibodies or antibody fragments and/or reduces the concentration of antibodies or antibody fragments to be administered. Antibodies having increased *in vivo* half-lives can be generated by techniques known to those of skill in the art. For example, antibodies with increased *in vivo* half-lives can be generated by modifying (e.g., substituting, deleting, or adding) amino acid residues identified as involved in the interaction between the Fc region and the FcRn receptor. Binding to human FcRn *in vivo* and serum half-life of human FcRn high affinity binding polypeptides can be assayed, e.g., in transgenic mice or transfected human cell lines expressing human FcRn, or in primates to which the polypeptides with a variant Fc region are administered.

[0095] In some embodiments, variants of anti-NK3R antibodies disclosed herein can encompass an Fc region with modifications that improve their half-lives (e.g., serum half-lives) in a human. Studies have shown that some Fc mutation that enhances FcRn binding results in increased binding to rheumatoid factor (RF), whereas some Fc mutation combinations enhance FcRn binding and prolong antibody half-life without increased binding to RF, e.g., N434A/Y436T/Q438R/S440E (ACT1), N434A/Y436V/Q438R/S440E (ACT2), M428L/N434A/Y436T/Q438R/S440E (ACT3), M428L/N434A/Y436V/Q438R/S440E (ACT4), M428L/N434A/Q438R/S440E (ACT5) (positions numbered according to EU Index numbering). In some embodiments, the anti-NK3R antibodies disclosed herein comprise an Fc region comprising any set of mutations selected from ACT1, ACT2, ACT3, ACT4, or ACT5. In other embodiments, the anti-NK3R antibody or antigen-binding fragment thereof is an Fc variant that comprises an Fc silencing mutation. In some embodiments, the Fc silencing mutation comprises one or more amino acid substitutions to reduce antibody binding to FcγRI, FcγRII, or FcγRIIIa. In particular embodiments, the Fc variant comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 252, 254, and 256, wherein the Fc variant further comprises an amino acid deletion at position 447, and wherein amino acid numbering is according to the EU index. Examples of such embodiments of these FC variants include L234S, L235T, G236R, wherein K447 is deleted and L234S, L235T, G236R, M252Y, S254T, and T256E, wherein K447 is deleted.

[0096] In still other embodiments, glycosylation patterns or compositions of the anti-NK3R antibodies disclosed herein may be modified. More particularly, preferred embodiments may comprise one or more engineered glycoforms, i.e., an altered glycosylation pattern or altered carbohydrate composition that is covalently attached to a molecule comprising an Fc region. Engineered glycoforms may be useful for a variety of purposes, including but not limited to enhancing or reducing effector function, increasing the affinity of the antibody for a target antigen or facilitating production of the antibody. In cases where reduced effector function is desired, it will be appreciated that the antibody may be engineered to express in an aglycosylated form. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. That is, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site.

[0097] The amino acid sequences of the antibodies described in the foregoing paragraphs are provided below:

mAb 20810 // mAb 27883 VH (SEQ ID NO: 1)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSS

mAb 20810 // mAb 25123 // mAb 27889 // mAb 27897 // mAb 27900 // mAb 27922 VL (SEQ ID NO: 2)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAIKPLIYYSSTLQSGVPSRFSGSGSGTDYTLTI
SSLQPEDFAIYYCQQYDSSPLTFGQGTKLEIK

mAb 20810 // mAb 27883 // mAb 27895 Heavy Chain (SEQ ID NO: 3)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 20810 // mAb 25123 // mAb 27897 // mAb 27900 // mAb 27922 Light Chain (SEQ ID NO: 4)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAIKPLIYYSSTLQSGVPSRFSGSGSGTDYTLTI
SSLQPEDFAIYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 20811 VH (SEQ ID NO: 5)

QVQLQQSRAELVKPAASVTLSCKASGYTFTDHYLHWVRQSPSQGLEWIGWIGPTKGDTNYAQKFKGKATMT
VDKSASTTYLQLSSLTSEDSAVYYCARQDLSYGYHLYYWYFDFWGPGTMVTVSS

mAb 20811 VL (SEQ ID NO: 6)

DIQMTQTPTSMPASLGERVTIRCRTSQDITGFLNWYQQKPDGTITPLIYYTSILLSGVPSRFSGSGSGTDYSLTIS
HLEPEDFAMYFCQQYDTSPYTFGPGTRLELK

mAb 20811 Heavy Chain (SEQ ID NO: 7)

QVQLQQSRAELVKPAASVTLSCKASGYTFTDHYLHWVRQSPSQGLEWIGWIGPTKGDTNYAQKFKGKATMT
VDKSASTTYLQLSSLTSEDSAVYYCARQDLSYGYHLYYWYFDFWGPGTMVTVSSASTKGPSVFPLAPSSKSTSG
GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKV
DKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE

MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 20811 Light Chain (SEQ ID NO: 8)

DIQMTQTPTSMPASLGERVTIRCRTSQDITGFLNWYQQKPDGTITPLIYYTSILLSGVPSRFSGSGSGTDYSLTIS
HLEPEDFAMYFCQQYDTSPYTFGPGTRLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWK
VDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 20812 VH (SEQ ID NO: 9)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQG
RVTMTRDTSISTAYMELSRLRSDDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSS

mAb 20812 // mAb 26105 // mAb 27860 // mAb 27864 // mAb 27926 VL (SEQ ID NO: 10)

DIQMTQSPSSLSASVGDRVTITCRTSQDITGFLNWYQQKPGKAPKLLLYYTSILLSGVPSRFSGSGSGTDYTLTIS
SLQPEDFATYYCQQYDTSPYTFGQGTRLEIK

mAb 20812 // mAb 27886 // mAb 27903 Heavy Chain (SEQ ID NO: 11)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQGRV
TMTRDTSISTAYMELSRLRSDDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 20812 // mAb 26105 // mAb 27860 // mAb 27864 // mAb 27926 Light Chain (SEQ ID NO: 12)

DIQMTQSPSSLSASVGDRVTITCRTSQDITGFLNWYQQKPGKAPKLLLYYTSILLSGVPSRFSGSGSGTDYTLTIS
SLQPEDFATYYCQQYDTSPYTFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 20813 VH (SEQ ID NO: 13)

QVQLQQSRAELVKPAGSVTLSCKASGYTFTDHYLHWVKQSPSQGLEWIGWIGPTNGDTSYAQKFKGKATMT
VDKSASTTFLQLSSLTSEDSAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSS

mAb 20813 VL (SEQ ID NO: 14)

DIQMTQTPSSMPASLGERVTISCRASQGINSYLNWYQQKPDGTIKPLIYYSSTLQSGVPSRFSGSGSGTDYSLTI
SSLEPEDFAIYYCQQYDSSPLTFGSGTKLEIK

mAb 20813 Heavy Chain (SEQ ID NO: 15)

QVQLQQSRAELVKPAGSVTLSCKASGYTFTDHYLHWVKQSPSQGLEWIGWIGPTNGDTSYAQKFKGKATMT
VDKSASTTFLQLSSLTSEDSAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 20813 Light Chain (SEQ ID NO: 16)

DIQMTQTPSSMPASLGERVTISCRASQGINSYLNWYQQKPDGTIKPLIYYSSTLQSGVPSRFSGSGSGTDYSLTI
SSLEPEDFAIYYCQQYDSSPLTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 25123 // mAb 27895 VH (SEQ ID NO: 17)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKG
RVTITVDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSS

mAb 25123 Heavy Chain (SEQ ID NO: 18)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWGPTNGDTSYAQKFKGRVTIT
VDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 25125 // mAb 25129 CDR-H1 (SEQ ID NO: 19)

NTWMN

mAb 25125 // mAb 25129 CDR-H2 (SEQ ID NO: 20)

LIKDKYSNYEANYAESIKG

mAb 25125 // mAb 25129 CDR-H3 (SEQ ID NO: 21)

DYYDGNFYYEDYYVMDA

mAb 25125 // mAb 25129 CDR-L1 (SEQ ID NO: 22)

KASQNVGTDVD

mAb 25125 // mAb 25129 CDR-L2 (SEQ ID NO: 23)

GASNRYS

mAb 25125 // mAb 25129 CDR-L3 (SEQ ID NO: 24)

LQYNYNPRT

mAb 25125 // mAb 25129 // mAb 27851 // mAb 27880 // mAb 27908 VH (SEQ ID NO: 25)

EVQLVESGGGLVQPGRSLRLSCTASGFTFSNTWMNWVRQAPGKGLEWVGLIKDKYSNYEANYAESIKGRFTI
SRDDSKSIAYLQMNSLKTEDTAVYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 25125 // mAb 25129 // mAb 27851 // mAb 27868 // mAb 27905 // mAb 27916 // mAb 27927 VL (SEQ ID NO: 26)

DIVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIYGASNRYSGVPDRFSGSGSGTDFT
LTISSLQAEDVAVYYCLQYNYNPRTFGQGTKLEIK

mAb 25125 // mAb 27860 // mAb 27870 CH (SEQ ID NO: 27)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLYITREPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

mAb 25125 // mAb 25129 // mAb 26105 // mAb 26106 // mAb 27860 // mAb 27870 CL (SEQ ID NO: 28)

RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTL
SKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 25125 Heavy Chain (SEQ ID NO: 29)

EVQLVESGGGLVQPGRSLRLSCTASGFTFSNTWMNWVRQAPGKGLEWVGLIKDKYSNYEANYAESIKGRFTI
SRDDSKSIAYLQMNSLKTEDTAVYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 25125 // mAb 25129 // mAb 27851 // mAb 27868 // mAb 27916 // mAb 27924 // mAb 27927 Light Chain (SEQ ID NO: 30)

DIVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIYGASNRYSGVPDRFSGSGSGTDFT
LTISSLQAEDVAVYYCLQYNYNPRTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ
WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 25128 // mAb 27862 VH (SEQ ID NO: 31)

EVQLVESGGGLVQPGRSLRLSCTASGFTFSNTWMNWVRQAPGKGLEWVGLIKDKYSNYEANYAESVKGRFTI
SRDDSKSIAYLQMNSLKTEDTAVYYCTRDYYDGNYFYEDHYVMDAWGQGTLVTVSS

mAb 25128 // mAb 27862 VL (SEQ ID NO: 32)

DIVMTQSPDSLAVSLGERATINCKASQKVVTNVDWYQQKPGQPPKLLIYGASNRYTGVPDRFSGSGSGTDFT
LTISSLQAEDVAVYYCLQYQYTPRTFGQGTKLEIK

mAb 25128 Heavy Chain (SEQ ID NO: 33)

EVQLVESGGGLVQPGRSLRLSCTASGFTFSNTWMNWVRQAPGKGLEWVGLIKDKYSNYEANYAESVKGRFTI
SRDDSKSIAYLQMNSLKTEDTAVYYCTRDYYDGNYFYEDHYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 25128 // mAb 27862 Light Chain (SEQ ID NO: 34)

DIVMTQSPDSLAVSLGERATINCKASQKVVTNVDWYQQKPGQPPKLLIYGASNRYTGVPDRFSGSGSGTDFT
LTISSLQAEDVAVYYCLQYQYTPRTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ
WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 25129 Heavy Chain (SEQ ID NO: 35)

EVQLVESGGGLVQPGRSLRLSCTASGFTFSNTWMNWVRQAPGKGLEWVGLIKDKYSNYEANYAESIKGRFTI
SRDDSKSIAYLQMNSLKTEDTAVYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 26105 // mAb 26106 // mAb 27860 // mAb 27870 CDR-H1 (SEQ ID NO: 36)

DHYLH

mAb 26105 // mAb 27860 CDR-H2 (SEQ ID NO: 37)

WIGPTKGDTNYAQKFQG

mAb 26105 // mAb 27860 CDR-H3 (SEQ ID NO: 38)

QDLSYGYHLYYWYFDF

mAb 26105 // mAb 27860 CDR-L1 (SEQ ID NO: 39)

RTSQDITGFLN

mAb 26105 // mAb 27860 CDR-L2 (SEQ ID NO: 40)

YTSILLS

mAb 26105 // mAb 27860 CDR-L3 (SEQ ID NO: 41)

QQYDTSPYT

mAb 26105 // mAb 27860 VH (SEQ ID NO: 42)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQGRV
TMTRDTSISTAYMELSRLRSDDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSS

mAb 26105 // mAb 26106 // mAb 25129 CH (SEQ ID NO: 43)

ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSL
GTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVS
HEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKA
KGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

mAb 26105 Heavy Chain (SEQ ID NO: 44)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQGRV
TMTRDTSISTAYMELSRLRSDDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 26106 // mAb 27870 CDR-H2 (SEQ ID NO: 45)

WIGPTNGDTSYAQKFQG

mAb 26106 // mAb 27870 CDR-H3 (SEQ ID NO: 46)

QDLTVYFGLLFYYFDY

mAb 26106 // mAb 27870 CDR-L1 (SEQ ID NO: 47)

RASQGISSYLN

mAb 26106 // mAb 27870 CDR-L2 (SEQ ID NO: 48)

YASTLQS

mAb 26106 // mAb 27870 CDR-L3 (SEQ ID NO: 49)

QQYDSSPLT

mAb 26106 // mAb 27859 // mAb 27870 // mAb 27873 // mAb 27879 VH (SEQ ID NO: 50)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFQGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDLTVYFGLLFYYFDYWGQGVMVTVSS

mAb 26106 // mAb 26107 // mAb 27859 // mAb 27870 // mAb 27920 VL (SEQ ID NO: 51)

DIQMTQSPSSLSASVGDRVTITCRASQGISSYLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTIS
SLQPEDFAIYYCQQYDSSPLTFGQGTKLEIK

mAb 26106 Heavy Chain (SEQ ID NO: 52)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFQGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDLTVYFGLLFYYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 26106 // mAb 26107 // mAb 27870 Light Chain (SEQ ID NO: 53)

DIQMTQSPSSLSASVGDRVTITCRASQGISSYLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTIS
SLQPEDFAIYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 26107 // mAb 26108 VH (SEQ ID NO: 54)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFQG
RVTITVDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSS

mAb 26107 // mAb 26108 Heavy Chain (SEQ ID NO: 55)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFQGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 26108 VL (SEQ ID NO: 56)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTI
SSLQPEDFAIYYCQQYDSSPLTFGQGTKLEIK

mAb 26108 Light Chain (SEQ ID NO: 57)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTI
SSLQPEDFAIYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27851 // mAb 27880 // mAb 27908 Heavy Chain (SEQ ID NO: 58)

EVQLVESGGGLVQPGRSLRLSCTASGFTFSNTWMNWVRQAPGKGLEWVGLIKDKYSNYEANYAESIKGRFTI
SRDDSKSIAYLQMNSLKTEDTAVYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27858 VH (SEQ ID NO: 59)

EVQLVETGGGLVQPGSSLKLSCATSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSRVYLQMNTLRDQDTATYYCTRDYYDGNFYYEDYYVMDAWGQGASVTVSS

mAb 27858 VL (SEQ ID NO: 60)

NTVMTQSPTTMFKSVGDRVTLNCKASQNVGTDVDWYQQKTGQSPKLLIFGASNRYSGVPDRFTGSGSGTD
FTLTITNMQAADLAFYYCLQYNYNPRTFGGGTKLELK

mAb 27858 Heavy Chain (SEQ ID NO: 61)

