(12) STANDARD PATENT (11) Application No. **AU 2016233309 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Anti-MUC16 antibodies and uses thereof

(51) International Patent Classification(s)
C07K 16/30 (2006.01) ***A61P 35/00*** (2006.01)
A61K 39/395 (2006.01) ***C12N 15/13*** (2006.01)

(21) Application No: **2016233309** (22) Date of Filing: **2016.03.16**

(87) WIPO No: **WO16/149368**

(30) Priority Data

(31) Number	(32) Date	(33) Country
62/134,402	**2015.03.17**	**US**

(43) Publication Date: **2016.09.22**
(44) Accepted Journal Date: **2021.11.18**

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(56) Related Art
WO 2011119979 A2
LARA MARCOS-SILVA ET AL, "A novel monoclonal antibody to a defined peptide epitope in MUC16", GLYCOBIOLOGY, US, (2015-07-22), vol. 25, no. 11, doi:10.1093/glycob/cwv056, ISSN 0959-6658, pages 1172 - 1182
WO 2015006043 A1
GUBBELS JENNIFER AA ET AL, MOLECULAR CANCER, BIOMED CENTRAL, LONDON, GB, (2006-10-26), vol. 5, no. 1, doi:10.1186/1476-4598-5-50, ISSN 1476-4598, page 50

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 September 2016 (22.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/149368 A1

(51) International Patent Classification:
C07K 16/30 (2006.01) *A61P 35/00* (2006.01)
C12N 15/13 (2006.01) *A61K 39/395* (2006.01)

(21) International Application Number:
PCT/US2016/022643

(22) International Filing Date:
16 March 2016 (16.03.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/134,402 17 March 2015 (17.03.2015) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

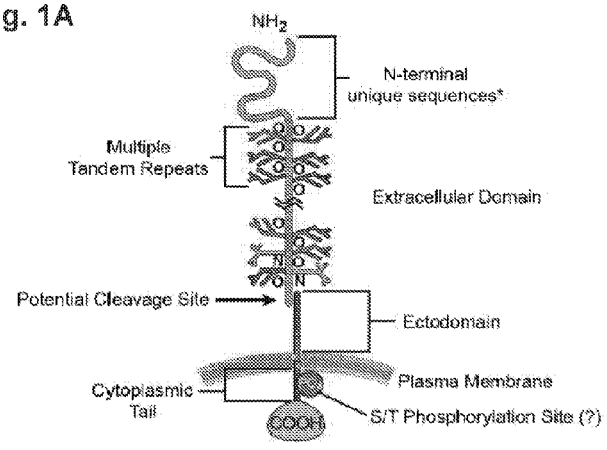
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2016/149368 A1

(54) Title: ANTI-MUC16 ANTIBODIES AND USES THEREOF

Fig. 1A



(57) Abstract: Provided herein are compositions, methods, and uses involving antibodies that immunospecifically bind glycosylated forms of MUC16, a tethered mucin protein. Also provided herein are uses and methods for managing, treating, or preventing disorders, such as cancer.

ANTI-MUC16 ANTIBODIES AND USES THEREOF

[0001] This application claims the benefit of U.S. Provisional Application No. 62/134,402, filed on March 17, 2015, which is incorporated by reference herein in its entirety.

[0002] This application incorporates by reference a Sequence Listing submitted with this application as a text file entitled "Sequence_Listing_13542-016-228.txt" created on March 14, 2016 and having a size of 375 Kbytes.

1. FIELD

[0003] Provided herein are compositions, methods, and uses involving antibodies that immunospecifically bind to MUC16, a tethered mucin protein, and modulate expression and/or activity of MUC16 for managing, treating, or preventing disorders, such as cancer.

2. BACKGROUND

[0004] Mucins are important biomolecules for cellular homeostasis and protection of epithelial surfaces. Changes to expression of mucins in ovarian cancer might be exploited in diagnosis, prognosis and treatment (Singh AP, et al. Lancet Oncol 2008;9(11):1076-85). MUC16 is one such mucin which is over expressed on most ovarian carcinomas and is an established surrogate serum marker (CA-125) for the detection and progression of ovarian cancers (Badgwell D, et al., Dis Markers 2007;23(5-6):397410; Bast RC, Jr, et al., Int J Gynecol Cancer 2005;15 Suppl 3:274-81; Fritsche HA, et al., Clin Chem 1998;44(7):1379-80; and Krivak TC, et al., Gynecol Oncol 2009;115(1):81-5). MUC16 is a highly glycosylated mucin composed of a large cleaved and released domain, termed CA-125, consisting of multiple repeat sequences, and a retained domain (MUC-CD) which includes a residual non-repeating extracellular fragment, a transmembrane domain, and a cytoplasmic tail (O'Brien TJ, et al. Tumour Biol 2001;22(6):348-66). Since the antigen is otherwise only expressed at low levels in the uterus, endometrium, fallopian tubes, ovaries, and serosa of the abdominal and thoracic cavities, MUC16 is a potentially attractive target for immune-based therapies.

[0005] However, the fact that most of the extracellular domain of MUC16 is cleaved and secreted limits the utility of MUC16 as a target antigen on ovarian carcinomas. In fact, to date, most reported MUC16 monoclonal antibodies bind to epitopes present on the large secreted CA-125 fraction of the glycoprotein, with none known to bind to the retained extra-cellular fraction (MUC-CD) of the antigen (Bellone S, Am J Obstet Gynecol 2009;200(1):75 el-10, Berek JS.

Expert Opin Biol Ther 2004;4(7):1159-65; O'Brien TJ, et al. Int J Biol Markers 1998;13(4):188-95). Thus, the generation of new antibodies to the non-shed region of MUC16 are needed for diagnostic and therapeutic approaches.

3. SUMMARY

[0006] Provided are antibodies and antigen-binding fragments thereof, and polypeptides including such antibodies or antigen-binding fragments, such as fusion proteins, conjugates, and/or chimeric antigen receptors, as well as cells expressing the same. Among the antibodies and antigen-binding fragments are those that specifically bind to epitopes of a MUC16 protein. Such antibodies are referred to herein as "MUC16 Glycosylation Antibodies". Such epitopes are typically epitopes within or substantially within an extracellular portion of a MUC16 molecule, generally a non-shed form of MUC16; in some embodiments, the epitope is not within, or the antibody or fragment does not bind to, a tandem repeat region of MUC16 and/or a secreted form of MUC16. In some embodiments, the epitope is within or includes residues within MUC16c114, and typically includes one or more glycosylated residues or glycosylation sites therein. In some embodiments, the epitope includes one or more glycosylation sites, such as sites for N-glycosylation. In some aspects, the epitope includes an asparagine residue corresponding to Asn1806 or Asn1800 of the MUC16 sequence set forth in SEQ ID NO: 150 (and/or a glycosylated form(s) thereof); in some aspects, the epitope includes an asparagine residue corresponding to Asn1806 of SEQ ID NO: 150, but does not include an asparagine residue corresponding to Asn1800 of SEQ ID NO: 150; in some aspects, the epitope includes an asparagine residue corresponding to Asn1800 of SEQ ID NO: 150, but does not include an asparagine residue corresponding to Asn1806 of of SEQ ID NO: 150. In some of any of such embodiments, such one or more asparagine is glycosylated, such as N-glycosylated. In some embodiments, the antibody or antigen-binding fragment binds to an epitope within or that includes residues within SEQ ID NO: 131; binds to an epitope within or that includes residues within SEQ ID NO: 130, or a combination thereof; in some embodiments, the antibody or fragment does not immunospecifically bind within a region of MUC16 corresponding to SEQ ID NO: 168, or within residues 2-19 of SEQ ID NO: 168.

[0007] In some embodiments, the provided antibodies or antigen-binding fragments include one or more complementarity determining regions (CDRs) corresponding to CDRs of the heavy chain and/or the light chain of an antibody sequence, such as a MUC16-glycosylation site-

targeted antibody sequence, described herein, such as of the antibody designated 18C6, of the antibody designated 10C6, and/or of the antibody designated 19C11. In some embodiments, the antibody or fragment has a heavy chain CDR3 (HCDR3) having a sequence corresponding to an HCDR3 of one of the heavy chain sequences provided herein, such as of the heavy chain sequences of the antibody designated 18C6, of the antibody designated 10C6, of the antibody designated 19C11, and/or of the antibody designated 7B12. In some aspects, the HCDR3 has a sequence selected from among IGTAQATDALDY (SEQ ID NO:105), GTAQATDALD (SEQ ID NO:111); X_{18}RIGTAQATDALDY (SEQ ID NO:117), wherein X_{18} is T, A, or S; SEQ ID NO: 5; SEQ ID NO: 25; SEQ ID NO: 45; SEQ ID NO: 65; and SEQ ID NO: 85; SEQ ID NO: 31, 51, 71, and 91; SEQ ID NO: 17; SEQ ID ON: 37; SEQ ID NO: 57; SEQ ID NO: 77; and SEQ ID NO: 97.

[0008] In some embodiments, the provided antibodies or antigen-binding fragments include a heavy chain CDR1 (HCDR1) having a sequence corresponding to an HCDR1 of one of the heavy chain sequences provided herein, such as of the heavy chain sequences of the antibody designated 18C6, of the antibody designated 10C6, of the antibody designated 19C11, and/or of the antibody designated 7B12. In some aspects, the HCDR1 has a sequence selected from among TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V, sequence GFSLX_8TX_9GM (SEQ ID NO:109), wherein X_8 is N or S, and wherein X_9 is L or V, GFSLX_{15}TX_{16}GMG (SEQ ID NO:115), wherein X_{15} is N or S, and X_{16} is V or L, and the sequence set forth as SEQ ID NO: 3; and the sequence set forth as SEQ ID NO: 9; and the sequence set forth as SEQ ID NO: 15; and the sequence set forth in any of SEQ ID NOs: 23, 43, 63, 83; and the sequence set forth in any of SEQ ID NOs: 29, 49, 69, and 89; and the sequence set forth in any of SEQ ID NOs: 35, 55, 75, and 95.

[0009] In some embodiments, the provided antibodies or antigen-binding fragments include a heavy chain CDR2 (HCDR2) having a sequence corresponding to an HCDR2 of one of the heavy chain sequences provided herein, such as of the heavy chain sequences of the antibody designated 18C6, of the antibody designated 10C6, of the antibody designated 19C11, and/or of the antibody designated 7B12. In some aspects, the HCDR2 has a sequence selected from among HIWWDDX_2DKYYX_3PALKS (SEQ ID NO:104), wherein X_2 is E or absent, and X_3 is Y or N; WDDX_{10} (SEQ ID NO:110), wherein X_{10} is E or absent; IWWDDX_{17}DK (SEQ ID NO:116), wherein X_{17} is E or absent; the sequence set forth as SEQ ID NO: 4; the sequence set forth as

SEQ ID NO: 10; and the sequence set forth as SEQ ID NO: 16; and the sequence set forth in any of SEQ ID NOs: 24, 44, 64, 84; and the sequence set forth in any of SEQ ID NOs: 30, 50, 70, 90; and the sequence set forth in any of SEQ ID NOs: 36, 56, 76, 96.

[0010] In some embodiments, including any of the aforementioned embodiments, the provided antibodies or antigen-binding fragments include, e.g., further include, a light chain CDR3 (LCDR3) having a sequence corresponding to an LCDR3 of one of the light chain sequences provided herein, such as of the light chain sequences of the antibody designated 18C6, of the antibody designated 10C6, of the antibody designated 19C11, and/or of the antibody designated 7B12. In some aspects, the LCDR3 has a sequence selected from among MQX_6LEX_7PLT (SEQ ID NO:108), wherein X_6 is G or S and wherein X_7 is H or Y; $X_{13}LEX_{14}PL$ (SEQ ID NO:114) wherein X_{13} is G or S, and wherein X_{14} is H or Y; and MQSLEYPLT (SEQ ID NO:120); a sequence selected from among SEQ ID NOs: 8, 28, 48, 68, and 88; a sequence selected from among SEQ ID NOs: 14, 34, 54, 74, and 94; and a sequence selected from among SEQ ID NOs: 20, 4, 60, 80, and 100.

[0011] In some embodiments, including any of the aforementioned embodiments, the provided antibodies or antigen-binding fragments include, e.g., further include, a light chain CDR1 (LCDR1) having a sequence corresponding to an LCDR1 of one of the light chain sequences provided herein, such as of the light chain sequences of the antibody designated 18C6, of the antibody designated 10C6, of the antibody designated 19C11, and/or of the antibody designated 7B12. In some aspects, the LCDR1 has a sequence selected from among $RSSKSLX_4X_5SNGNTYLY$ (SEQ ID NO:106); $SKSLX_{11}X_{12}SNGNTY$ (SEQ ID NO:112), wherein X_{11} is L or R, and wherein X_{12} is H or K; $KSLX_{19}X_{20}SNGNTY$ (SEQ ID NO:118), wherein X_{19} is V or L, and wherein X_{20} is H or K; a sequence selected from among SEQ ID NOs: 6, 26, 46, 66, and 86; a sequence selected from among SEQ ID NOs: 12, 32, 52, 72, and 92; and a sequence selected from among SEQ ID NOs: 18, 38, 58, 78, and 98.