EVQLVETGGGLVQPGSSLKLSCATSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSRVYLQMNTLRDQDTATYYCTRDYYDGNFYYEDYYVMDAWGQGASVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27858 Light Chain (SEQ ID NO: 62)

NTVMTQSPTTMFKSVGDRVTLNCKASQNVGTDVDWYQQKTGQSPKLLIFGASNRYSGVPDRFTGSGSGTD
FTLTITNMQAADLAFYYCLQYNYNPRTFGGGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27859 // mAb 27873 // mAb 27879 Heavy Chain (SEQ ID NO: 63)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFQGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDLTVYFGLLFYYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE

EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 27859 Light Chain (SEQ ID NO: 64)

DIQMTQSPSSLSASVGDRVTITCRASQGISSYLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLIS
SLQPEDFAIYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27860 Heavy Chain (SEQ ID NO: 65)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQGRV
TMTRDTSISTAYMELSRLRSDDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 27862 Heavy Chain (SEQ ID NO: 66)

EVQLVESGGGLVQPGRSLRLSCTASGFTFSNTWMNWVRQAPGKGLEWVGLIKDKYSNYEANYAESVKGRFTI
SRDDSKSIAYLQMNSLKTEDTAVYYCTRDYYDGNYFYEDHYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27863 VH (SEQ ID NO: 67)

EVQLVETGGGLVQPGSSLKLSCATSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESVKGRCTI
SRDDSKSRVYLQMNTLRDQDTATYYCTRDYYDGNYFYEDHYVMDAWGQGASVTVSS

mAb 27863 VL (SEQ ID NO: 68)

NTVMTQSPTSMIISVGDRVTMNCKASQKVVTNVDWYQQKTGQSPKLLIYGASNRYTGVPDRFTGSGSGTDF
TLTITNMQAEDLAVYYCLQYNYTPRTFGGGTKLELK

mAb 27863 Heavy Chain (SEQ ID NO: 69)

EVQLVETGGGLVQPGSSLKLSCATSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESVKGRCTI
SRDDSKSRVYLQMNTLRDQDTATYYCTRDYYDGNYFYEDHYVMDAWGQGASVTVSSASTKGPSVFPLAPSS
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPS
NTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV
DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP

PSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQG
NVFSCSVMHEALHNHYTQKSLSLSPG

mAb 27863 Light Chain (SEQ ID NO: 70)

NTVMTQSPTSMIISVGDRVTMNCKASQKVVTNVDWYQQKTGQSPKLLIYGASNRYTGVPDRFTGSGSGTDF
TLTITNMQAEDLAVYYCLQYNYTPRTFGGGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27864 // mAb 27869 // mAb 27912 VH (SEQ ID NO: 71)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQRLEWMGWIGPTKGDTNYAQKFQGRVT
ITRDTSASTAYMELSSLRSEDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSS

mAb 27864 // mAb 27869 // mAb 27912 Heavy Chain (SEQ ID NO: 72)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQRLEWMGWIGPTKGDTNYAQKFQGRVT
ITRDTSASTAYMELSSLRSEDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 27867 // mAb 27922 VH (SEQ ID NO: 73)

QVQLVQSGAELKKPGSSVKVSCKASGYTFTDHYLHWVKQAPGQGLEWIGWIGPTNGDTSYAQKFKGRATM
TVDKSTSTTYMELSSLRSEDSAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSS

mAb 27867 // mAb 27875 // mAb 27883 // mAb 27888 VL (SEQ ID NO: 74)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAPKLLIYYSSTLQSGVPSRFSGSGSGTDFTLTI
SSLQPEDFATYYCQQYDSSPLTFGQGTKLEIK

mAb 27867 // mAb 27878 // mAb 27922 Heavy Chain (SEQ ID NO: 75)

QVQLVQSGAELKKPGSSVKVSCKASGYTFTDHYLHWVKQAPGQGLEWIGWIGPTNGDTSYAQKFKGRATM
TVDKSTSTTYMELSSLRSEDSAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27867 // mAb 27875 // mAb 27883 // mAb 27888 // mAb 27920 Light Chain (SEQ ID NO: 76)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAPKLLIYYSSTLQSGVPSRFSGSGSGTDFTLTI
SSLQPEDFATYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27868 // mAb 27890 VH (SEQ ID NO: 77)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKG
RFTISRDDSKSIVYLQMNSLKTEDTAVYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 27868 // mAb 27890 // mAb 27931 Heavy Chain (SEQ ID NO: 78)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSIVYLQMNSLKTEDTAVYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27869 // mAb 27886 // mAb 27887 VL (SEQ ID NO: 79)

DIQMTQSPSSLSASVGDRVTITCRTSQDITGFLNWYQQKPGKAPKLLIYYTSILLSGVPSRFSGSGSGTDFTFTIS
SLQPEDIATYYCQQYDTSPYTFGQGTRLEIK

mAb 27869 // mAb 27886 // mAb 27887 Light Chain (SEQ ID NO: 80)

DIQMTQSPSSLSASVGDRVTITCRTSQDITGFLNWYQQKPGKAPKLLIYYTSILLSGVPSRFSGSGSGTDFTFTIS
SLQPEDIATYYCQQYDTSPYTFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27870 Heavy Chain (SEQ ID NO: 81)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFQGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDLTVYFGLLFYYFDYWGQGVMVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPESTRGPSVFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVDGVE
VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREE
MTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 27871 // mAb 27905 VH (SEQ ID NO: 82)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKG
RFTISRDDSKSIVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 27871 // mAb 27876 // mAb 27931 VL (SEQ ID NO: 83)

DTVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIFGASNRYSGVPDRFTGSGSGTD
FTLTISSLQAEDVAFYYCLQYNYNPRTFGQGTKLEIK

mAb 27871 // mAb 27881 // mAb 27905 Heavy Chain (SEQ ID NO: 84)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSIVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27871 // mAb 27880 Light Chain (SEQ ID NO: 85)

DTVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIFGASNRYSGVPDRFTGSGSGTD
FTLTISSLQAEDVAFYYCLQYNYNPRTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27873 VL (SEQ ID NO: 86)

DIQMTQSPSSLSASVGDRVTITCRASQGITGFLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTI
SSLQPEDFAIYYCQQYDSSPLTFGQGTKLEIK

mAb 27873 Light Chain (SEQ ID NO: 87)

DIQMTQSPSSLSASVGDRVTITCRASQGITGFLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTI
SSLQPEDFAIYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27875 // mAb 27900 // mAb 27933 VH (SEQ ID NO: 88)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWIGWIGPTNGDTSYAQKFKGRVTIT
VDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSS

mAb 27875 // mAb 27900 // mAb 27933 Heavy Chain (SEQ ID NO: 89)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWIGWIGPTNGDTSYAQKFKGRVTIT
VDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE
EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 27876 // mAb 27898 VH (SEQ ID NO: 90)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKG
RFTISRDDSKSRVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 27876 // mAb 27898 // mAb 27916 Heavy Chain (SEQ ID NO: 91)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSRVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27876 // mAb 27894 // mAb 27931 Light Chain (SEQ ID NO: 92)

DTVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIFGASNRYSGVPDRFTGSGSGTDF
TLTISSLQAEDVAFYYCLQYNYNPRTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ
WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27878 VH (SEQ ID NO: 93)

QVQLVQSGAELKKPGSSVKVSCKASGYTFTDHYLHWVKQAPGQGLEWIGWIGPTNGDTSYAQKFKG
RATMTVDKSTSTTYMELSSLRSEDSAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSS

mAb 27878 // mAb 27895 // mAb 27907 // mAb 27924 // mAb 27933 VL (SEQ ID NO: 94)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAPKPLIYYSSTLQSGVPSRFSGSGSGTDFTLTI
SSLQPEDFATYYCQQYDSSPLTFGQGTKLEIK

mAb 27878 // mAb 27895 // mAb 27907 // mAb 27924 // mAb 27933 Light Chain (SEQ ID NO: 95)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAPKPLIYYSSTLQSGVPSRFSGSGSGTDFTLTI
SSLQPEDFATYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27879 VL (SEQ ID NO: 96)

DIQMTQSPSSLSASVGDRVTITCRASQGITSYLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTIS
SLQPEDFAIYYCQQYDSSPLTFGQGTKLEIK

mAb 27879 Light Chain (SEQ ID NO: 97)

DIQMTQSPSSLSASVGDRVTITCRASQGITSYLNWYQQKPGKAIKPLIYYASTLQSGVPSRFSGSGSGTDYTLTIS
SLQPEDFAIYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27880 // mAb 27894 VL (SEQ ID NO: 98)

DTVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIFGASNRYSGVPDRFTGSGSGTDF
TLTISSLQAEDVAFYYCLQYNYNPRTFGQGTKLEIK

mAb 27881 VH (SEQ ID NO: 99)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSIVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 27881 // mAb 27890 // mAb 27898 // mAb 27902 // mAb 27908 VL (SEQ ID NO: 100)

NTVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIFGASNRYSGVPDRFTGSGSGTDF
TLTISSLQAEDVAFYYCLQYNYNPRTFGQGTKLEIK

mAb 27881 // mAb 27890 // mAb 27898 // mAb 27902 // mAb 27908 Light Chain (SEQ ID NO: 101)

NTVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIFGASNRYSGVPDRFTGSGSGTDF
TLTISSLQAEDVAFYYCLQYNYNPRTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQ
WKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27887 VH (SEQ ID NO: 102)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQGRV
TMTRDTSTSTVYMELSSLRSEDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSS

mAb 27887 // mAb 27926 // mAb 27929 Heavy Chain (SEQ ID NO: 103)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQGRV
TMTRDTSTSTVYMELSSLRSEDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27888 // mAb 27907 VH (SEQ ID NO: 104)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKGRVTI
TADKSTSTAYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSS

mAb 27888 // mAb 27889 // mAb 27907 Heavy Chain (SEQ ID NO: 105)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKGRVTI
TADKSTSTAYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSSASTKGPSVFPLAPSSKSTS
GGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTK
VDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV
EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRE

EMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVM
HEALHNHYTQKSLSLSPG

mAb 27889 VH (SEQ ID NO: 106)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKG
RVTITADKSTSTAYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSS

mAb 27889 Light Chain (SEQ ID NO: 107)

DIQMTQSPSSLSASVGDRVTITCRASQGINSYLNWYQQKPGKAIKPLIYYSSTLQSGVPSRFSGSGSGTDYTLTI
SSLQPEDFAIYYCQQYDSSPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSG NSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27894 VH (SEQ ID NO: 108)

EVQLVETGGGLVQPGRSLRLSCATSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSIVYLQM NSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 27894 // mAb 27902 // mAb 27927 Heavy Chain (SEQ ID NO: 109)

EVQLVETGGGLVQPGRSLRLSCATSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTI
SRDDSKSIVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN
TKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPP
SREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27897 // mAb 27924 VH (SEQ ID NO: 110)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSS

mAb 27897 // mAb 27920 // mAb 27924 Heavy Chain (SEQ ID NO: 111)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFKGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDMTVYFGLLFYYFDYWGQGTMVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNT
KVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG
VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCS
VMHEALHNHYTQKSLSLSPG

mAb 27902 // mAb 27927 VH (SEQ ID NO: 112)

EVQLVETGGGLVQPGRSLRLSCATSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSIVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 27903 // mAb 27912 // mAb 27929 VL (SEQ ID NO: 113)

DIQMTQSPSSLSASVGDRVTITCRTSQDITGFLNWYQQKPEKAPKSLIYYTSILLSGVPSRFSGSGSGTDFTLTIS
SLQPEDFATYYCQQYDTSPYTFGQGTRLEIK

mAb 27903 // mAb 27912 // mAb 27929 Light Chain (SEQ ID NO: 114)

DIQMTQSPSSLSASVGDRVTITCRTSQDITGFLNWYQQKPEKAPKSLIYYTSILLSGVPSRFSGSGSGTDFTLTIS
SLQPEDFATYYCQQYDTSPYTFGQGTRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27905 Light Chain (SEQ ID NO: 115)

DIVMTQSPDSLAVSLGERATINCKASQNVGTDVDWYQQKPGQPPKLLIYGASNRYSGVPDRFSGSGSGTDFT
LTISSLQAEDVAVYYCLQYNYNPRTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNFYPREAKVQW
KVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

mAb 27916 VH (SEQ ID NO: 116)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSRVYLQMNSLKTEDTATYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

mAb 27920 VH (SEQ ID NO: 117)

EVQLVQSGAEVKKPGSSVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTNGDTSYAQKFQGRVTI
TVDKSTSTTYMELSSLRSEDTAVYYCARQDLTVYFGLLFYYFDYWGQGVMVTVSS

mAb 27926 // mAb 27929 VH (SEQ ID NO: 118)

QVQLVQSGAEVKKPGASVKVSCKASGYTFTDHYLHWVRQAPGQGLEWMGWIGPTKGDTNYAQKFQG
RVTMTRDTSTSTVYMELSSLRSEDTAVYYCARQDLSYGYHLYYWYFDFWGQGTLVTVSS

mAb 27931 VH (SEQ ID NO: 119)

EVQLVESGGGLVQPGRSLRLSCTTSGFTFSNTWMNWVRQAPGKGLEWVALIKDKYSNYEANYAESIKGRFTIS
RDDSKSIVYLQMNSLKTEDTAVYYCTRDYYDGNFYYEDYYVMDAWGQGTLVTVSS

[0098] Characterization of Anti-NK3R antibodies

[0099] Anti-NK3R antibodies disclosed herein exhibit one or more desirable characteristics. Thus, anti-NK3R antibody-producing cells (e.g., human B cells) may be selected, cloned, and further screened for these desirable characteristics including, for example, robust growth, high antibody production, or desirable antibody characteristics. Hybridomas can be expanded *in vivo* in syngeneic animals, in animals that lack an immune system, e.g., nude mice, or in cell culture *in vitro*. Methods of selecting, cloning, and expanding hybridomas and/or colonies, each of which produces a discrete antibody species, are well known to those of ordinary skill in the art.

[00100] For example, anti-NK3R antibodies disclosed herein may be characterized by their epitope specificity. Anti-NK3R antibodies disclosed herein will associate with, or bind to, discrete epitopes or determinants presented by the selected target(s). As used herein, the term "epitope" refers to that portion of the target antigen capable of being recognized and specifically bound by a particular antibody. Epitopes can be formed both from contiguous amino acids and noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained upon protein denaturing, whereas epitopes formed by tertiary folding are typically lost upon protein denaturing. An epitope typically includes at least 3, and more usually, at least 5 to 10 amino acids in a unique spatial conformation. More specifically, the skilled artisan will appreciate the term epitope includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor or otherwise interacting with a molecule. Epitopic determinants generally consist of chemically active surface groupings of molecules such as amino acids or carbohydrate or sugar side chains and generally have specific three-dimensional structural characteristics, as well as specific charge characteristics. Additionally, an epitope may be linear or conformational. In a linear epitope, all of the points of interaction between the protein and the interacting molecule (such as an antibody) occur linearly along the primary amino acid sequence of the protein. In a conformational epitope, the points of interaction occur across amino acid residues on the protein that are linearly separated from one another.

[00101] The term "epitope" refers to the amino acid residues of an antigen that are bound by an antibody. An epitope can be a linear epitope, a conformational epitope, or a hybrid epitope. An epitope can be determined according to different experimental techniques, also called "epitope mapping techniques." It is understood that the determination of an epitope may vary based on the different epitope mapping techniques used and may also vary with the different experimental conditions used, e.g., due to the conformational changes or cleavages of the antigen induced by specific experimental conditions. Epitope mapping techniques are known in the art, including, but not limited to, X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, electron microscopy, site-directed mutagenesis, species swap mutagenesis, alanine-scanning mutagenesis, hydrogen-deuterium exchange (HDX), and cross-blocking assays.

[00102] Once a desired epitope on an antigen is determined, it is possible to generate antibodies to that epitope, e.g., by immunizing with a peptide comprising the epitope using techniques known in the art. Alternatively, during the discovery process, the generation and characterization of antibodies may elucidate information about desirable epitopes. From this information, it is then

possible to competitively screen antibodies for binding to the same epitope. An approach to achieve this is to conduct competition studies to find antibodies that competitively bind with one another, i.e., the antibodies compete for binding to the antigen. A high throughput process for binning antibodies based upon their cross-competition is known in the art.

[00103] As used herein, the term "binning" refers to a method to group antibodies based on their antigen binding characteristics. The grouping is somewhat arbitrary, depending on how different the observed binding patterns of the antibodies tested. Thus, while the technique is a useful tool for categorizing antibodies, the bins do not always directly correlate with epitopes and such initial determinations of epitope binding should be further confirmed by other art recognized methodology.

[00104] With this caveat one can determine whether a selected antibody (or fragment thereof) binds to the same epitope or cross competes for binding with a second antibody by using methods known in the art. If the second antibody is able to bind NK3R, then the second antibody binds to a different epitope than the first antibody. However, if the second antibody is not able to bind, then the second antibody binds to the same epitope, an overlapping epitope, or an epitope that is in close proximity to the epitope bound by the first antibody. As known in the art, the desired data can be obtained using solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay, surface plasmon resonance, bio-layer interferometry, or flow cytometric methodology.

[00105] As used herein, the term "compete" means competition between antibodies as determined by an assay in which the antibody or immunologically-reactive fragment under test prevents or inhibits specific binding of a reference antibody to a common antigen. Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabeled test immunoglobulin and a labeled reference immunoglobulin. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test immunoglobulin. Usually, the test immunoglobulin is present in excess. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur. Additional details regarding methods for determining competitive binding are provided in the Examples herein. Usually, when a competing antibody is present in excess, it will inhibit specific binding of a reference antibody to a common antigen by at least 40%, 45%, 50%, 55%, 60%, 65%,

70% or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 95%, or 97% or more.

[00106] Anti-NK3R antibodies disclosed herein may also be characterized by their binding affinity. In some embodiments, anti-NK3R antibodies specifically bind to a target antigen expressed on a virion or infected cell, i.e., the dissociation constant K_d (k_{off}/k_{on}) is$\leq 10^{-8}$M. The antibody specifically binds it antigen with high affinity when the K_d is$\leq 5x\ 10^{-9}$M, and with very high affinity when the K_d is$\leq 5x10^{-10}$M. In particular embodiments, the antibody has a K_d of$\leq 10^{-9}$M and an off-rate of about 1 x 10^{-4}/sec. In other embodiments, the off-rate is$\leq$ 1 x 10^{-5}/sec. In other embodiments, the antibodies will bind with a K_d of between about 10^{-8}M and 10^{-10}M, and in yet other embodiments, antibodies bind with a $K_d\leq 2x\ 10^{-10}$M. Still other selected embodiments comprise antibodies that have a disassociation constant or K_d (k_{off}/k_{on}) of less than 10^{-2}M, less than $5x10^{-2}$M, less than 10^{-3}M, less than $5x10^{-3}$M, less than 10^{-4}M, less than $5x10^{-4}$M, less than 10^{-5}M, less than $5x10^{-5}$M, less than 10^{-6}M, less than $5x10^{-6}$M, less than 10^{-7}M, less than $5x10^{-7}$M, less than 10^{-8}M, less than $5x10^{-8}$M, less than 10^{-9}M, less than $5x10^{-9}$M, less than 10^{-10}M, less than $5x10^{-10}$M, less than 10^{-11}M, less than $5x10^{-11}$M, less than 10^{-12}M, less than $5x10^{-12}$M, less than 10^{-13}M, less than $5x10^{-13}$M, less than 10^{-14}M, less than $5x10^{-14}$M, less than 10^{-15}M, or less than $5x10^{-15}$M.

[00107] In another embodiment, an anti-NK3R antibody that specifically binds to its antigen has an association rate constant or k_{on} rate ((Ab) + antigen (Ag)$^{k_{on}}\leftarrow$Ab-Ag) of at least $10^5M^{-1}s^{-1}$, at least $2x10^5M^{-1}s^{-1}$, at least $5x10^5M^{-1}s^{-1}$, at least $10^6M^{-1}s^{-1}$, at least $5x10^6M^{-1}s^{-1}$, at least $10^7M^{-1}s^{-1}$, at least $5x10^7M^{-1}s^{-1}$, or at least $10^8M^{-1}s^{-1}$.

[00108] In another embodiment, an anti-NK3R antibody that specifically binds to its antigen has a disassociation rate constant or k_{off} rate ((Ab) + antigen (Ag)$^{k_{off}}\leftarrow$ Ab-Ag) of less than $10^{-1}s^{-1}$, less than $5x10^{-1}s^{-1}$, less than $10^{-2}s^{-1}$, less than $5x10^{-2}s^{-1}$, less than $10^{-3}s^{-1}$, less than $5x10^{-3}s^{-1}$, less than $10^{-4}s^{-1}$, less than $5x10^{-4}s^{-1}$, less than $10^{-5}s^{-1}$, less than $5x10^{-5}s^{-1}$, less than $10^{-6}s^{-1}$, less than $5x10^{-6}s^{-1}$, less than $10^{-7}s^{-1}$, less than $5x10^{-7}s^{-1}$, less than $10^{-8}s^{-1}$, less than $5x10^{-8}s^{-1}$, less than $10^{-9}s^{-1}$, less than $5x10^{-9}s^{-1}$ or less than $10^{-10}s^{-1}$.

[00109] In another embodiment, an anti-NK3R antibody that specifically binds to its antigen will have an affinity constant or K_a (k_{on}/k_{off}) of at least 10^2M^{-1}, at least 5x 10^2M^{-1}, at least 10^3M^{-1}, at least $5x10^3M^{-1}$, at least 10^4M^{-1}, at least $5xl0^4M^{-1}$, at least 10^5M^{-1}, at least $5xl0^5M^{-1}$, at least 10^6M^{-1}, at least $5x10^6M^{-1}$, at least 10^7M^{-1}, at least $5xl\ 0^7M^{-1}$, at least 10^8M^{-1}, at least $5x10^8M^{-1}$, at least 10^9M^{-1}, at least $5x10^9M^{-1}$, at least $10^{10}M^{-1}$, at least $5x10^{10}M^{-1}$, at least 10 nM^{-1}, at least 5x10 nM^{-1},

at least $10^{12}M^{-1}$, at least $5x10^{12}M^{-1}$, at least $10^{13}M^{-1}$, at least $5x10^{13}M^{-1}$, at least $10^{14}M^{-1}$, at least $5x10^{14}M^{-1}$, at least $10^{15}M^{-1}$ or at least $5x10^{15}M^{-1}$.

[00110] Anti-NK3R antibodies disclosed herein may also be characterized by their thermal stability as reflected by their respective melting point (T_m). The T_m of the Fab region of an antibody can be a good indicator of the thermal stability of an antibody and may further provide an indication of the shelf life. T_m is merely the temperature of 50% unfolding for a given region or sequence. A lower T_m indicates more aggregation/less stability, whereas a higher T_m indicates less aggregation/more stability. Thus, antibodies or fragments or derivatives having higher T_m are preferable. Moreover, using art-recognized techniques it is possible to alter the composition of antibodies or regions thereof to increase or optimize molecular stability. Thermal melting temperatures (T_m) of a protein region (e.g., a Fab region) can be measured using any standard method known in the art, e.g., by differential scanning calorimetry.

[00111] In some embodiments, the Fab region of an anti-NK3R antibody disclosed herein has a T_m value higher than at least 50°C, 55°C, 60°C, 65°C, 70°C, 75°C, 80°C, 85°C, 90°C, 95°C, 100°C, 105°C, 110°C, 115°C or 120°C. In another embodiment, the Fab region of an anti-NK3R antibody disclosed herein has a T_m value higher than at least about 50°C, about 55°C, about 60°C, about 65°C, about 70°C, about 75°C, about 80°C, about 85°C, about 90°C, about 95°C, about 100°C, about 105°C, about 110°C, about 115°C or about 120°C.

[00112] Anti-NK3R antibodies disclosed herein may also be characterized by their isoelectric point (pI), which is generally defined as the pH at which a polypeptide carries no net charge. It is known in the art that protein solubility is typically lowest when the pH of the solution is equal to the isoelectric point (pI) of the protein. Therefore, it is possible to optimize solubility by altering the number and location of ionizable residues in the antibody to adjust the pI. For example, the pI of a polypeptide can be manipulated by making the appropriate amino acid substitutions (e.g., by substituting a charged amino acid such as a lysine, for an uncharged residue such as alanine). Without wishing to be bound by any particular theory, amino acid substitutions of an antibody that result in changes of the pI of the antibody may improve solubility and/or the stability of the antibody. One skilled in the art would understand which amino acid substitutions would be most appropriate for a particular antibody to achieve a desired pI. The pI of a protein may be determined by a variety of methods including but not limited to, isoelectric focusing and various computer algorithms.

[00113] In some embodiments, the pI of an anti-NK3R antibody disclosed herein is higher than about 6.5, about 7.0, about 7.5, about 8.0, about 8.5, or about 9.0. In another embodiment, the pI of an anti-NK3R antibody disclosed herein is higher than 6.5, 7.0, 7.5, 8.0, 8.5, or 9.0. In yet another embodiment, substitutions resulting in alterations in the pI of an anti-NK3R antibody disclosed herein will not significantly diminish its binding affinity. As discussed in more detail below, it is specifically contemplated that the substitution(s) of the Fc region that result in altered binding to FcγR may also result in a change in the pI. In a preferred embodiment, substitution(s) of the Fc region are specifically chosen to effect both the desired alteration in FcγR binding and any desired change in pI. As used herein, the pI value is defined as the pI of the predominant charge form.

[00114] Nucleic Acids and Anti-NK3R Antibody Expression

[00115] Provided herein are also nucleic acids encoding a heavy chain or light chain, or a V_H or V_L, of the anti-NK3R antibodies disclosed herein, and vectors comprising one or more such nucleic acids. The terms "nucleic acid" or "polynucleotide," as used interchangeably herein, refer to polymers of nucleotides, including single-stranded and/or double-stranded nucleotide-containing molecules, such as DNA, cDNA, and RNA molecules, incorporating native, modified, and/or analogs of, nucleotides. Polynucleotides of the present disclosure may also include substrates incorporated therein, for example, by DNA or RNA polymerase or a synthetic reaction. In some embodiments, provided herein are nucleic acids encoding a V_H or V_L of an anti-NK3R antibody described herein, e.g., any one of the antibodies identified by internal designation numbers 20810-27933.

[00116] DNA encoding the anti-NK3R antibodies disclosed herein may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding antibody heavy and light chains). Isolated and subcloned hybridoma cells (or phage or yeast derived colonies) may serve as a preferred source of such DNA. More particularly, the isolated DNA (which may be modified) can be used to clone constant and variable region sequences for the manufacture of antibodies.

[00117] One exemplary method entails extraction of RNA from selected cells, conversion to cDNA, and amplification by PCR using antibody specific primers. Suitable primers are well known in the art, and as exemplified herein, are readily available from numerous commercial sources. It will be appreciated that, to express a recombinant human or non-human antibody

isolated by screening of a combinatorial library, the DNA encoding the antibody is cloned into a recombinant expression vector and introduced into host cells including mammalian cells, insect cells, plant cells, yeast, and bacteria. In yet other embodiments, the antibodies are introduced into and expressed by simian COS cells, NS0 cells, Chinese Hamster Ovary (CHO) cells or myeloma cells that do not otherwise produce the desired construct. As will be discussed in more detail below, transformed cells expressing the desired antibody may be grown in relatively large quantities to provide clinical and commercial supplies of the antibody.

[00118] However, the nucleic acid encoding an anti-NK3R antibody disclosed herein is obtained or derived, it should be understood that the inventions disclosed herein encompass nucleic acid molecules and sequences encoding anti-NK3R antibodies, fusion proteins, or antigen-binding fragments or derivatives thereof. The inventions disclosed herein further encompass nucleic acids or nucleic acid molecules (e.g., polynucleotides) that hybridize under high stringency, or alternatively, under intermediate or lower stringency hybridization conditions (e.g., as defined below), to polynucleotides complementary to nucleic acids having a polynucleotide sequence that encodes an antibody in accordance with the invention or a fragment or variant thereof. The term nucleic acid molecule or isolated nucleic acid molecule, as used herein, is intended to include at least DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA. Moreover, the present invention comprises any vehicle or construct, incorporating such an antibody-encoding polynucleotide including, without limitation, vectors, plasmids, host cells, cosmids, or viral constructs.

[00119] As used herein, the term "isolated nucleic acid" refers to a nucleic acid that was (i) amplified *in vitro*, for example by polymerase chain reaction (PCR), (ii) recombinantly produced by cloning, (iii) purified, for example by cleavage and gel-electrophoretic fractionation, or (iv) synthesized, for example by chemical synthesis. An isolated nucleic acid is a nucleic acid that is available for manipulation by recombinant DNA techniques.

[00120] More specifically, nucleic acids that encode anti-NK3R antibodies described herein, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating, or amplifying a polynucleotide encoding a polypeptide, anti-sense nucleic acids for inhibiting expression of a polynucleotide, and complementary sequences of the foregoing are also encompassed herein. Such nucleic acids can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleotides in length, and/or can comprise one

or more additional sequences, for example, regulatory sequences, and/or be part of a larger nucleic acid, for example, a vector. These nucleic acids can be single-stranded or double-stranded and can comprise RNA and/or DNA nucleotides, and artificial variants thereof (e.g., peptide nucleic acids).

[00121] As indicated, the invention further provides nucleic acids that hybridize to other nucleic acids under particular hybridization conditions. Methods for hybridizing nucleic acids are well known in the art. For example, a moderately stringent hybridization condition uses a prewashing solution containing 5x sodium chloride/sodium citrate (SSC), 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridization buffer of about 50% formamide, 6xSSC, and a hybridization temperature of 55°C (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42°C), and washing conditions of 60°C, in 0.5xSSC, 0.1 % SDS. A stringent hybridization condition hybridizes in 6xSSC at 45°C, followed by one or more washes in 0.1xSSC, 0.2% SDS at 68°C. One of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that nucleic acids comprising nucleotide sequences that are at least 65, 70, 75, 80, 85, 90, 95, 98 or 99% identical to each other typically remain hybridized to each other. More generally, for the purposes of the instant disclosure the term "substantially identical" with regard to a nucleic acid sequence refers to a sequence of nucleotides exhibiting at least about 85%, or 90%, or 95%, or 97% sequence identity to the reference nucleic acid sequence. The basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are well known, and can be readily determined by those having ordinary skill in the art based on, for example, the length and/or base composition of the nucleic acid.