[0012] In some embodiments, including any of the aforementioned embodiments, the provided antibodies or antigen-binding fragments include, e.g., further include, a light chain CDR2 (LCDR2) having a sequence corresponding to an LCDR2 of one of the light chain sequences provided herein, such as of the light chain sequences of the antibody designated 18C6, of the antibody designated 10C6, of the antibody designated 19C11, and/or of the antibody designated 7B12. In some aspects, the LCDR2 has a sequence selected from among YMSNLAS

(SEQ ID NO:107); YMS (SEQ ID NO:113); and the sequence set forth in any of SEQ ID NOs: 7, 27, 47, 67, 87; 13, 33, 53, 73, 93, 19, 39, 59, 79, 99, 119.

[0013] Among the antibodies and antigen-binding fragments of any of the embodiments are those having (a) a VH complementarity determining region (CDR)1 comprising the amino acid sequence TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V; (b) a VH CDR2 comprising the amino acid sequence $HIWWDDX_2DKYYX_3PALKS$ (SEQ ID NO:104), wherein X_2 is E or absent, and X_3 is Y or N; and (c) a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105).

[0014] Among the antibodies and antigen-binding fragments of any of the embodiments are those having (a) a VH CDR1 comprising the amino acid sequence $GFSLX_8TX_9GM$ (SEQ ID NO:109), wherein X_8 is N or S, and wherein X_9 is L or V; (b) a VH CDR2 comprising the amino acid sequence $WDDX_{10}$ (SEQ ID NO:110), wherein X_{10} is E or absent; and (c) a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111).

[0015] Among the antibodies and antigen-binding fragments of any of the embodiments are those having (a) a VH CDR1 comprising the amino acid sequence $GFSLX_{15}TX_{16}GMG$ (SEQ ID NO:115), wherein X_{15} is N or S, and X_{16} is V or L; (b) a VH CDR2 comprising the amino acid sequence $IWWDDX_{17}DK$ (SEQ ID NO:116), wherein X_{17} is E or absent; and(c) a VH CDR3 comprising the amino acid sequence $X_{18}RIGTAQATDALDY$ (SEQ ID NO:117), wherein X_{18} is T, A, or S.

[0016] Among the antibodies and antigen-binding fragments of any of the embodiments are those having a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:16, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:25; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VH CDR3 comprising the amino

acid sequence of SEQ ID NO:31; a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:45; a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:50, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:51; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:56, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:57; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:63, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:64, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:65; aVH CDR1 comprising the amino acid sequence of SEQ ID NO:69, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:70, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:71; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:75, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:76, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:77; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85; a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91; a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:97.

[0017] Among the antibodies and antigen-binding fragments of any of the embodiments are those having (a) a VL CDR1 comprising the amino acid sequence RSSKSLX$_4$X$_5$SNGNTYLY (SEQ ID NO:106), wherein X$_4$ is R or L, and X$_5$ is K or H; (b) a VL CDR2 comprising the amino acid sequence YMSNLAS (SEQ ID NO:107); and (c) a VL CDR3 comprising the amino acid sequence MQX$_6$LEX$_7$PLT (SEQ ID NO:108), wherein X$_6$ is G or S, and X$_7$ is H or Y.

[0018] Among the antibodies and antigen-binding fragments of any of the embodiments are those having (a) a VL CDR1 comprising the amino acid sequence SKSLX$_{11}$X$_{12}$SNGNTY (SEQ

ID NO:112), wherein X_{11} is L or R, and X_{12} is H or K; (b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:113); and (c) a VL CDR3 comprising the amino acid sequence $X_{13}LEX_{14}PL$ (SEQ ID NO:114), wherein X_{13} is G or S, and X_{14} is H or Y.

[0019] Among the antibodies and antigen-binding fragments of any of the embodiments are those having a VL CDR1 comprising the amino acid sequence $KSLX_{19}X_{20}SNGNTY$ (SEQ ID NO:118), wherein X_{19} is V or L, and X_{20} is H or K; (b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:119); and (c) a VL CDR3 comprising the amino acid sequence MQSLEYPLT (SEQ ID NO:120).

[0020] Among the antibodies and antigen-binding fragments of any of the embodiments are those having a VL CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:38, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:39, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:48; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:52, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:53, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:54; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3

comprising the amino acid sequence of SEQ ID NO:8; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:66, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:67, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:68; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:72, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:73, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:74; or a VL CDR1 comprising the amino acid sequence of SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:80.

[0021] Among the antibodies and antigen-binding fragments of any of the embodiments are those having (a) (i) a VH comprising a VH CDR1 comprising the amino acid sequence TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V; a VH CDR2 comprising the amino acid sequence $HIWWDDX_2DKYYX_3PALKS$ (SEQ ID NO:104), wherein X_2 is E or absent, and X_3 is Y or N; and a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105); and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence $RSSKSLX_4X_5SNGNTYLY$ (SEQ ID NO:106), wherein X_4 is R or L, and X_5 is K or H; a VL CDR2 comprising the amino acid sequence YMSNLAS (SEQ ID NO:107); and a VL CDR3 comprising the amino acid sequence MQX_6LEX_7PLT (SEQ ID NO:108), wherein X_6 is G or S, and X_7 is H or Y; or (b) (i) a VH comprising a VH CDR1 comprising the amino acid sequence $GFSLX_8TX_9GM$ (SEQ ID NO:109), wherein X_8 is N or S, and wherein X_9 is L or V; a VH CDR2 comprising the amino acid sequence $WDDX_{10}$ (SEQ ID NO:110), wherein X_{10} is E or absent; and a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111); and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence $SKSLX_{11}X_{12}SNGNTY$ (SEQ ID NO:112), wherein X_{11} is L or R, and X_{12} is H or K; a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:113); and a VL CDR3 comprising the amino acid sequence $X_{13}LEX_{14}PL$ (SEQ ID NO:114), wherein X_{13} is G or S, and X_{14} is H or Y; or (c) (i) a VH CDR1 comprising the amino acid sequence $GFSLX_{15}TX_{16}GMG$ (SEQ ID NO:115), wherein X_{15} is N or S, and X_{16} is V or L; a VH CDR2 comprising the amino acid