[00122] It will further be appreciated that nucleic acids may be present alone or in combination with other nucleic acids, which may be homologous or heterologous. In preferred embodiments, a nucleic acid is functionally linked to expression control sequences that may be homologous or heterologous with respect to that nucleic acid. In this context, the term "homologous" means that a nucleic acid is also functionally linked to the expression control sequence naturally and the term "heterologous" means that a nucleic acid is not functionally linked to the expression control sequence naturally.

[00123] A nucleic acid, such as a nucleic acid expressing RNA and/or protein or peptide, and an expression control sequence are functionally linked to one another, if they are covalently linked to one another in such a way that expression or transcription of the nucleic acid is under the control or under the influence of the expression control sequence. If the nucleic acid is to be translated

into a functional protein, then, with an expression control sequence functionally linked to a coding sequence, induction of the expression control sequence results in transcription of the nucleic acid, without causing a frame shift in the coding sequence or the coding sequence not being capable of being translated into the desired protein or peptide. As used herein, the term "expression control sequence" includes promoters, ribosome binding sites, enhancers and other control elements that regulate transcription of a gene or translation of mRNA. In particular embodiments, the expression control sequences can be regulated. The exact structure of expression control sequences may vary as a function of the species or cell type, but generally comprises 5'-untranscribed and 5'- and 3'-untranslated sequences which are involved in initiation of transcription and translation, respectively, such as TATA box, capping sequence, CAAT sequence, and the like. More specifically, 5'-untranscribed expression control sequences comprise a promoter region that includes a promoter sequence for transcriptional control of the functionally linked nucleic acid. Expression control sequences may also comprise enhancer sequences or upstream activator sequences.

[00124] As used herein, the term "promoter" or "promoter region" relates to a nucleic acid sequence which is located upstream (5') to the nucleic acid sequence being expressed and controls expression of the sequence by providing a recognition and binding site for RNA-polymerase. The promoter region may include further recognition and binding sites for further factors that are involved in the regulation of transcription of a gene. A promoter may control the transcription of a prokaryotic or eukaryotic gene. Furthermore, a promoter may be inducible and may initiate transcription in response to an inducing agent or may be constitutive if transcription is not controlled by an inducing agent. A gene that is under the control of an inducible promoter is not expressed or only expressed to a small extent if an inducing agent is absent. In the presence of the inducing agent the gene is switched on or the level of transcription is increased. This is mediated, in general, by binding of a specific transcription factor.

[00125] Promoters for use in the production of anti-NK3R antibodies disclosed herein include promoters for SP6, T3 and T7 polymerase, human U6 RNA promoter, CMV promoter, and artificial hybrid promoters thereof (e.g., CMV) where a part or parts are fused to a part or parts of promoters of genes of other cellular proteins such as, e.g., human GAPDH (glyceraldehyde-3-phosphate dehydrogenase), and may include (an) additional intron(s).

[00126] As used herein, the term "expression" is used in its most general meaning and comprises the production of RNA or of RNA and protein/peptide. It also comprises partial expression of nucleic acids. Furthermore, expression may be carried out transiently or stably.

[00127] In a preferred embodiment, a nucleic acid molecule is present in a vector, where appropriate with a promoter, which controls expression of the nucleic acid. As used herein, the term "vector" is used here in its most general meaning and comprises any intermediary vehicle for a nucleic acid that enables the nucleic acid, for example, to be introduced into prokaryotic and/or eukaryotic cells and, where appropriate, to be integrated into a genome. Vectors of this kind are preferably replicated and/or expressed in the cells. Vectors may comprise plasmids, phagemids, bacteriophages or viral genomes. As used herein, the term "plasmid" generally relates to a construct of extrachromosomal genetic material, usually a circular DNA duplex, which can replicate independently of chromosomal DNA.

[00128] It will be appreciated by those of skill in the art, that many conventional techniques in molecular biology, microbiology, and recombinant DNA technology are optionally used. Such conventional techniques relate to vectors, host cells and recombinant methods as defined herein. In addition, essentially any polynucleotide (including, e.g., labeled or biotinylated polynucleotides) can be obtained from any of a variety of commercial sources.

[00129] The inventions disclosed herein also encompass recombinant host cells allowing recombinant expression of antibodies of the invention or portions thereof. Anti-NK3R antibodies disclosed herein produced by expression in such recombinant host cells are referred to herein as recombinant antibodies. The inventions disclosed herein also encompass progeny cells of such host cells, and anti-NK3R antibodies produced by the same.

[00130] As used herein, the term "recombinant host cell" or "host cell" means a cell into which a recombinant expression vector has been introduced. It should be understood that recombinant host cell and host cell mean not only the particular subject cell but also the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term host cell as used herein. Such cells may comprise a vector as described above.

[00131] The inventions disclosed herein also encompass methods for making anti-NK3R antibodies disclosed herein. According to one embodiment, such a method comprises culturing a cell transfected or transformed with a vector as described above, and isolating the antibody.

[00132] As indicated above, expression of an antibody preferably comprises expression vector(s) containing a polynucleotide that encodes the anti-NK3R antibody. Methods that are well known to those skilled in the art can be used to construct expression vectors comprising antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Particular embodiments provide replicable vectors comprising a nucleotide sequence encoding an anti-NK3R antibody disclosed herein operably linked to a promoter. In preferred embodiments, such vectors may include a nucleotide sequence encoding the heavy chain of an antibody molecule (or fragment thereof), a nucleotide sequence encoding the light chain of an antibody (or fragment thereof), or both the heavy and light chain.

[00133] Using art recognized molecular biology techniques and current protein expression methodology, substantial quantities of the anti-NK3R antibodies disclosed herein may be produced. More specifically, nucleic acid molecules encoding such antibodies may be integrated into well-known and commercially available protein production systems comprising various types of host cells to provide preclinical, clinical, or commercial quantities of the desired pharmaceutical product. In preferred embodiments the nucleic acid molecules encoding the antibodies are engineered into vectors or expression vectors that provide for efficient integration into the selected host cell and subsequent high expression levels of the antibody.

[00134] Preferably nucleic acid molecules encoding anti-NK3R antibodies disclosed herein and vectors comprising these nucleic acid molecules can be used for transfection of a suitable mammalian, plant, bacterial or yeast host cell though it will be appreciated that prokaryotic systems may also be used. Transfection can be by any known method for introducing polynucleotides into a host cell. Methods for the introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors. Methods of transforming mammalian cells are well known in the art. Methods of transforming plant cells are also well known in the art, including, e.g., agrobacterium-mediated transformation, biolistic transformation, direct injection, electroporation, and viral transformation. Methods of transforming bacterial and yeast cells are also well known in the art.

[00135] Moreover, the host cell may be co-transfected with two expression vectors of the invention, for example, the first vector encoding a heavy chain polypeptide and the second vector encoding a light chain polypeptide. The two vectors may contain identical selectable markers that enable substantially equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain is preferably placed before the heavy chain to avoid an excess of toxic free heavy chain. The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[00136] A variety of host-expression vector systems, many commercially available, may be used to express anti-NK3R antibodies disclosed herein. Such host-expression systems represent vehicles by which the coding sequences of interest may be expressed and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express a molecule of the invention in situ. Such systems include, but are not limited to, microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*, *streptomyces*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transfected with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems (e.g., *Nicotiana, Arabidopsis*, duckweed, corn, wheat, potato, etc.) infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transfected with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter).

[00137] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable.

[00138] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) may be used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The

coding sequences may be cloned individually into non-essential regions (for example, the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example, the polyhedrin promoter).

[00139] In mammalian host cells, a number of viral-based expression systems may be used to introduce the desired nucleotide sequence. In cases where an adenovirus is used as an expression vector, the coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the molecule in infected hosts. Specific initiation signals may also be required for efficient translation of inserted coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, and the like. Thus, compatible mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, *inter alia*, Chinese hamster ovary (CHO) cells, NS0 cells, SP2 cells, HEK-293T cells, 293 Freestyle cells (Life Technologies), NIH-3T3 cells, HeLa cells, baby hamster kidney (BHK) cells, African green monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), A549 cells, and a number of other cell lines.

[00140] For long-term, high-yield production of recombinant proteins stable expression is preferred. Accordingly, cell lines that stably express the selected antibody may be engineered using standard art recognized techniques. Rather than using expression vectors that contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1 to 2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously

be used to engineer cell lines which express the molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compositions that interact directly or indirectly with the molecule.

[00141] A number of selection systems are well known in the art and may be used including, but not limited to, the herpes simplex virus thymidine kinase, hypoxanthineguanine phosphoribosyltransferase, and adenine phosphoribosyltransferase genes can be employed in *tk-*, *hgprt-* or *aprt-* cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: *dhfr,* which confers resistance to methotrexate; *gpt*, which confers resistance to mycophenolic acid; *neo*, which confers resistance to the aminoglycoside G-418; and *hygro*, which confers resistance to hygromycin.

[00142] Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone. It will be appreciated by those of skill in the art that one particularly preferred method of establishing a stable, high yield cell line comprises the glutamine synthetase gene expression system (the GS system), which provides an efficient approach for enhancing expression under certain conditions.

[00143] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function and/or purification of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. As known in the art, appropriate cell lines or host systems can be chosen to ensure the desired modification and processing of the expressed polypeptide. To this end, eukaryotic host cells that possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product are particularly effective. Accordingly, some preferred mammalian host lines include, but are not limited to, CHO, VERY, BHK, HeLa, COS, NS0, MDCK, 293, 3T3, and W138. Depending on the anti-NK3R antibody and the selected production system, those of skill in the art may easily select and optimize appropriate host cells for efficient expression of the antibody.

[00144] Those of skill in the art will appreciate that anti-NK3R antibodies disclosed herein may be chemically synthesized using techniques known in the art. For example, a peptide corresponding to a polypeptide fragment of the invention can be synthesized by use of a peptide

synthesizer. If desired, non-genetically encoded amino acids or synthetic amino acids can be substituted or added into a polypeptide sequence.

[00145] Representative non-genetically encoded amino acids include but are not limited to 2-aminoadipic acid; 3-aminoadipic acid; β-aminopropionic acid; 2-aminobutyric acid; 4-aminobutyric acid (piperidinic acid); 6-aminocaproic acid; 2-aminoheptanoic acid; 2-aminoisobutyric acid; 3-aminoisobutyric acid; 2-aminopimelic acid; 2,4-diaminobutyric acid; desmosine; 2,2'-diaminopimelic acid; 2,3-diaminopropionic acid; N-ethylglycine; N-ethylasparagine; hydroxylysine; allo-hydroxylysine; 3-hydroxyproline; 4-hydroxyproline; isodesmosine; allo-isoleucine; N-methylglycine (sarcosine); N-methylisoleucine; N-methylvaline; norvaline; norleucine; and ornithine.

[00146] Representative synthetic amino acids include, for example, those molecules in which free amino groups have been derivatized to form amine hydrochlorides, p-toluene sulfonyl groups, carbobenzoxy groups, t-butyloxycarbonyl groups, chloroacetyl groups or formyl groups. Free carboxyl groups may be derivatized to form salts, methyl and ethyl esters or other types of esters or hydrazides. Free hydroxyl groups may be derivatized to form O-acyl or O-alkyl derivatives. The imidazole nitrogen of histidine may be derivatized to form N-im-benzylhistidine.

[00147] Anti-NK3R antibodies disclosed herein also can be produced transgenically through the generation of a mammal or plant that is transgenic for the immunoglobulin heavy and light chain sequences (or fragments or derivatives or variants thereof) of interest and production of the desired compounds in a recoverable form. For example, anti-NK3R antibodies can be produced in, and recovered from, e.g., the milk of goats, cows, or other mammals.

[00148] Non-human transgenic animals or plants may be produced by introducing one or more nucleic acid molecules encoding an anti-NK3R antibody into the animal or plant by standard transgenic techniques. The transgenic cells used for making the transgenic animal can be embryonic stem cells or somatic cells or a fertilized egg. The transgenic non-human organisms can be chimeric, nonchimeric heterozygotes, and nonchimeric homozygotes. In some embodiments, the transgenic non-human animals have a targeted disruption and replacement by a targeting construct that encodes, for example, a heavy chain and/or a light chain of interest. While anti-NK3R antibodies disclosed herein may be produced in any transgenic animal, particularly preferred embodiments include mice, rats, sheep, pigs, goats, cattle, and horses. In particular embodiments, the non-human transgenic animal expresses the desired pharmaceutical product in

blood, milk, urine, saliva, tears, mucus, and other bodily fluids from which it is readily obtainable using art recognized purification techniques.

[00149] It is likely that antibodies, including antibodies, expressed by different cell lines or in transgenic animals will have different glycosylation patterns from each other. However, the instant inventions encompass anti-NK3R antibodies encoded by the nucleic acid molecules provided herein, or comprising the amino acid sequences provided herein, regardless of the glycosylation state of the molecule, and more generally, regardless of the presence or absence of post-translational modification(s). The instant inventions also encompass anti-NK3R antibodies that are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc. Various post-translational modifications are also encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends, attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of prokaryotic host cell expression. Moreover, anti-NK3R antibodies disclosed herein may also be modified with a detectable label, such as an enzymatic, fluorescent, radioisotopic or affinity label to allow for their detection and isolation.

[00150] Once anti-NK3R antibodies disclosed herein have been produced by recombinant expression or any one of the other techniques disclosed herein, they may be purified by any method known in the art for purification of immunoglobulins, or more generally by any other standard technique for the purification of proteins. In this respect the anti-NK3R antibody may be isolated. As used herein, an "isolated anti-NK3R antibody" is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses of the antibody and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. Isolated anti-NK3R antibodies include antibodies *in situ* within recombinant cells because at least one component of the antibody's natural environment will not be present.

[00151] When using recombinant techniques, anti-NK3R antibodies disclosed herein can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the desired molecule is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, may be removed, for example, by centrifugation or ultrafiltration. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious contaminants.

[00152] Compositions comprising anti-NK3R antibodies disclosed herein prepared from cells can be purified using, for example, hydroxyapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc region that is present in the selected construct. Protein A can be used to purify antibodies that are based on human IgG1, IgG2 or IgG4 heavy chains. Protein G is recommended for all mouse isotypes and for human IgG3. The matrix to which the affinity ligand is attached is most often agarose, but other matrices are available. Mechanically-stable matrices such as controlled pore glass or poly(styrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_H3 region, the BAKERBOND ABX™ resin is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, reverse phase HPLC, chromatography on silica, chromatography on heparin, SEPHAROSE® chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

[00153] By way of illustration of the foregoing, cDNA sequences encoding an anti-NK3R antibody heavy chain and light chain may be cloned and engineered into an appropriate expression vector. The engineered immunoglobulin expression vector may then be stably transfected into a mammalian (e.g., human) cell. As one skilled in the art will appreciate, mammalian expression of antibodies will result in glycosylation, typically at highly conserved N-glycosylation sites in the Fc region. Positive clones may be expanded into serum-free culture medium for antibody production in bioreactors. Medium, into which an antibody has been secreted, may be purified by conventional techniques. For example, the medium may be conveniently applied to a Protein A or G SEPHAROSE® FF column that has been equilibrated with a compatible buffer, such as

phosphate buffered saline. The column is washed to remove nonspecific binding components. The bound antibody is eluted, for example, by pH gradient and antibody fractions are detected, such as by SDS-PAGE, and then pooled. The antibody may be concentrated and/or sterile filtered using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion, hydrophobic interaction, ion exchange, or hydroxyapatite chromatography. The product may be immediately frozen, for example, at -70°C, or may be lyophilized.