sequence IWWDDX$_{17}$DK (SEQ ID NO:116), wherein X$_{17}$ is E or absent; and a VH CDR3 comprising the amino acid sequence X$_{18}$RIGTAQATDALDY (SEQ ID NO:117), wherein X$_{18}$ is T, A, or S; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence KSLX$_{19}$X$_{20}$SNGNTY (SEQ ID NO:118), wherein X$_{19}$ is V or L, and X$_{20}$ is H or K; a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:119); and a VL CDR3 comprising the amino acid sequence MQSLEYPLT (SEQ ID NO:120); or (d) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:25; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28; or (e) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:31; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34; or (f) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:38, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:39, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40; or (g) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:45; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:48; or (h) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:50, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:51; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:52, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:53, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:54; or (i) (i) a VH comprising a VH CDR1

comprising the amino acid sequence of SEQ ID NO:55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:56, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:57; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60; or (j) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88; or (k) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94; or (l) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:97 and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100; or (m) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8; or (n) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14; or (o) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR2 comprising the amino acid

sequence of SEQ ID NO:16, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20; or (p) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:63, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:64, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:65; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:66, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:67, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:68; or (q) (i) a VH comprising aVH CDR1 comprising the amino acid sequence of SEQ ID NO:69, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:70, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:71; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:72, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:73, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:74; or (r) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:75, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:76, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:77; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:80.

[0022] Among the antibodies and antigen-binding fragments of any of the embodiments are those having: (a) (i) a VH comprising the amino acid sequence of QVX$_{21}$LKESGPGX$_{22}$LQPSQTLSLTCSFSGFSLX$_{23}$TX$_{24}$GMGVGWX$_{25}$RQX$_{26}$SGKGLEWLAH IWWDDX$_{27}$DKYYX$_{28}$PALKSRLTISX$_{29}$X$_{30}$X$_{31}$SKNQVFLKIX$_{32}$NVX$_{33}$TADX$_{34}$ATYYCX$_{35}$RI GTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X$_{21}$ is T or N, X$_{22}$ is I or K, X$_{23}$ is N or S, X$_{24}$ is V or L, X$_{25}$ is S or I, X$_{26}$ is P or S, X$_{27}$ is E or absent, X$_{28}$ is N or Y, X$_{29}$ is K or R, X$_{30}$ is A or D, X$_{31}$ is T or S, X$_{32}$ is V or A, X$_{33}$ is G or D, X$_{34}$ is T, I, or S, and X$_{35}$ is T, S, or A; and (ii) a VL comprising the amino acid sequence of DIVMTQAAPSX$_{36}$X$_{37}$VTPGESVSISCRSSKSLX$_{38}$X$_{39}$SNGNTYLYWFLQRPGQSPQRLIYY MSNLASGVPDRFSGRGSGTDFTLX$_{40}$ISRVEAX$_{41}$DVGVYYCMQX$_{42}$LEX$_{43}$PLTFGGGTKL EIK (SEQ ID NO:102), wherein X$_{36}$ is I or V, X$_{37}$ is P or S, X$_{38}$ is R or L, X$_{39}$ is K or H, X$_{40}$ is R or K, X$_{41}$ is E or G, X$_{42}$ is S or G, and X$_{43}$ is Y or H; or (b) (i) a VH comprising the amino acid

sequence of SEQ ID NO:1; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:2; or (c) (i) a VH comprising the amino acid sequence of SEQ ID NO:21; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:22; or (d) (i) a VH comprising the amino acid sequence of SEQ ID NO:41; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:42; or (e) (i) a VH comprising the amino acid sequence of SEQ ID NO:61; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:62; or (f) (i) a VH comprising the amino acid sequence of SEQ ID NO:81; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:82.

[0023] Also among the provided antibodies or antigen-binding fragments are those having at least 90, 95, 96, 97, 98, 99, or 100 % identity with the VH and/or VL sequence(s) of any such antibodies and/or of any of the antibodies set forth in Tables 1 and 2. Also among the provided antibodies and fragments thereof are those that compete for binding to MUC16 and/or an epitope thereof with any of such antibodies.

[0024] Also provided are fusion proteins, such as chimeric molecules, and/or conjugates, comprising any of the antibodies, such as chimeric antigen receptors (CARs) containing such antibodies or fragments, and cells epressing such molecules. Also provided are humanized versions of any such antibodies.

[0025] In some embodiments, provided herein is an antibody or an antigen-binding fragment thereof, wherein the antibody (a) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (b) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (c) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16. In certain embodiments, (i) the cell recombinantly expressing the first form of MUC16 is a SKOV3 cell; (ii) the cell recombinantly expressing the second form of MUC16 is a SKOV3 cell; and (iii) the cells in step (c) are SKOV3 cells. In a specific embodiment, the antibody lacks immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139. In certain embodiments, (i) the cell recombinantly expressing the first form of MUC16 is a SKOV3 cell; (ii) the cell recombinantly expressing the second form of MUC16 is a SKOV3 cell; and (iii) the cells in step (c) are SKOV3 cells. In certain embodiments, (i) the cell recombinantly expressing the first

form of MUC16 is a SKOV3 cell; (ii) the cell recombinantly expressing the second form of MUC16 is a SKOV3 cell; (iii) the cell recombinantly expressing the third form of MUC16 is a SKOV3 cell; and (iv) the cells in step (c) are SKOV3 cells.

[0026] Also provided herein is an antibody or an antigen-binding fragment thereof, wherein the antibody (a) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (b) lacks immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (c) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16. In certain embodiments, (i) the cell recombinantly expressing the first form of MUC16 is a SKOV3 cell; (ii) the cell recombinantly expressing the third form of MUC16 is a SKOV3 cell; and (iii) the cells in step (c) are SKOV3 cells.

[0027] In certain embodiments the antibody or antigen-binding fragment thereof immunospecifically binds to an epitope comprising *N*-glycosylated asparagine 1806 of SEQ ID NO: 150.

[0028] In certain embodiments, the antibody or antigen-binding fragment thereof immunospecifically binds to the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are glycosylated. In certain embodiments, the antibody or antigen-binding fragment thereof immunospecifically binds to the amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated. In certain embodiments, the glycosylation consists of an N-linked chitobiose.

[0029] In certain embodiments, the antibody or antigen-binding fragment thereof is internalized into a cell expressing the first form of MUC16 upon contacting the cell with the antibody or antigen-binding fragment. In certain embodiments, the cell is a SKOV3 cell that recombinantly expresses the first form of MUC16.

[0030] In certain embodiments, the antibody or antigen-binding fragment thereof inhibits growth of a tumor that expresses a glycosylated form of MUC16.

[0031] In certain embodiments, the antibody is a monoclonal antibody.

[0032] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH), which comprises (a) a VH complementarity determining region (CDR)1 comprising the amino acid sequence TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V; (b) a VH CDR2 comprising the amino acid sequence $HIWWDDX_2DKYYX_3PALKS$ (SEQ ID NO:104), wherein X_2 is E or absent, and X_3 is Y or N; and (c) a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105).

[0033] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises (a) a VH CDR1 comprising the amino acid sequence $GFSLX_8TX_9GM$ (SEQ ID NO:109), wherein X_8 is N or S, and wherein X_9 is L or V; (b) a VH CDR2 comprising the amino acid sequence $WDDX_{10}$ (SEQ ID NO:110), wherein X_{10} is E or absent; and (c) a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111).

[0034] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises (a) a VH CDR1 comprising the amino acid sequence $GFSLX_{15}TX_{16}GMG$ (SEQ ID NO:115), wherein X_{15} is N or S, and X_{16} is V or L; (b) a VH CDR2 comprising the amino acid sequence $IWWDDX_{17}DK$ (SEQ ID NO:116), wherein X_{17} is E or absent; and (c) a VH CDR3 comprising the amino acid sequence $X_{18}RIGTAQATDALDY$ (SEQ ID NO:117), wherein X_{18} is T, A, or S.

[0035] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5.

[0036] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11.

[0037] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:16, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17.

[0038] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:23, a

VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:25.

[0039] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:31.

[0040] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37.

[0041] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:45.

[0042] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:50, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:51.

[0043] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:56, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:57.

[0044] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:63, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:64, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:65.

[0045] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:69, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:70, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:71.

[0046] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:75, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:76, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:77.

[0047] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85.

[0048] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91.

[0049] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:97.

[0050] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of $QVX_{21}LKESGPGX_{22}LQPSQTLSLTCSFSGFSLX_{23}TX_{24}GMGVGWX_{25}RQX_{26}SGKGLEWLAH$ $IWWDDX_{27}DKYYX_{28}PALKSRLTISX_{29}X_{30}X_{31}SKNQVFLKIX_{32}NVX_{33}TADX_{34}ATYYCX_{35}RI$ GTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X_{21} is T or N, X_{22} is I or K, X_{23} is N or S, X_{24} is V or L, X_{25} is S or I, X_{26} is P or S, X_{27} is E or absent, X_{28} is N or Y, X_{29} is K or R, X_{30} is A or D, X_{31} is T or S, X_{32} is V or A, X_{33} is G or D, X_{34} is T, I, or S, and X_{35} is T, S, or A.

[0051] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:1.

[0052] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:21.

[0053] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:41.

[0054] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:61.

[0055] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:81.

[0056] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a light chain variable region (VL), which comprises (a) a VL CDR1 comprising the amino acid sequence RSSKSLX$_4$X$_5$SNGNTYLY (SEQ ID NO:106), wherein X$_4$ is R or L, and X$_5$ is K or H; (b) a VL CDR2 comprising the amino acid sequence YMSNLAS (SEQ ID NO:107); and (c) a VL CDR3 comprising the amino acid sequence MQX$_6$LEX$_7$PLT (SEQ ID NO:108), wherein X$_6$ is G or S, and X$_7$ is H or Y.

[0057] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises

(a) a VL CDR1 comprising the amino acid sequence SKSLX$_{11}$X$_{12}$SNGNTY (SEQ ID NO:112), wherein X$_{11}$ is L or R, and X$_{12}$ is H or K; (b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:113); and (c) a VL CDR3 comprising the amino acid sequence X$_{13}$LEX$_{14}$PL (SEQ ID NO:114), wherein X$_{13}$ is G or S, and X$_{14}$ is H or Y.

[0058] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises (a) a VL CDR1 comprising the amino acid sequence KSLX$_{19}$X$_{20}$SNGNTY (SEQ ID NO:118), wherein X$_{19}$ is V or L, and X$_{20}$ is H or K; (b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:119); and (c) a VL CDR3 comprising the amino acid sequence MQSLEYPLT (SEQ ID NO:120).

[0059] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a light chain variable region (VL), which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28.

[0060] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34.

[0061] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:38, a

VL CDR2 comprising the amino acid sequence of SEQ ID NO:39, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40.

[0062] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:48.

[0063] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:52, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:53, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:54.

[0064] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60.

[0065] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88.

[0066] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94.

[0067] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100.

[0068] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8.

[0069] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14.

[0070] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20.

[0071] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:66, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:67, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:68.

[0072] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:72, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:73, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:74.

[0073] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:80.

[0074] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of DIVMTQAAPS$X_{36}X_{37}$VTPGESVSISCRSSKSL$X_{38}X_{39}$SNGNTYLYWFLQRPGQSPQRLIYY MSNLASGVPDRFSGRGSGTDFTLX_{40}ISRVEAX_{41}DVGVYYCMQX_{42}LEX_{43}PLTFGGGTKL EIK (SEQ ID NO:102), wherein X_{36} is I or V, X_{37} is P or S, X_{38} is R or L, X_{39} is K or H, X_{40} is R or K, X_{41} is E or G, X_{42} is S or G, and X_{43} is Y or H.

[0075] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:22.

[0076] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:42.

[0077] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:82.

[0078] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:2.

[0079] In certain embodiments, the antibody or antigen-binding fragment thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:62.

[0080] In certain embodiments, the antibody comprises human-derived heavy and light chain constant regions. In certain embodiments, the heavy chain constant region has an isotype selected from the group consisting of gamma1, gamma2, gamma3, and gamma4. In certain embodiments, the light chain constant region has an isotype selected from the group consisting of kappa and lambda.

[0081] In certain embodiments, the antibody or antigen-binding fragment thereof is humanized. In certain embodiments, the antibody or antigen-binding fragment thereof is a humanized form of a rodent antibody.

[0082] In certain embodiments, the antibody is an immunoglobulin comprising two identical heavy chains and two identical light chains. In certain embodiments, the immunoglobulin is an IgG.

[0083] Also provided herein is an antibody conjugate comprising an antibody or antigen-binding fragment thereof provided herein conjugated to an agent. In certain embodiments, the agent is an imaging agent or a cytotoxic agent.