[00154] Pharmaceutical Compositions and Therapeutic Uses

[00155] Also provided herein are methods of treating a sex hormone-related disorder by administering to a subject a therapeutically effective amount of one or more anti-NK3R antibodies described herein, or a pharmaceutical composition comprising one or more (e.g., two or three) anti-NK3R antibodies described herein in combination with another anti-NK3R antibody or therapy.

[00156] As used interchangeably herein, "treatment" or "treating" or "treat" refers to all processes wherein there may be a slowing, interrupting, arresting, controlling, stopping, alleviating, or ameliorating symptoms or complications, or reversing of the progression of a sex hormone-related disorder, but does not necessarily indicate a total elimination of all symptoms.

[00157] A variety of sex hormone-related disorders may be treated using one or more anti-NK3R antibodies described herein, or a pharmaceutical composition comprising the same. A non-exhaustive list of sex hormone-related disorders includes vasomotor symptoms, vasomotor symptoms secondary to natural, premature or iatrogenic menopause, vasomotor symptoms secondary to hormone deprivation therapy in women, vasomotor symptoms secondary to hormone deprivation therapy in men, medically induced vasomotor symptoms, advanced hormone sensitive prostate cancer (HSPC), estrogen-dependent breast cancer, estrogen-dependent ovarian cancer, and estrogen-dependent uterine cancer, which includes endometrial cancer and uterine sarcoma.

[00158] In some embodiments, methods of preventing or treating sex hormone-related disorder comprise administering to a subject a pharmaceutical composition comprising one or more (e.g., two or three) anti-NK3R antibodies described herein. In some embodiments, such methods comprise administering to a subject a pharmaceutical composition comprising two or three anti-NK3R antibodies or antigen-binding fragments thereof that bind different epitopes present on NK3R.

[00159] Also provided are anti-NK3R antibodies or antigen-binding fragments or pharmaceutical compositions comprising one or more (e.g., two or three) anti-NK3R antibodies or antigen-binding fragments for use in therapy. In some embodiments anti-NK3R antibodies or antigen-binding fragments thereof or pharmaceutical compositions comprise one or more (e.g., two or three) anti-NK3R antibodies or antigen-binding fragments, for use in the treatment of a sex hormone-related disorder. Further provided herein are uses of anti-NK3R antibodies or antigen-binding fragments described herein in the manufacture of a medicament for the treatment of a sex hormone-related disorder.

[00160] Depending on the form of anti-NK3R antibody, mode of intended delivery, and numerous other variables, anti-NK3R antibodies disclosed herein may be formulated as desired using art recognized techniques. Various pharmaceutically acceptable carriers, which include vehicles, adjuvants, and diluents, are readily available from numerous commercial sources. Moreover, an assortment of pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents, and the like, are also available. Certain non-limiting exemplary carriers include saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof.

[00161] In some embodiments, anti-NK3R antibodies may be administered to a subject neat or with a minimum of additional components. In other embodiments, anti-NK3R antibodies may be formulated to contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that are well known in the art and are relatively inert substances that facilitate administration or which aid processing of the active compounds into preparations that are pharmaceutically optimized for delivery. For example, an excipient can give form or consistency or act as a diluent to improve the pharmacokinetics of the antibody. Suitable excipients include but are not limited to stabilizing agents, wetting, and emulsifying agents, salts for varying osmolality, encapsulating agents, buffers, and skin penetration enhancers.

[00162] Anti-NK3R antibodies disclosed herein may be formulated for enteral, parenteral, or topical administration. Indeed, all three types of formulation may be used simultaneously to achieve systemic administration of the active ingredient. Excipients as well as formulations for parenteral and non-parenteral drug delivery are known in the art. Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts. In addition, suspensions of the active compounds as appropriate for oily injection suspensions may be administered. Suitable lipophilic solvents or

vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers. Liposomes can also be used to encapsulate the agent for delivery into cells.

[00163] In general, anti-NK3R antibodies disclosed herein may be administered *in vivo* to a subject in need thereof, by various routes, including, but not limited to, oral, intravenous, intra-arterial, subcutaneous, parenteral, intranasal, intramuscular, intracardiac, intraventricular, intratracheal, buccal, rectal, intraperitoneal, intradermal, topical, transdermal, and intrathecal, or otherwise by implantation or inhalation. Compositions may be formulated into preparations in solid, semi-solid, liquid, or gaseous forms; including, but not limited to, tablets, capsules, powders, granules, ointments, solutions, suppositories, enemas, injections, inhalants, and aerosols. The appropriate formulation and route of administration may be selected according to the intended application and therapeutic regimen. In preferred embodiments, anti-NK3R antibodies disclosed herein are either administered intravenously or subcutaneously.

[00164] Similarly, the particular dosage regimen, i.e., dose, timing, and repetition, will depend on the particular individual and that individual's medical history. Empirical considerations such as pharmacokinetics (e.g., half-life, clearance rate, etc.) will contribute to the determination of the dosage. Frequency of administration may be determined and adjusted over the course of therapy. Alternatively, sustained continuous release formulations of a subject therapeutic composition may be appropriate. Various formulations and devices for achieving sustained release are known in the art.

[00165] Pharmaceutical compositions are administered in therapeutically effective amount in order to treat a sex hormone-related disorder in a subject. As used herein, the term "therapeutically effective amount" means that amount of an anti-NK3R antibody or pharmaceutical composition comprising the same that will elicit the biological or medical response in the subject that is sought by a medical doctor or other clinician. In particular, with regard to contemplated sex hormone-related disorders, a "therapeutically effective amount" is intended to include an amount sufficient to address one or more symptoms commonly observed in, e.g., VMS, such as hot flashes.

[00166] In some embodiments, a therapeutically effective amount of an anti-NK3R antibody or pharmaceutical composition comprising the same has a beneficial effect but does not cure a sex hormone-related disorder. In certain embodiments, therapy may encompass the administration of

multiple doses of an anti-NK3R antibody or pharmaceutical composition comprising the same at a certain frequency to achieve a therapeutic effect.

[00167] A therapeutically effective amount is typically dependent on the weight of the subject being treated, his or her physical condition, the extensiveness of the condition to be treated, and the age of the subject being treated. In general, anti-NK3R antibodies disclosed herein may be administered in an amount in the range of about 10 ng/kg body weight to about 1000 mg/kg body weight per dose. In certain embodiments, antibodies may be administered in an amount in the range of about 50 μg/kg body weight to about 500 mg/kg body weight per dose. In other embodiments, antibodies may be administered in an amount in the range of about 100 μg/kg body weight to about 1000 mg/kg body weight per dose. In other embodiments, antibodies may be administered in an amount in the range of about 100 μg/kg body weight to about 200 mg/kg body weight per dose. In other embodiments, antibodies may be administered in an amount in the range of about 0.45 mg/kg body weight to about 12.5 mg/kg body weight per dose. In other embodiments, antibodies may be administered in an amount in the range of about 0.5 mg/kg body weight to about 20 mg/kg body weight per dose. In other embodiments, antibodies may be administered in a dose of at least about 100 μg/kg body weight, at least about 250 μg/kg body weight, at least about 750 μg/kg body weight, at least about 3 mg/kg body weight, at least about 5 mg/kg body weight, or at least about 10 mg/kg body weight.

[00168] In some embodiments, dosage regimens comprise a loading dose and one or more maintenance doses as part of an induction phase and maintenance phase respectively. In some embodiments, the induction dose is between about 20 mg and about 1800 mg. In some embodiments, the maintenance dose is between about 20 mg and about 600 mg. In some embodiments, the interval between two or more induction phase injections is between about 2 weeks and about 24 weeks, and the interval between two or more maintenance phase injections is between about 2 weeks and about 52 weeks.

[00169] In particular embodiments, the first injection of the antibody or antigen-binding fragment thereof can be a loading dose, wherein the loading dose of the antibody or antigen-binding fragment thereof is up to three times the mass of the treatment dose, or the loading dose of the antibody or antigen-binding fragment thereof is between about 100 mg and about 600 mg; and the second and additional injections of the antibody or antigen-binding fragment thereof can be treatment doses of at least 5 treatment injections, wherein the treatment dose of the antibody or antigen-binding fragment is between about 50 mg and about 300 mg

[00170] Other dosing regimens may be predicated on Body Surface Area (BSA) calculations. As is well known in the art, a subject's BSA is calculated using the subject's height and weight and provides a measure of a subject's size as represented by the surface area of his or her body. In some embodiments, anti-NK3R antibodies disclosed herein are administered in dosages from 10 mg/m^2 to 800 mg/m^2. In other embodiments, antibodies are administered in dosages from 50 mg/m^2 to 500 mg/m^2 and even more preferably at dosages of 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 350 mg/m^2, 400 mg/m^2 or 450 mg/m^2.

[00171] Escalation for an individual subject can occur at the discretion of a clinician in the absence of any clinically significant occurrence that the clinician might reasonably believe would present an undue safety risk for the subject, such as, for example, infusion reactions, acute anaphylaxis, and serum sickness.

[00172] Anti-NK3R antibodies disclosed herein are usually administered to a subject on multiple occasions in accordance with regimens known in the art. In some instances, two or more antibodies with different binding specificities may be administered simultaneously, in which case the dosage of each antibody administered falls within the ranges indicated. Intervals between single dosages can be weekly, monthly, or yearly. Intervals can also be irregular depending upon levels of antibody in the blood and other clinical indicia, In some embodiments, the dosage is adjusted so that minimum blood serum concentration reached between any two injections (Cmin) is at least between about 0.9 μg/mL and 250 μg/mL or the maximum blood serum concentration reached after administration of an injection and prior to administration of a subsequent injection (Cmax) is at least between about 1.5 μg/mL and 275 μg/mL or blood serum concentrations of the during treatment range between about 1.5 μg/mL and about 550 μg/mL or the area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [AUC0-inf]) injection may be at least around 75,000 ng*day/mL to at least around 10,500,000 ng*day/mL. Alternatively, antibodies can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency will vary depending on the half-life of the antibody in the subject. In general, human antibodies show the longest half-life, followed by humanized antibodies, chimeric antibodies, and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some subjects continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes

required until progression of the disease is reduced or terminated, until a partial or complete response is achieved, and/or until the subject shows lessening or amelioration of symptoms of disease. Thereafter, the patent can be administered a prophylactic regime.

[00173] The duration of a therapeutic regimen depends on a variety of factors that are readily appreciated by one of skill in the art. A clinician can observe the therapy's effects closely and make any adjustments as needed. When agents are used in combination, the two or more therapeutic agents are administered simultaneously or sequentially in any order, i.e., an antibody disclosed herein is administered prior to administering a second therapeutic agent, concurrently with a second therapeutic agent, or subsequent to administration of a second therapeutic agent. For example, a combination therapy may be performed by administering a first therapeutic agent prior to (e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concurrently with, or subsequent to (*e.g.*, 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) administering a second therapeutic agent. Exemplary second therapeutic agents include selective estrogen receptor modulators (SERM), gonadotropin-releasing hormone (GnRH) agonists, gonadotropin-releasing hormone (GnRH) antagonists, nonsteroidal anti-androgens, kappa opioid agonists, and selective estrogen receptor degraders (SERD).

[00174] The dosage, frequency, and mode of administration of each component of a combination therapy can be controlled independently. For example, one therapeutic agent may be administered orally three times per day, while the second therapeutic agent may be administered intravenously once per day. Combination therapy may be given in on-and-off cycles that include rest periods. The compounds may also be admixed or otherwise formulated together such that one administration delivers both therapeutic agents. In this case, each therapeutic agent is generally present in an amount of 1-95% by weight of the total weight of the composition. Alternatively, therapeutic agents can be formulated separately and in individual dosage amounts. Combinations of therapeutic agents for treatment can be provided as components of a pharmaceutical pack.

[00175] Preferably, combination therapies elicit a synergistic therapeutic effect, i.e., an effect greater than the sum of their individual effects or therapeutic outcomes, such as those described above. For example, a synergistic therapeutic effect may be an effect of at least about two-fold greater than sum of the therapeutic effects elicited by the single agents of a given combination, or

at least about five-fold greater, or at least about ten-fold greater, or at least about twenty-fold greater, or at least about fifty-fold greater, or at least about one hundred-fold greater. A synergistic therapeutic effect may also be observed as an increase in therapeutic effect of at least 10% compared to the sum of the therapeutic effects elicited by the single agents of a given combination, or at least 20%, or at least 30%, or at least 40%, or at least 50%, or at least 60%, or at least 70%, or at least 80%, or at least 90%, or at least 100%, or more. A synergistic effect is also an effect that permits reduced dosing of therapeutic agents when they are used in combination.

[00176] Articles of Manufacture

[00177] The inventions disclosed herein also encompass pharmaceutical packs and kits comprising one or more containers and comprising one or more doses of an anti-NK3R antibody disclosed herein. In certain embodiments, a unit dosage is provided wherein the unit dosage contains a predetermined amount of a composition comprising, for example, an anti-NK3R antibody disclosed herein, with or without one or more additional agents. For other embodiments, such a unit dosage is supplied in single-use prefilled syringe for injection. In still other embodiments, the composition contained in the unit dosage may comprise saline, sucrose, or the like; a buffer, such as phosphate, or the like; and/or be formulated within a stable and effective pH range. Alternatively, in certain embodiments, the composition may be provided as a lyophilized powder that may be reconstituted upon addition of an appropriate liquid, for example, sterile water. In certain preferred embodiments, the composition comprises one or more substances that inhibit protein aggregation, including, but not limited to, sucrose and arginine. Any label on, or associated with, the container(s) indicates that the enclosed composition is used for diagnosis or treatment.

[00178] The present invention also provides kits for producing single-dose or multi-dose administration units of an anti-NK3R antibody disclosed herein and, optionally, one or more other diagnostic or therapeutic agents. The kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition that is effective for treating the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits will generally contain in a suitable container a pharmaceutically acceptable formulation of the anti-NK3R antibody and, optionally, one or more

other diagnostic or therapeutic agents in the same or different containers. The kits may also contain other pharmaceutically acceptable formulations, either for diagnosis or combined therapy.

[00179] More specifically the kits may have a single container that contains the anti-NK3R antibody with or without additional components, or they may have distinct containers for each desired agent. Where combined therapeutics are provided for conjugation, a single solution may be pre-mixed, either in a molar equivalent combination, or with one component in excess of the other. Alternatively, the anti-NK3R antibody and any optional diagnostic or therapeutic agent of the kit may be maintained separately within distinct containers prior to administration to a subject. The kits may also comprise a second/third container means for containing a sterile, pharmaceutically acceptable buffer or other diluent such as bacteriostatic water for injection (BWFI), phosphate-buffered saline (PBS), Ringer's solution and dextrose solution.

[00180] When the components of the kit are provided in one or more liquid solutions, the liquid solution is preferably an aqueous solution, with a sterile aqueous solution being particularly preferred. However, the components of the kit may be provided as dried powder(s). When reagents or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent. It is envisioned that the solvent may also be provided in another container.

[00181] As indicated briefly above the kits may also contain a means by which to administer the antibody and any optional components to the subject, e.g., one or more needles or syringes, or even an eye dropper, pipette, or other such like apparatus, from which the formulation may be injected or introduced into the subject. Such kits will also typically include a means for containing the vials, or such like, and other component in close confinement for commercial sale, such as, e.g., injection or blow-molded plastic containers into which the desired vials and other apparatus are placed and retained. Any label or package insert indicates that the anti-NK3R antibody composition is used for treating, for example, VMS.

[00182] In other preferred embodiments, anti-NK3R antibodies disclosed herein may be used in conjunction with, or comprise, diagnostic or therapeutic devices useful in the diagnosis or treatment of a sex hormone-related disorder. For example, in one embodiment, anti-NK3R antibodies may be combined with certain diagnostic devices or instruments that may be used to detect, monitor, quantify or profile cells or marker compounds involved in the etiology or manifestation of a sex hormone-related disorder.

EXAMPLES

[00183] The following examples have been included to illustrate aspects of the inventions disclosed herein. In light of the present disclosure and the general level of skill in the art, those of skill appreciate that the following examples are intended to be exemplary only and that numerous changes, modifications, and alterations may be employed without departing from the scope of the disclosure.

[00184] Example 1

[00185] Generation of anti-NK3R antibodies

[00186] Wild-type rats were immunized with recombinant human NK3R (Accession No. NP_001050.1) using standard methods of DNA immunization. Plasma titer response was assessed using a dilution series of plasma. Plasma samples were incubated with either EXPICHO™ or EXPICHO™ cells (Thermo Fisher Scientific) transiently expressing human or rat NK3R. Binding of antigen-specific antibodies in the plasma to the cells was then detected using a fluorescently-labelled secondary antibody via high-throughput, plate-based flow cytometry.

[00187] Lymph nodes (brachial, axillary, inguinal, popliteal, mesenteric, and sciatic) and bone marrow from femur and tibia were collected from immunized rats with significant serum titers to human NK3R. Cells were isolated and enriched for antibody-secreting cells using species-specific B cell selection markers. Enriched plasma cell suspension was injected into microfluidic screening devices with 91,000 individual nanoliter-volume reaction chambers. Single B cells secreting target-specific antibodies were identified and isolated using a multiplexed live cell-binding assay, consisting of EXPICHO™ cells (Thermo Fisher Scientific) transiently transfected with human NK3R or rat NK3R (Accession No. NP_058749.1). Binding was detected using a fluorescently labelled secondary antibody specific to rodent IgG. Positive hits were identified using machine vision and recovered using automated robotics-based protocols.

[00188] Single-cell polymerase chain reaction (PCR) and custom molecular biology protocols generated NGS sequencing libraries (MiSeq, Illumina) using automated workstations (Bravo, Agilent). Sequencing data were analyzed using a custom bioinformatics pipeline to yield heavy and light chain sequences for recovered antibody-secreting cells. Each sequence was annotated with the closest germline (V(D)J) genes and degree of somatic hypermutation. Antibodies were considered members of the same clonal family if they shared the same inferred heavy and light V and J genes and had the same CDR3 length (Figure 1).

[00189] Paired heavy and light chains were expressed as full length human IgG1 isotype antibodies. Specifically, heavy and light chains were transiently transfected into EXPI293F™ cells (Thermo Fisher Scientific). Enhancers were added 18-24 hours after transfection. Supernatants were harvested 4 to 5 days after transfection. Cells were pelleted by centrifugation at 3000xg for 10 minutes at 4°C and supernatants were collected and aliquoted into 50 mL FALCON® tubes.

[00190] Supernatants were decanted into new 50 mL tubes containing Protein A magnetic beads. The supernatants were incubated overnight on the rotator and purified the following day using a semi-automated antibody purification system. Briefly, the antibodies were eluted from the Protein A magnetic beads into buffer containing 100 mM sodium phosphate, 3M NaCl pH 11 at a 1:15 ratio resulting in PBS pH 6.0.

[00191] In order to generate sufficient material for *in vivo* studies, a different method was used for large-scale antibody production. Specifically, EXPI293F™ cells (Thermo Fisher Scientific) were co-transfected with the heavy and light chains and enhancers were added 18-24 hours after transfection. Supernatants were harvested 5 days after transfection. Supernatants were mixed with SARTOCLEAR DYNAMICS® Diatomaceous Earth powder (Sartorius) and then passed through a 0.2 μM polyethersulfone (PES) filter and stored at 4°C until needed. The supernatant was loaded through a custom packed MABSELECT PRISMA™ protein A column (Cytiva) using the ÄKTA Avant 25 (Cytiva). The antibody was eluted from the column and neutralized with 3.5% w/v of 2M Tris pH 9.5 solution. The eluted and neutralized sample was desalted using SUPERDEX® 200 26/600 (Cytiva) into PBS pH 6.0.

[00192] Example 2

[00193] Identification of antagonist anti-NK3R antibodies

[00194] Recombinant antibodies were confirmed to bind specifically to NK3R via high-throughput flow cytometry assays. Binding assays were performed on EXPICHO™ cells electroporated with either human or rat NK3R. EXPICHO™ cells were plated in 96 well plates and incubated with 10 μg/mL of recombinant antibodies for 15-20 minutes at 4°C. Cells were washed accordingly, and binding was detected using a fluorescently labelled secondary anti-human Fc antibody. Following the final wash step, the cells were resuspended in fluorescence-activated cell sorting (FACS) buffer. Median fluorescence intensity of each antibody was assessed to determine if the antibody bound specifically to human and/or rat NK3R.

[00195] PATHHUNTER® CHO-K1 human TACR3 cell line (Eurofins) was seeded at 10,000 cells per well in 20 µL of reduced serum basal growth media into 384 well plates and incubated overnight at 37°C. The following day, the components of the Calcium 6 assay kit (Molecular Devices) were reconstituted fresh using assay buffer (HBSS, 20 mM HEPES, 1% w/v BSA). Probenecid (2 mM) was added to this mixture followed by addition to the plates at 20 µL per well. Plates were incubated with the dye for 90 minutes in the dark. Antibodies were added to the plates in 20 µL per well of assay buffer as an 8 or 10-point serial dilution, starting at 300 nM and serially diluted 1 in 4. Each concentration was tested on cells in triplicate or quadruplicate. Following incubation at room temperature for 30 minutes in the dark after antibody addition, the agonist, senktide or NKB was added to the cells in 10 µL per well at a pre-determined EC_{80} concentration using the FLIPR® Penta (Molecular Devices). Fluorescence was measured immediately after addition of agonist for 200s. Data was collected and relative fluorescence units (RFU) plotted against log of antibody concentration using nonlinear regression analysis (4-parameter logistic curve fit) in GRAPHPAD PRISM® 10 (GraphPad LLC). The potency of the anti-NK3R antibodies for inhibition of NK3R signaling in a calcium mobilization assay is listed in Table 1 (see Figure 2).

[00196] Table 1: Potency of chimeric antibody antagonists against a human NK3R cell line using the calcium mobilization assay

Antibody ID	IC_{50} (nM)
mAb 27863	2.07
mAb 27858	2.24
mAb 20813	6.94
mAb 20811	4.41

[00197] Example 3

[00198] Humanization of anti-NK3R antibodies

[00199] In order to reduce potential immunogenicity, the sequences of potent anti-NK3R antibodies were analyzed and subsequently humanized. Briefly, human V and J genes were selected for grafting based on high sequence homology to the rodent anti-NK3R antibody. Kabat defined CDRs from the rodent anti-NK3R antibodies were then grafted onto the selected human V and J genes, except for the heavy chain CDR1 and CDR2 where Kabat and/or Chothia defined CDRs were grafted. Back-mutations were introduced as part of the humanization process to

maintain function. Humanized variants of anti-NK3R antibodies which exhibited similar or improvements in the calcium mobilization assays are listed in Table 2 below and illustrated in Figures 3, 4 and 5. Values in Table 2 are averages taken from multiple independent experiments.

[00200] Table 2: Potency of humanized antibody antagonists against a human NK3R cell line using the calcium mobilization assay

Antibody ID	Human IC_{50} (nM)
mAb 27851	2.27
mAb 27880	2.59
mAb 27908	2.607
mAb 27868	2.93
mAb 27931	3.10
mAb 27890	3.11
mAb 27905	3.93
mAb 27871	3.47
mAb 27881	3.49
mAb 27927	4.10
mAb 27894	3.43
mAb 27902	3.87
mAb 27916	2.22
mAb 27876	2.17
mAb 27898	3.19
mAb 27888	8.30
mAb 27907	5.15
mAb 27889	4.30
mAb 27920	3.30
mAb 27924	4.25
mAb 27897	4.75
mAb 27875	3.50
mAb 27933	4.70
mAb 27900	3.85
mAb 27867	3.20
mAb 27878	4.20
mAb 27922	4.40
mAb 27883	4.20
mAb 27895	5.05
mAb 20810	4.10

mAb 27903	1.97
mAb 27886	1.90
mAb 20812	1.40
mAb 27929	6.10
mAb 27887	2.43
mAb 27926	2.07
mAb 27912	3.70
mAb 27869	4.10
mAb 27864	2.57

[00201] Example 4

[00202] Optimization of humanized anti-NK3R antibodies

[00203] During the lead optimization process, it was possible to conduct both germlining and remediation of manufacturing liabilities at the same time on the humanized antibodies, generating optimized antibodies. Utilizing mammalian cell production systems for antibody expression can lead to unintended post-translational modifications (PTMs), which may present challenges in subsequent bioprocessing stages and influence various molecular physicochemical characteristics, including shape, size, hydrophobicity, and charge. These alterations, in turn, have the potential to impact the pharmacokinetic (PK) and pharmacodynamic (PD) properties.

[00204] Amino acid motifs often responsible for these PTMs are referred to as potential manufacturing liabilities. To mitigate risk of these unintended PTMs the complementary determining regions (CDR) of humanized lead antibodies were scanned to identify the potential manufacturing liability motifs as described in Table 3. Using Kabat numbering, the following residue change was made to the heavy chain of mAb 20810 to remove a potential methionine oxidation site (M97L). The following residue changes were made to the light chain of mAb 20810 to remove a potential asparagine deamidation site (N30S, N30T, N30T + S31G + Y32F).

[00205] In order to further reduce potential immunogenicity whilst increasing the percentage of human identity, a selection of humanized antibodies were germlined. Using Kabat numbering, the following germline change, K64Q, was made to the heavy chain of humanized antibody mAb 20810. The following germline change, S51A, was made to the light chain of mAb 20810.

Table 3: Description of amino acid substitutions in mAb 20810 and mAb 27917

Antibody ID	Heavy chain	Light chain
mAb 27859	M97L	N30S

mAb 27879	M97L	N30T
mAb 27873	M97L	N30T+S31G+Y32F
mAb 27862	-	N92Q

[00206] In addition to the substitutions made to mAb 27917 in Table 3, the heavy and light chain sequences of the optimized antibody are screened for remaining *in silico* liabilities such as deamidation, isomerization, and oxidation. Ways to address such liabilities include, for example, N31S/T/Q/G, W33Y/F/I/H/A and D98S/T/A/Q/E/A/V substitutions in the heavy chain, and such substitutions may be found within the sequences of mAb 27317 to mAb 27407.

[00207] In order to determine if these substitutions affect functional activity against human NK3R, different combinatorial variants of each antibody were purified and tested for NK3R antagonism using the calcium mobilization assay and stable cell lines expressing human, cynomolgus monkey (Accession No. NP_001032951.1), or rat NK3R. IC_{50} values shown in Table 4 are taken from an independent experiment where the antibodies were tested together. (Data is illustrated in Figure 6).

[00208] Table 4: Potency of optimized antibody antagonists against human, cynomolgus monkey and rat NK3R cell line using the calcium mobilization assays

Antibody ID	Human IC_{50} (nM)	Cyno IC_{50} (nM)	Rat IC_{50} (nM)
mAb 27859	8.28	24.37	8.33
mAb 26106	8.84	26.43	8.55
mAb 25123	12.15	33.6	10.78
mAb 26105	6.83	15.51	3.46
mAb 26107	7.34	17.15	4.37
mAb 26108	6.20	15.23	2.82
mAb 27851	7.79	56.63	461.6
mAb 25129	8.51	104.70	1226
mAb 25128	7.20	21.49	44.86

[00209] Example 5

[00210] Antigen purification and binding affinity of antibodies

[00211] Expi293F cells (Thermo Fisher Scientific) were transfected with human NK3R and enhancers were added 18 hours after transfection. Cells were harvested 48 hours after transfection. Membranes were isolated and solubilized in buffer containing 20 mM HEPES pH7.5, 400 mM NaCl, 1 mM EDTA, 5% glycerol and 1% DDM (Anatrace), 0.1% CHS (Anatrace) for 4 hours at

4°C degrees. Proteins were purified using M2 ANTI-FLAG® resin (Sigma) and eluted in 20 mM HEPES pH 7.5, 150 mM NaCl, 1 mM EDTA, 5% Glycerol, 0.05% DDM, 0.005% CHS and 0.3 mg/mL 3X FLAG® peptide (Genscript). The human NK3R antigen was further purified by size exclusion chromatography (SEC) using a SUPEROSE® 6 increase 10/300 GL column (Cytiva) equilibrated with SEC running buffer containing 20 mM HEPES pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.01% LMNG (Anatrace), 0.001% CHS (Anatrace) and 0.003% GDN (Anatrace). The antigen was concentrated to 1 mg/mL for use in downstream assays.

[00212] Affinity of the antibodies for human NK3R antigen were measured using surface plasmon resonance (SPR) as analyzed on BIACORE® S200 and T200 systems (Cytiva). In brief, lead antibodies were captured on a Series S Protein A coated surface (Cytiva) at a concentration of 10 nM to give a relative response of 150-250 RU. The antigen was flowed over the surface in increasing concentrations between 1 and 80 nM and kinetic data from the resulting curves were fitted to a 1:1 binding model using the BIACORE® S200 evaluation software. All parameters were fit globally except for R_{max} due to variation between experiments. Antibody samples were run in duplicates and randomly ordered in the experiment to allow for experimental drift. Values of K_D in Table 2 below are averages of multiple independent experiments.

[00213] Table 5: Summary of binding affinity for optimized antibodies, K_D on human NK3R

Antibody ID	K_D (nM)
mAb 26106	0.10
mAb 27859	0.10
mAb 25123	0.18
mAb 26107	0.25
mAb 26108	0.28
mAb 26105	0.59
mAb 20812	0.57
mAb 25129	3.47
mAb 25128	4.26

[00214] Example 6

[00215] Pharmacological Study In Male SPRAGUE DAWLEY® Rats

[00216] The study was designed to evaluate changes in testosterone levels following administration of anti NK3R antibody in jugular vein cannulated male SPRAGUE DAWLEY® rats. A total of 26 male jugular cannulated rats (8-10 weeks) were used for the study. Animals were dosed with the test or isotype control antibody (5 mg/kg, n=10 and 8 respectively) on Day -1 (t=-

24 h), or fezolinetant (10 mg/kg; n=8) on Day 0, t=0hr. Dosing was done via intravenous administration at 4 mL/kg based on the day's body weight.

[00217] Plasma samples were analyzed for testosterone levels via a Luminex analysis (Millipore Cat# MSHMAG-21K). Male rats that were administered fezolinetant and mAb 20811 demonstrated an inhibition of plasma testosterone levels particularly in $AUC_{0\text{-}7.5h}$ (fezolinetant = 2.2±0.5; mAb 20811 = 1.4±0.4; isotype = 4.0±1.0) and $AUC_{0\text{-}9h}$ (fezolinetant = 2.4±0.5; mAb 20811 = 1.6±0.5; isotype control = 4.8±1.1) compared to the isotype control group (*see* Figure 7).