[0084] In certain embodiments, the antibody or antigen-binding fragment thereof is a bispecific antibody. In certain embodiments, the bispecific antibody immunospecifically binds CD3. In certain embodiments, the bispecific antibody comprises an immunoglobulin that immunospecifically binds MUC16, wherein the light chain of the immunoglublin is conjugated via a peptide linker to a single chain variable fragment (scFv) that immunospecifically binds CD3. Also provided herein is a bispecific antibody conjugate comprising a bispecific antibody provided herein conjugated to an agent. In certain embodiments, the agent is an imaging agent or a cytotoxic agent.

[0085] In certain embodiments, the antigen-binding fragment thereof is a single chain variable fragment (scFv). Also provided herein is a scFv conjugate comprising a scFv provided

herein conjugated to an agent. In certain embodiments, the agent is an imaging agent or a cytotoxic agent.

[0086] Also provided herein are fusion proteins, chimeric molecules, and conjugates comprising the antibodies and antigen-binding fragments. Provided are chimeric antigen receptors (CARs) including one or more of any of the provided antibodies or antigen-binding fragments thereof, such as a CAR comprising any of the scFvs provided herein or a scFv conjugate provided herein; and/or CARs comprising antigen-binding domains that compete for binding to MUC16 therewith.

[0087] Also provided herein is an antibody heavy chain or an antigen-binding portion thereof. Among the provided antibodies and antigen-binding fragments thereof are those having heavy chains and/or antigen-binding portions thereof such as VH regions thereof; also provided are such heavy chains and antigen-binding portions thereof. In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises (a) a VH CDR1 comprising the amino acid sequence TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V; (b) a VH CDR2 comprising the amino acid sequence $HIWWDDX_2DKYYX_3PALKS$ (SEQ ID NO:104), wherein X_2 is E or absent, and X_3 is Y or N; and (c) a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105); wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0088] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises (a) a VH CDR1 comprising the amino acid sequence $GFSLX_8TX_9GM$ (SEQ ID NO:109), wherein X_8 is N or S, and X_9 is L or V; (b) a VH CDR2 comprising the amino acid sequence $WDDX_{10}$ (SEQ ID NO:110), wherein X_{10} is E or absent; and (c) a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111); wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly

expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0089] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises (a) a VH CDR1 comprising the amino acid sequence GFSLX$_{15}$TX$_{16}$GMG (SEQ ID NO:115), wherein X$_{15}$ is N or S, and X$_{16}$ is V or L; (b) a VH CDR2 comprising the amino acid sequence IWWDDX$_{17}$DK (SEQ ID NO:116), wherein X$_{17}$ is E or absent; and (c) a VH CDR3 comprising the amino acid sequence X$_{18}$RIGTAQATDALDY (SEQ ID NO:117), wherein X$_{18}$ is T, A, or S; wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0090] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0091] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH

CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0092] In some embodiments, the heavy chain or antigen-binding portions thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:16, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0093] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:25, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0094] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:31, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0095] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0096] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:45, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form

is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0097] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:50, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:51, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0098] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:56, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:57, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[0099] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:63, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:64, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:65, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133;

(ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00100] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:69, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:70, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:71, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00101] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:75, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:76, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:77, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00102] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i)

immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00103] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00104] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH, which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:97, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00105] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH comprising the amino acid sequence of

$QVX_{21}LKESGPGX_{22}LQPSQTLSLTCSFSGFSLX_{23}TX_{24}GMGVGWX_{25}RQX_{26}SGKGLEWLAH$

IWWDDX_{27}DKYYX_{28}PALKSRLTIS$X_{29}X_{30}X_{31}$SKNQVFLKIX_{32}NVX_{33}TADX_{34}ATYYCX_{35}RI GTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X_{21} is T or N, X_{22} is I or K, X_{23} is N or S, X_{24} is V or L, X_{25} is S or I, X_{26} is P or S, X_{27} is E or absent, X_{28} is N or Y, X_{29} is K or R, X_{30} is A or D, X_{31} is T or S, X_{32} is V or A, X_{33} is G or D, X_{34} is T, I, or S, and X_{35} is T, S, or A, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00106] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:1, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00107] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:21, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00108] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:41, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00109] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:61, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00110] In some embodiments, the heavy chain or antigen-binding portion thereof comprises a VH comprising the amino acid sequence of SEQ ID NO:81, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody heavy chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00111] In certain embodiments, the antibody heavy chain or antigen-binding portion thereof comprises a human-derived heavy chain constant region. In certain embodiments, the heavy chain constant region has an isotype selected from the group consisting of gamma1, gamma2,

gamma3, and gamma4. In certain embodiments, the antibody heavy chain is humanized. In certain embodiments, the antibody heavy chain is a humanized form of a rodent heavy chain.

[00112] Also provided herein is an antibody heavy chain conjugate comprising an antibody heavy chain provided herein, wherein said antibody heavy chain is conjugated to an agent. In certain embodiments, the agent is an imaging agent or a cytotoxic agent.

[00113] Among the provided antibodies and antigen-binding fragments thereof are those having light chains and/or portions thereof such as VL regions thereof; also provided are such light chains and antigen-binding portions thereof. In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises (a) a VL CDR1 comprising the amino acid sequence RSSKSLX$_4$X$_5$SNGNTYLY (SEQ ID NO:106), wherein X$_4$ is R or L, and X$_5$ is K or H; (b) a VL CDR2 comprising the amino acid sequence YMSNLAS (SEQ ID NO:107); and (c) a VL CDR3 comprising the amino acid sequence MQX$_6$LEX$_7$PLT (SEQ ID NO:108), wherein X$_6$ is G or S, and X$_7$ is H or Y, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00114] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises (a) a VL CDR1 comprising the amino acid sequence SKSLX$_{11}$X$_{12}$SNGNTY (SEQ ID NO:112), wherein X$_{11}$ is L or R, and X$_{12}$ is H or K; (b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:113); and (c) a VL CDR3 comprising the amino acid sequence X$_{13}$LEX$_{14}$PL (SEQ ID NO:114), wherein X$_{13}$ is G or S, and X$_{14}$ is H or Y, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139;

and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00115] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises (a) a VL CDR1 comprising the amino acid sequence $KSLX_{19}X_{20}SNGNTY$ (SEQ ID NO:118), wherein X_{19} is V or L, and X_{20} is H or K; (b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:119); and (c) a VL CDR3 comprising the amino acid sequence MQSLEYPLT (SEQ ID NO:120) , wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00116] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00117] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first

form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00118] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00119] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00120] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34, wherein, optionally, an antibody or antigen-binding

fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00121] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:38, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:39, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00122] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:48, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00123] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:52, a VL

CDR2 comprising the amino acid sequence of SEQ ID NO:53, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:54, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00124] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00125] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:66, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:67, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:68, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00126] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:72, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:73, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:74, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00127] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:80, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00128] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form

is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00129] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00130] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL, which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00131] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL comprising the amino acid sequence of DIVMTQAAPS$X_{36}X_{37}$VTPGESVSISCRSSKSL$X_{38}X_{39}$SNGNTYLYWFLQRPGQSPQRLIYY MSNLASGVPDRFSGRGSGTDFTLX_{40}ISRVEAX_{41}DVGVYYCMQX_{42}LEX_{43}PLTFGGGTKL EIK (SEQ ID NO:102), wherein X_{36} is I or V, X_{37} is P or S, X_{38} is R or L, X_{39} is K or H, X_{40} is R or K, X_{41} is E or G, X_{42} is S or G, and X_{43} is Y or H, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof

(i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00132] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:2, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00133] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:22, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00134] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:42, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the

second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00135] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:62, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00136] In some embodiments, the light chain or antigen-binding portion thereof comprises a VL comprising the amino acid sequence of SEQ ID NO:82, wherein, optionally, an antibody or antigen-binding fragment thereof comprising the antibody light chain or antigen-binding portion thereof (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16.

[00137] In certain embodiments, the antibody light chain or antigen-binding portion thereof comprises a human-derived light chain constant region. In certain embodiments, the light chain constant region has an isotype selected from the group consisting of kappa and lambda. In certain embodiments, the antibody light chain is humanized. In certain embodiments, the antibody light chain is a humanized form of a rodent antibody.

[00138] Also provided herein is an antibody light chain conjugate comprising an antibody light chain provided herein conjugated to an agent. In certain embodiments, the agent is an imaging agent or a cytotoxic agent.

[00139] Also provided herein is a fusion protein comprising an antibody light chain provided herein conjugated via a peptide linker to a scFv. In certain embodiments, the scFv binds CD3.

[00140] Also provided herein is a cell, such as an immune cell, such as a T cell, which recombinantly expresses one or more of the molecules provided herein such as a CAR provided herein.

[00141] Also provided herein is a polynucleotide comprising nucleic acid sequences encoding a scFv provided herein. Also provided herein is a polynucleotide comprising nucleic acid sequences encoding a scFv, or conjugate thereof, provided herein. Also provided herein is a polynucleotide comprising nucleic acid sequences encoding a CAR provided herein. Also provided herein is a polynucleotide comprising nucleic acid sequences encoding an antibody heavy chain, or antigen-binding portion thereof, provided herein. Also provided herein is a polynucleotide comprising nucleic acid sequences encoding an antibody heavy chain conjugate provided herein. Also provided herein is a polynucleotide comprising nucleic acid sequences encoding an antibody light chain, or antigen-binding portion thereof, provided herein. Also provided herein is a polynucleotide comprising nucleic acid sequences encoding an antibody light chain conjugate provided herein. Also provided herein is a polynucleotide comprising nucleic acid sequences encoding the fusion protein provided herein. A polynucleotide comprising nucleic acid sequences encoding (a) an antibody heavy chain, or antigen-binding portion thereof, provided herein or an antibody heavy chain conjugate provided herein; and (b) an antibody light chain, or antigen-binding portion thereof, provided herein, an antibody light chain conjugate provided herein, or a fusion protein provided herein.

[00142] Also provided herein is a vector comprising a polynucleotide provided herein operably linked to a promoter. Also provided herein is a vector comprising (a) a first polynucleotide provided herein operably linked to a first promoter; and (b) a second polynucleotide provided herein operably linked to a second promoter.

[00143] Also provided herein is an ex vivo cell comprising a polynucleotide provided herein operably linked to a promoter. Also provided herein is an *ex vivo* cell comprising a polynucleotide provided herein operably linked to a promoter. Also provided herein is an *ex vivo* cell comprising a vector provided herein. Also provided herein is an *ex vivo* cell comprising one or more polynucleotides encoding an antibody or antigen-binding fragment thereof of provided herein operably linked to a promoter.

[00144] Also provided herein is a method of producing an antibody heavy chain, or antigen-binding portion thereof, comprising culturing a cell provided herein under conditions such that a

polynucleotide is expressed by the cell to produce an antibody heavy chain, or antigen-binding portion thereof, or antibody heavy chain conjugate encoded by the polynucleotide.

[00145] Also provided herein is a method of producing an antibody light chain, or antigen-binding portion thereof, comprising culturing a cell provided herein under conditions such that a polynucleotide is expressed by the cell to produce the antibody light chain, or antigen-binding portion thereof, antibody light chain conjugate, or fusion protein encoded by the polynucleotide.

[00146] Also provided herein is a method of producing an antibody or antigen-binding fragment thereof comprising culturing an *ex vivo* cell provided herein under conditions such that a polynucleotide operably linked to a first promoter and a polynucleotide operably linked to a second promoter are expressed by the cell to produce (i) an antibody heavy chain or an antibody heavy chain conjugate encoded by the polynucleotide; and (ii) an antibody light chain, an antibody light chain conjugate, or a fusion protein encoded by the polynucleotide.

[00147] Also provided herein is a pharmaceutical composition comprising: a therapeutically effective amount of an antibody or antigen-binding fragment thereof provided herein, an antibody conjugate provided herein, a bispecific antibody provided herein, a bispecific antibody conjugate provided herein, a scFv, a scFv conjugate provided herein, a CAR provided herein, an antibody heavy chain, or antigen-binding portion thereof, provided herein, an antibody heavy chain conjugate provided herein, an antibody light chain, or antigen-binding portion thereof, provided herein, an antibody light chain conjugate provided herein, a fusion protein provided herein, or a T cell provided herein; and a pharmaceutically acceptable carrier.

[00148] Also provided herein is a method of treating cancer in a patient in need thereof, comprising administering to said patient the pharmaceutical composition provided herein. In certain embodiments, the cancer is a cancer of the lung, pancreas, breast, uterine, fallopian tube, or primary peritoneum. In certain embodiments, the cancer is a cancer of the ovary. In certain embodiments, the patient is a human patient. In specific embodiments, the method is a combination therapy method, further comprising administering a therapeutically effective amount of an additional therapeutic agent to the patient.