[00218] Example 7

[00219] Pharmacological Study In Female Wistar Rats

[00220] A study of the pharmacologic effect of a monoclonal antibody was conducted using ovariectomized (OVX) female Wistar rats. Sham surgery (non-ovariectomized) animals were included in the study as a control. The monoclonal antibody (or isotype control; a control antibody that binds an irrelevant target that is not present in rat) was administered to OVX rats as 15 mg/kg intravenous bolus injections on Day 0 and Day 7 of the study (2 doses total per animal across the duration of the study). Blood samples were collected from the tail vein, processed to serum, and analyzed for luteinizing hormone (LH) using a LUMINEX® immunoassay. Serum luteinizing hormone levels were measured on 8 study days, comprising 48, 96, 168, 216, 264 and 336 hours after antibody administration as well as a pre-dose baselines measured 24 h and immediately prior to antibody administration. LH response to antibody administration is shown in Figure 8 as the group mean (n=4-6) and the error bars represent standard deviation of the mean. Ovariectomized rats that were administered mAb 26106 showed inhibition of circulating luteinizing hormone.

[00221] Example 8

[00222] Pharmacology Study In Male Cynomolgus Monkeys

[00223] A study of the pharmacologic effect of a monoclonal antibody was conducted using male cynomolgus monkeys. The monoclonal antibody, mAb 26106 (5 mg/kg) was administered as a single intravenous bolus injection to animals (n=5) on Day 0 of the study. Blood samples were collected into tubes with K_2EDTA anticoagulant, processed to plasma using centrifugation, and analyzed for testosterone via LC-MS/MS following nitrogen purging with acetonitrile. Testosterone levels in plasma were monitored in individual animals on 4 study days, comprising 2, 5 and 12 days after antibody administration as well as a pre-dose baseline measured 2 days prior

to antibody administration. On each of these 4 days, blood samples were taken every 30 minutes across a 4 hour period in the morning and every 30 minutes across a 4 hour period in the evening. The plasma testosterone value for a given animal on a given day was calculated by averaging all samples collected for that animal on that day. Male cynomolgus monkeys treated with mAb 26106 demonstrated an inhibition of plasma testosterone levels by 2 days after administration.

[00224] Table 6: Plasma testosterone levels in male cynomolgus monkeys treated with mAb 26106

	Plasma Testosterone (ng/mL)	
	Group Mean	Standard Deviation
Pre-dose baseline	7.56	7.27
2 days after administration	1.28	1.05
5 days after administration	1.19	1.14
12 days after administration	2.12	1.42

[00225] Example 9

[00226] Pharmacokinetics

[00227] Homozygous Tg32 SCID mice were used to understand the single dose pharmacokinetics of human IgG monoclonal antibodies. Each treatment group consisted of four mice whereby each test antibody was administered at 5 mg/kg via intravenous administration. Antibody concentrations in sera samples were determined using the electrochemiluminescence technology from Meso Scale Discovery. MULTI-ARRAY™ plates were coated with goat anti-human IgG antibody and the secondary antibody was MSD® SULFO-TAG anti-human IgG. Data was analyzed using Phoenix 8.4 to extract relevant PK parameters. In conclusion, the anti-NK3R antagonist antibodies exhibited expected biphasic PK profiles in circulation similar to that of a monoclonal antibody.

[00228] Example 10

[00229] Epitope analysis via cryo-electron microscopy (cryoEM)

[00230] The Fab portion of the heavy and light chains is expressed and purified via standard methods of purification. In the final step, the Fab is concentrated and desalted into 20 mM HEPES

pH 7.5, 150 mM NaCl. The human NK3R antigen and Fab are mixed to a final 1:2 molar ratio and incubated overnight at 4°C. The human NK3R-Fab complex is purified by size exclusion chromatography (SEC) using a SUPEROSE® 6 Increase 10/300 GL column (Cytiva) equilibrated with SEC running buffer containing 20 mM HEPES pH 7.5, 150 mM NaCl, 1 mM EDTA, 0.01% LMNG (Anatrace), 0.001% CHS (Anatrace) and 0.003% GDN (Anatrace). Human NK3R-Fab complex is concentrated to 1 mg/mL for cryoEM studies. Human NK3R-Fab complex is applied to a glow-discharged UltrAuFoil 0.6/1.3 300 mesh grid. Using a VITROBOT™ Mark IV (FEI), grids are blotted for 5s at 10°C and 100% humidity, before flash-freezing in liquid ethane. Grids are imaged with Thermo Fisher KRIOS™ G3i TEM operating at 300kV (Thermo Fisher Scientific) equipped with a Gatan BIOQUANTUM™ energy filter with a 15eV slit detector (Gatan). Data processing is performed in CRYOSPARC™ v4 software. Finally, the human NK3R-Fab model is docked into the density maps and refined by several rounds of real-space refinement in Phenix software.

[00231] Example 11

[00232] Clinical Trial Design for Treatment of Advanced Hormone-Sensitive Prostate Cancer

[00233] A single-arm pilot study will be conducted to evaluate the use of an anti-NK3R antibody to reduce testosterone levels in men with advanced hormone-sensitive prostate cancer (HSPC). Ten patients with prostate cancer will undergo prostatectomy and levels of four hormones (FSH, LH, estradiol, and testosterone) will be measured prior to prostatectomy and the levels of the four hormones will be measured on days 2, 3, 7, 14, and 28 after administration of the antibody.

[00234] Subjects will undergo baseline screening (serum PSA, testosterone, physical examination, and medical history). Those men who meet inclusion criteria and elect to participate will be scheduled for the study protocol, which begins 35 days prior to scheduled surgery. An anti-NK3R antibody (mAb 26106) will be administered by the investigational pharmacy as a single dose between 3 mg and 1800 mg to each participant. On days 2, 3, 7, and 14, and 28, FSH, LH, estradiol, and testosterone levels will be obtained. On day 35 (one week after completing protocol therapy), each participant will undergo standard of care surgery. On day 42 post-operatively (+/- 3 days) FSH, LH, estradiol, testosterone, and PSA levels will be measured. Achievement of castrate testosterone levels (defined as testosterone <50 ng/mL) and reversibility of hormonal changes will be observed in some or all participants.

[00235] Example 12

[00236] Clinical Trial Design for Treatment of Estrogen-Dependent Breast Cancer

[00237] A single-arm pilot study will be conducted to evaluate the use of an anti-NK3R antibody to reduce tumor burden in women with estrogen-dependent breast cancer. Ten patients with breast cancer will be evaluated prior to treatment and on days 2, 3, 7, 14, and 28 after administration of the antibody. Evaluation will include measurement of four hormones (FSH, LH, estradiol, and testosterone) at all time points as well as assessments known in the art, e.g., measuring tumor lesions and other parameters described in Response Evaluation Criteria in Solid Tumors (RECIST).

[00238] At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable per RECIST 1.1 guidance. An anti-NK3R antibody (mAb 26106) will be administered by the investigational pharmacy as a single dose between 3 mg and 1800 mg to each participant. On days 2, 3, 7, and 14, and 28, FSH, LH, estradiol, and testosterone levels will be obtained. One week after cessation of treatment, target lesions will be evaluated and a partial response (defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) will be expected in some or all participants.

[00239] While this invention has been disclosed with reference to particular embodiments, it is apparent that other embodiments and variations of the inventions disclosed herein can be devised by others skilled in the art without departing from the true spirit and scope thereof. The appended claims include all such embodiments and equivalent variations.

CLAIMS

What is claimed is:

1. An antibody or antigen-binding fragment thereof that specifically binds to NK3R, wherein the antibody or antigen-binding fragment thereof comprises:

(a) three CDRs of a heavy chain variable region set forth as SEQ ID NO: 50 and three CDRs of a light chain variable region set forth as SEQ ID NO: 51; or

(b) three CDRs of a heavy chain variable region set forth as SEQ ID NO: 25 and three CDRs of a light chain variable region set forth as SEQ ID NO: 26; or

(c) three CDRs of a heavy chain variable region set forth as SEQ ID NO: 42 and three CDRs of a light chain variable region set forth as SEQ ID NO: 10.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment thereof comprises (a) a CDR-H1 comprising residues 31-35 of the heavy chain variable region (VH), a CDR-H2 comprising residues 50-66 of the VH, a CDR-H3 comprising residues 99-114 of the VH, a CDR-L1 comprising residues 24-34 of the light chain variable region (VL), CDR-L2 comprising residues 50-56 of the VL, and CDR-L3 comprising residues 89-97 of the VL;

wherein the CDR numbering is according to Kabat.

3. The antibody or antigen-binding fragment thereof of claim 1 or claim 2, comprising:

(a) a heavy chain variable region having an amino acid sequence that is at least 95% identical to the heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region having an amino acid sequence that is at least 95% identical to the light chain variable region set forth as SEQ ID NO: 51; or

(b) a heavy chain variable region having an amino acid sequence that is at least 95% identical to the heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region having an amino acid sequence that is at least 95% identical to the light chain variable region set forth as SEQ ID NO: 26; or

(c) a heavy chain variable region having an amino acid sequence that is at least 95% identical to the heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable

region having an amino acid sequence that is at least 95% identical to the light chain variable region set forth as SEQ ID NO: 10.

4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, comprising:

(a) a heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region set forth as SEQ ID NO: 51; or

(b) a heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region set forth as SEQ ID NO: 26; or

(c) a heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable region set forth as SEQ ID NO: 10.

5. The antibody or antigen-binding fragment thereof of any one of claims 1-4, comprising:

(a) a heavy chain constant region set forth as SEQ ID NO: 43 and a light chain constant region set forth as SEQ ID NO: 28; or

(b) a heavy chain constant region set forth as SEQ ID NO: 27 and a light chain constant region set forth as SEQ ID NO: 28.

6. The antibody or antigen-binding fragment thereof of any one of claims 1-5, comprising:

(a) a heavy chain set forth as SEQ ID NO: 52 and a light chain set forth as SEQ ID NO: 53; or

(b) a heavy chain set forth as SEQ ID NO: 81 and a light chain set forth as SEQ ID NO: 53; or

(c) a heavy chain set forth as SEQ ID NO: 35 and a light chain set forth as SEQ ID NO: 30; or

(d) a heavy chain set forth as SEQ ID NO: 29 and a light chain set forth as SEQ ID NO: 30; or

(e) a heavy chain set forth as SEQ ID NO: 44 and a light chain set forth as SEQ ID NO: 12; or

(f) a heavy chain set forth as SEQ ID NO: 65 and a light chain set forth as SEQ ID NO: 12.

7. An antibody or antigen-binding fragment thereof that specifically binds to NK3R, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 36, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 45, a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 46, a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 47, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 48, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 49; or

(b) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20, a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21, a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 22, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 23, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 24; or

(c) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 36, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 37, a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 38, a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 39, a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 40, and a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 41.

8. The antibody or antigen-binding fragment thereof of claim 7, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region having an amino acid sequence that is at least 90% identical to the heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region having an amino acid sequence that is at least 90% identical to the light chain variable region set forth as SEQ ID NO: 51; or

(b) a heavy chain variable region having an amino acid sequence that is at least 90% identical to the heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region having an amino acid sequence that is at least 90% identical to the light chain variable region set forth as SEQ ID NO: 26; or

(c) a heavy chain variable region having an amino acid sequence that is at least 90% identical to the heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable region having an amino acid sequence that is at least 90% identical to the light chain variable region set forth as SEQ ID NO: 10.

9. The antibody or antigen-binding fragment thereof of claim 7, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region having an amino acid sequence that is at least 95% identical to the heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region having an amino acid sequence that is at least 95% identical to the light chain variable region set forth as SEQ ID NO: 51; or

(b) a heavy chain variable region having an amino acid sequence that is at least 95% identical to the heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region having an amino acid sequence that is at least 95% identical to the light chain variable region set forth as SEQ ID NO: 26; or

(c) a heavy chain variable region having an amino acid sequence that is at least 95% identical to the heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable region having an amino acid sequence that is at least 95% identical to the light chain variable region set forth as SEQ ID NO: 10.

10. The antibody or antigen-binding fragment thereof of claim 7, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region having an amino acid sequence that is at least 98% identical to the heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region having an amino acid sequence that is at least 98% identical to the light chain variable region set forth as SEQ ID NO: 51; or

(b) a heavy chain variable region having an amino acid sequence that is at least 98% identical to the heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region having an amino acid sequence that is at least 98% identical to the light chain variable region set forth as SEQ ID NO: 26; or

(c) a heavy chain variable region having an amino acid sequence that is at least 98% identical to the heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable

region having an amino acid sequence that is at least 98% identical to the light chain variable region set forth as SEQ ID NO: 10.

11. The antibody or antigen-binding fragment thereof of claim 7, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region having an amino acid sequence that is at least 99% identical to the heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region having an amino acid sequence that is at least 99% identical to the light chain variable region set forth as SEQ ID NO: 51; or

(b) a heavy chain variable region having an amino acid sequence that is at least 99% identical to the heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region having an amino acid sequence that is at least 99% identical to the light chain variable region set forth as SEQ ID NO: 26; or

(c) a heavy chain variable region having an amino acid sequence that is at least 99% identical to the heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable region having an amino acid sequence that is at least 99% identical to the light chain variable region set forth as SEQ ID NO: 10.

12. The antibody or antigen-binding fragment thereof of claim 7, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region set forth as SEQ ID NO: 51; or

(b) a heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region set forth as SEQ ID NO: 26; or

(c) a heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable region set forth as SEQ ID NO: 10.

13. The antibody or antigen-binding fragment thereof of any one of claims 7-12, wherein the antibody or antigen-binding fragment thereof is selected from the group consisting of Fab, Fab′, $F(ab')_2$, Fab′-SH, Fv, linear antibody, and single-chain antibody fragment.

14. The antibody or antigen-binding fragment thereof of any one of claims 7-13, wherein the antibody or antigen binding fragment thereof is a full-length antibody.

15. The antibody or antigen-binding fragment thereof of any one of claims 7-14, wherein the heavy chain variable region is fused to a heavy chain constant region and the light chain variable region is fused to a light chain constant region.

16. The antibody or antigen-binding fragment thereof of any one of claims 7-15, wherein the heavy chain constant region is selected from the group consisting of IgA1, IgA2, IgD, IgE, IgG1, IgG2, IgG3, IgG4, and IgM.

17. The antibody or antigen-binding fragment thereof of any one of claims 7-16, wherein the heavy chain constant region is of the IgG1 isotype.

18. The antibody or antigen-binding fragment thereof of any one of claims 7-17, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain constant region comprising an amino acid sequence at least 90% identical to SEQ ID NO: 43 and a light chain constant region comprising an amino acid sequence at least 90% identical to SEQ ID NO: 28; or

(b) a heavy chain constant region comprising an amino acid sequence at least 90% identical to SEQ ID NO: 27 and a light chain constant region comprising an amino acid sequence at least 90% identical to SEQ ID NO: 28.

19. The antibody or antigen-binding fragment thereof of any one of claims 7-18, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 43 and a light chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 28; or

(b) a heavy chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 27 and a light chain constant region comprising an amino acid sequence at least 95% identical to SEQ ID NO: 28.

20. The antibody or antigen-binding fragment thereof of any one of claims 7-19, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 43 and a light chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 28; or

(b) a heavy chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 27 and a light chain constant region comprising an amino acid sequence at least 98% identical to SEQ ID NO: 28.

21. The antibody or antigen-binding fragment thereof of any one of claims 7-20, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain constant region comprising an amino acid sequence at least 99% identical to SEQ ID NO: 43 and a light chain constant region comprising an amino acid sequence at least 99% identical to SEQ ID NO: 28; or

(b) a heavy chain constant region comprising an amino acid sequence at least 99% identical to SEQ ID NO: 27 and a light chain constant region comprising an amino acid sequence at least 99% identical to SEQ ID NO: 28.

22. The antibody or antigen-binding fragment thereof of any one of claims 7-21, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 43 and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 28; or

(b) a heavy chain constant region comprising the amino acid sequence of SEQ ID NO: 27 and a light chain constant region comprising the amino acid sequence of SEQ ID NO: 28.

23. The antibody or antigen-binding fragment thereof of any one of claims 7-22, comprising an Fc variant of a parent heavy chain constant region, the Fc variant comprising an amino acid substitution to block antibody binding to FcγRI, FcγRII, FcγRIII, or FcRn.

24. The antibody or antigen-binding fragment thereof of claim 23, wherein the Fc variant comprises an amino acid substitution at a position selected from the group consisting of 234, 235, 236, 252, 254, and 256, and wherein the Fc variant further comprises an amino acid deletion at position 447, and wherein amino acid numbering is according to the EU index.

25. The antibody or antigen-binding fragment thereof of claim 24, wherein the Fc variant is selected from one of:

(a) L234S, L235T, G236R, and wherein K447 is deleted; or

(b) L234S, L235T, G236R, M252Y, S254T, and T256E, and wherein K447 is deleted, and

wherein amino acid numbering is according to the EU index.

26. The antibody or antigen-binding fragment thereof of any one of claims 7-25, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 52 and a light chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 53;

(b) a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 81 and a light chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 53;

(c) a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 35 and a light chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 30;

(d) a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 29 and a light chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 30;

(e) a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 44 and a light chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 12; or

(f) a heavy chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 65 and a light chain comprising an amino acid sequence at least 90% identical to SEQ ID NO: 12.

27. The antibody or antigen-binding fragment thereof of any one of claims 7-26, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 52 and a light chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 53;

(b) a heavy chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 81 and a light chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 53;

(c) a heavy chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 35 and a light chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 30;

(d) a heavy chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 29 and a light chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 30;

(e) a heavy chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 44 and a light chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 12; or

(f) a heavy chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 65 and a light chain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 12.

28. The antibody or antigen-binding fragment thereof of any one of claims 7-27, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 52 and a light chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 53;

(b) a heavy chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 81 and a light chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 53;

(c) a heavy chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 35 and a light chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 30;

(d) a heavy chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 29 and a light chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 30;

(e) a heavy chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 44 and a light chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 12; or

(f) a heavy chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 65 and a light chain comprising an amino acid sequence at least 98% identical to SEQ ID NO: 12.

29. The antibody or antigen-binding fragment thereof of any one of claims 7-28, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 52 and a light chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 53;

(b) a heavy chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 81 and a light chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 53;

(c) a heavy chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 35 and a light chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 30;

(d) a heavy chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 29 and a light chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 30;

(e) a heavy chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 44 and a light chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 12; or

(f) a heavy chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 65 and a light chain comprising an amino acid sequence at least 99% identical to SEQ ID NO: 12.

30. The antibody or antigen-binding fragment thereof of any one of claims 7-29, wherein the antibody or antigen-binding fragment thereof comprises:

(a) a heavy chain comprising SEQ ID NO: 52 and a light chain comprising SEQ ID NO: 53;

(b) a heavy chain comprising SEQ ID NO: 81 and a light chain comprising SEQ ID NO: 53;

(c) a heavy chain comprising SEQ ID NO: 35 and a light chain comprising SEQ ID NO: 30;

(d) a heavy chain comprising SEQ ID NO: 29 and a light chain comprising SEQ ID NO: 30;

(e) a heavy chain comprising SEQ ID NO: 44 and a light chain comprising SEQ ID NO: 12; or

(f) a heavy chain comprising SEQ ID NO: 65 and a light chain comprising SEQ ID NO: 12.

31. The antibody or antigen-binding fragment thereof of any one of claims 7-30, wherein the heavy chain constant region further comprises a C-terminal lysine residue.

32. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-31, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

33. A nucleic acid encoding:

(a) an antibody or antigen-binding fragment thereof comprising a heavy chain variable region comprising the amino acid sequence set forth in any one of SEQ ID NOs: 50, 25, or 42; or

(b) an antibody or antigen-binding fragment thereof comprising a light chain variable region comprising the amino acid sequence set forth in any one of SEQ ID NOs: 51, 26, or 10; or

(c) an antibody or antigen-binding fragment thereof comprising a heavy chain variable region set forth as SEQ ID NO: 50 and a light chain variable region set forth as SEQ ID NO: 51; or

(d) an antibody or antigen-binding fragment thereof comprising a heavy chain variable region set forth as SEQ ID NO: 25 and a light chain variable region set forth as SEQ ID NO: 26; or

(e) an antibody or antigen-binding fragment thereof comprising a heavy chain variable region set forth as SEQ ID NO: 42 and a light chain variable region set forth as SEQ ID NO: 10.

34. An expression vector comprising the nucleic acid of claim 33.

35. A host cell comprising the nucleic acid of claim 33 or the expression vector of claim 34.

36. A method for producing an anti-NK3R antibody or antigen-binding fragment thereof comprising:

(a) culturing the host cell of claim 35 under a condition suitable for production of the anti-NK3R antibody or antigen-binding fragment thereof; and

(b) isolating the anti-NK3R antibody or antigen-binding fragment thereof produced by the host cell.

37. An article of manufacture useful for diagnosing or treating a moderate to severe vasomotor symptom comprising a receptacle comprising the antibody or antigen-binding fragment thereof of any one of claims 1-31, or the pharmaceutical composition of claim 32 and instructional materials for using the same to diagnose or treat the moderate to severe vasomotor symptom.

38. An article of manufacture useful for diagnosing or treating prostate cancer comprising a receptacle comprising the antibody or antigen-binding fragment thereof of any one of claims 1-31, or the pharmaceutical composition of claim 32 and instructional materials for using the same to diagnose or treat the prostate cancer.

39. An article of manufacture useful for diagnosing or treating estrogen-dependent cancer comprising a receptacle comprising the antibody or antigen-binding fragment thereof of any one of claims 1-31, or the pharmaceutical composition of claim 32 and instructional materials for using the same to diagnose or treat the estrogen-dependent cancer.

40. A method of treating a moderate to severe vasomotor symptom, the method comprising administering a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1-31 or the pharmaceutical composition of claim 32 to a subject.

41. The method of claim 40, wherein the moderate to severe vasomotor symptom is caused by peri-menopause, menopause, or post-menopause.

42. The method of claim 40, wherein the moderate to severe vasomotor symptom is caused by endocrine therapy for a hormone-sensitive tumor.

43. The method of any one of claims 40-42, wherein the frequency and severity of the moderate to severe vasomotor symptom is reduced compared to a placebo or no treatment.

44. The method of any one of claims 40-43, wherein the moderate to severe vasomotor symptom is a hot flash.

45. The method of any one of claims 40-44, wherein prior to treatment, the patient has a serum estradiol level of $\leq$50 pg/mL.

46. The method of any one of claims 40-45, wherein prior to treatment, the patient has at least about 7 moderate to severe hot flushes per day.

47. The method of any one of claims 40-46, wherein prior to treatment, the patient has at least about 50 moderate to severe hot flushes per week.

48. The method of any one of claims 40-47, wherein the frequency and severity of moderate to severe vasomotor symptoms associated with menopause is reduced when compared with placebo treatment at 4 weeks.

49. The method of any one of claims 40-48, wherein the frequency and severity of moderate to severe vasomotor symptoms associated with menopause is reduced when compared with placebo treatment at 12 weeks.

50. The method according to claim 40-49, wherein the levels of luteinizing hormone (LH) in the patient are each reduced by at least 70% compared to baseline levels of LH.

51. The method according to claim 50, wherein the reduction in levels of LH is reversible.

52. A method of treating prostate cancer comprising administering a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1-31 or the pharmaceutical composition of claim 32 to a subject.

53. The method according to claim 52, wherein the prostate cancer is a hormone responsive prostate cancer.

54. The method of any one of claims 52 or 53, wherein administering the effective amount of the anti-NK3R antibody or antigen-binding fragment thereof reversibly lowers the patient's serum testosterone to a concentration lower than or equal to 20 ng/dL.

55. The method of any one of claims 52-54, wherein the patient is a lower risk patient, an intermediate risk patient, or a high-risk patient.

56. The method of any one of claims 52-55, wherein the patient is not undergoing androgen deprivation therapy (ADT).

57. The method of any one of claims 52-56, wherein the patient is undergoing androgen deprivation therapy and the anti-NK3R antibody or antigen-binding fragment thereof is administered in combination with the ADT.

58. The method of claim 57, wherein the androgen deprivation therapy comprises administration of a gonadotropin releasing hormone (GnRH) agonist, a GnRH antagonist, a histamine H2 receptor antagonist, a non-steroidal antiandrogen (NSAA), or an androgen receptor antagonist.

59. The method of claim 57, wherein the androgen deprivation therapy comprises leuprolide, elagolix, linzagolix, relugolix, goserelin, triptorelin, buserelin, deslorelin, fertirelin, gonadorelin, histrelin, lecirelin, nafarelin, peforelin, triptorelin, abarelix, cetrorelix, degarelix, ganirelix, flutamide, nilutamide, bicalutamide, topilutamide, apalutamide, enzalutamide, darolutamide, cimetidine, proxalutamide, seviteronel, cioteronel, inocoterone acetate, RU-58841, dimethylcurcumin, AZ3514, arv-110, MTX-23, ARD-61, UT-34, FL442, MK-4541, LY2452473, GTx-024/Enobosarm, or GSK2881078.

60. The method of any one of claims 52-59, wherein the anti-NK3R antibody is administered in combination with radiation treatment.

61. The method of any one of claims 52-60, wherein the levels of testosterone in the patient are each reduced by at least 70% compared to baseline levels of testosterone.

62. The method of claim 61, wherein the reduction in levels of testosterone is reversible.

63. The method of any one of claims 52-62, wherein the patient has undergone prostatectomy.

64. The method of any one of claims 52-63, wherein the patient is suffering from non-metastatic prostate cancer.

65. A method of treating estrogen-dependent cancer comprising administering a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1-31 or the pharmaceutical composition of claim 32 to a subject.

66. The method of claim 65, wherein the estrogen-dependent cancer is selected from the group consisting of breast cancer, ovarian cancer, endometrial cancer, and uterine cancer.

67. The method of any one of claims 40-66, wherein:

(a) the antibody or antigen-binding fragment thereof is administered via injection; or

(b) the antibody or antigen-binding fragment thereof is administered via subcutaneous injection; or

(c) the antibody or antigen-binding fragment thereof is administered via injection and the method comprises administering at least one injection at a dose of at least about 20 mg of the antibody or antigen-binding fragment thereof; or

(d) the antibody or antigen-binding fragment thereof is a disease modifying drug; or

(e) the antibody or antigen-binding fragment thereof is administered at least twice with at least one interval of 1 to 6 months; or

(f) the antibody or antigen-binding fragment thereof is administered at least twice with at least one interval of around 3 months.

68. The method as in any one of claims 40-66, wherein:

(a) each dose of the antibody or antigen-binding fragment thereof is between about 20 mg and about 1800 mg; or

(b) each dose of the antibody or antigen-binding fragment thereof is about 75 mg, about 100 mg, about 150 mg, about 300 mg, or about 600 mg; or

(c) the dose of the antibody or antigen-binding fragment thereof is about 75 mg; or

(d) the dose of the antibody or antigen-binding fragment thereof is about 100 mg; or

(e) the dose of the antibody or antigen-binding fragment thereof is about 150 mg; or

(f) the dose of the antibody or antigen-binding fragment thereof is about 300 mg; or

(g) the dose of the antibody or antigen-binding fragment thereof is about 600 mg; or

(h) the dose of the antibody or antigen-binding fragment thereof is between about 0.45 mg/kg and about 12 mg/kg.

69. The method as in any one of claims 40-66, wherein:

(a) the antibody or antigen-binding fragment thereof is administered via injection and the minimum blood serum concentration reached by the antibody or antigen-binding fragment thereof between any two injections (Cmin) is at least between 0.9 μg/mL and 250 μg/mL; or

(b) the maximum blood serum concentration reached by the antibody or antigen-binding fragment thereof after administration of an injection and prior to administration of a subsequent injection (Cmax) is at least between about 1.5 μg/mL and 275 μg/mL; or

(c) blood serum concentrations of the antibody or antigen-binding fragment thereof during treatment range between about 1.5 μg/mL and about 550 μg/mL; or

(d) the area under the serum concentration-time curve (AUC) following the first (AUC extrapolated to infinity [$AUC_{0\text{-}inf}$]) injection may be at least around 75,000 ng*day/mL to at least around 10,500,000 ng*day/mL.

70. The method as in any one of claims 40-66, wherein the method comprises an induction phase and a maintenance phase.

71. The method of claim 70, wherein:

(a) the induction dose of the antibody or antigen-binding fragment thereof is between about 20 mg and about 1000 mg; or

(b) the maintenance dose of the antibody or antigen-binding fragment thereof is between about 20 mg and about 600 mg; or

(c) the antibody or antigen-binding fragment thereof is administered via injection and the interval between two or more induction phase injections is between about 2 weeks and about 24 weeks, and the interval between two or more maintenance phase injections is between about 2 weeks and about 52 weeks.

72. The method as in any one of claims 40-66, wherein:

(a) the first injection of the antibody or antigen-binding fragment thereof can be a loading dose, wherein:

(i) the loading dose of the antibody or antigen-binding fragment thereof is up to three times the mass of the treatment dose, or

(ii) the loading dose of the antibody or antigen-binding fragment thereof is between about 100 mg and about 600 mg; and

(b) the second and additional injections of the antibody or antigen-binding fragment thereof can be treatment doses of at least 5 treatment injections, wherein:

(i) the treatment dose of the antibody or antigen-binding fragment is between about 50 mg and about 300 mg.

73. The method as in any one of claims 40-66, wherein administering the anti-NK3R antibody or antigen-binding fragment thereof results in:

(a) the administration of the anti-NK3R antibody, or antigen-binding fragment thereof results in the decrease in serum levels of at least one biomarker selected from the group consisting of: gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, or testosterone; or

(b) the administration of the anti-NK3R antibody, or antigen-binding fragment thereof results in the decrease in serum levels of at least one biomarker selected from the group consisting of: gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, or testosterone, and wherein the decrease is maintained for at least 12 weeks or at least 24 weeks following the final dose.

74. The method as in any one of claims 40-73, wherein the method further comprises administering one or more additional therapeutic agents selected from the group consisting of a selective estrogen receptor modulator (SERM), a gonadotropin-releasing hormone (GnRH) agonist, a gonadotropin-releasing hormone (GnRH) antagonist, nonsteroidal anti-androgen, kappa opioid agonist, selective estrogen receptor degrader (SERD).