[00149] In a specific embodiment of the combination therapy method, the pharmaceutical composition comprises a therapeutically effective amount of a first antibody that is an antibody or antigen-binding fragment thereof described herein, wherein the antibody or antigen-binding fragment thereof recognizes an epitope in MUC16 that comprises N-glycosylated Asn1806 of of

SEQ ID NO: 150 but does not comprise N-glycosylated Asn1800 of SEQ ID NO: 150, wherein the additional therapeutic agent is a second antibody or antigen-binding fragment thereof, wherein the second antibody or antigen-binding fragment thereof recognizes an epitope in MUC16 that comprises N-glycosylated Asn1806 of SEQ ID NO: 150 and also comprises N-glycosylated Asn1800 of SEQ ID NO: 150. In a specific embodiment, the first antibody or antigen-binding fragment thereof is identified by (i) its ability to immunospecifically bind a cell recombinantly expressing a first form of MUC16, which first form of MUC16 is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO: 133; (ii) its lack of immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, wherein the amino acid sequence of the third form is SEQ ID NO: 139; and (iii) its ability to immunospecifically bind a cell recombinantly expressing a fourth form of MUC16, which fourth form is glycosylated, and wherein the amino acid sequence of the fourth form is SEQ ID NO: 152, and wherein the cell recombinantly expressing the first form of MUC16, the cell recombinantly expressing the third form of MUC16, and the cell recombinantly expressing the fourth form of MUC16 are of the same cell type, and wherein the second antibody or antigen-binding fragment thereof is identified by (i) its ability to immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; and (ii) its lack of immunospecific binding to a cell recombinantly expressing a fifth form of MUC16, which fifth form is glycosylated, and wherein the amino acid sequence of the fifth form is SEQ ID NO:172, wherein the cell recombinantly expressing the first form of MUC16 is the same type of cell as the cell recombinantly expressing the fifth form of MUC16.

[00150] In a specific embodiment of the combination therapy method, the pharmaceutical composition comprises a therapeutically effective amount of a first antibody or antigen-binding fragment thereof that is an antibody or antigen-binding fragment thereof described herein, wherein the antibody or antigen-binding fragment thereof recognizes an epitope in MUC16 that comprises N-glycosylated Asn1806 of SEQ ID NO: 150 but does not comprise N-glycosylated Asn1800 of SEQ ID NO: 150, wherein the additional therapeutic agent is a therapeutically effective amount of a second antibody or antigen-binding fragment thereof, wherein the second antibody or antigen-binding fragment thereof recognizes an epitope in MUC16 that comprises N-glycosylated Asn1800 of SEQ ID NO: 150 but does not comprise N-glycosylated Asn1806 of

SEQ ID NO: 150. In a specific embodiment, the first antibody or antigen-binding fragment thereof is identified by (i) its ability to immunospecifically bind a cell recombinantly expressing a first form of MUC16, which first form of MUC16 is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO: 133; (ii) its lack of immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139; and (iii) its ability to immunospecifically bind a cell recombinantly expressing a fourth form of MUC16, which fourth form is glycosylated, and wherein the amino acid sequence of the fourth form is SEQ ID NO: 152, wherein the cell recombinantly expressing the first form of MUC16, the cell recombinantly expressing the third form of MUC16, and the cell recombinantly expressing the fourth form of MUC16 are of the same cell type, and wherein the second antibody or antigen-binding fragment thereof is identified by (i) its ability to immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) its ability to immunospecifically bind to a cell recombinantly expressing a third form of MUC16, which third form of MUC16 is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139; and (iii) its lack of immunospecific binding to a cell recombinantly expressing a fourth form of MUC16, wherein the amino acid sequence of the fourth form is SEQ ID NO:152; and, wherein the cell recombinantly expressing the first form of MUC16, the cell recombinantly expressing the third form of MUC16, and the cell recombinantly expressing the fourth form of MUC16 are of the same type of cell.

[00151] Also provided herein is an immunogenic glycopeptide comprising one or more glycosylation sites, wherein (i) the immunogenic glycopeptide is 10 to 60 amino acid residues, 10 to 30 amino acid residues, 15 to 25 amino acid residues, 15 to 20 amino acid residues, or 15 to 18 amino acid residues in length, and (ii) at least one of the one or more glycosylation sites is linked with a carbohydrate. In certain embodiments, the immunogenic glycopeptide comprises one, two, or three glycosylation sites. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site that is linked with a carbohydrate. In certain embodiments, the immunogenic glycopeptide comprises two glycosylation sites that are each linked with a carbohydrate. In certain embodiments, the carbohydrate is an N- or O-linked carbohydrate. In certain embodiments, the carbohydrate is a monosaccharide, a disaccharide, a trisaccharide, a

tetrasaccharide, or a pentasaccharide. In certain embodiments, the carbohydrate is a disaccharide. In certain embodiments, the disaccharide is a chitobiose.

[00152] In certain embodiments, the N-terminus of the immunogenic glycopeptide is acetylated. In certain embodiments, the C-terminus of the glycopeptide is in the form of an N-methylcarboxamide derivative. In certain embodiments, the immunogenic glycopeptide is conjugated to an immunogenic carrier protein. In certain embodiments, the immunogenic carrier protein is keyhole limpet hemocyanin.

[00153] In certain embodiments, the immunogenic glycopeptide is 15 to 18 amino acid residues in length. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site that is linked with a chitobiose. In certain embodiments, the immunogenic glycopeptide comprises two glycosylation sites that are each linked with a chitobiose.

[00154] In certain embodiments, the immunogenic glycopeptide is 18 amino acid residues in length. In certain embodiments, the immunogenic glycopeptides comprises two glycosylation sites that are each linked with a chitobiose.

[00155] In certain embodiments, the immunogenic glycopeptides is 15 amino acid residues in length. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site that is linked with a chitobiose.

[00156] In certain embodiments, the immunogenic glycopeptide comprises an at least 10 amino acid portion of the amino acid sequence of SEQ ID NO: 150, wherein at least one of the one or more glycosylation sites is in said portion of the amino acid sequence.

[00157] In certain embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO:129.

[00158] In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site at the 30^{th} residue (Asn) of SEQ ID NO:129 that is linked with a chitobiose.

[00159] In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site at the 30^{th} residue (Asn) of SEQ ID NO:129 that is linked with a $Man_3GlcNAc_2$ moiety.

[00160] In certain embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO: 130. In certain embodiments, the immunogenic glycopeptides comprises two glycosylation sites at the 4^{th} residue (Asn) and the 10^{th} residue (Asn) of SEQ ID NO:130 that are each linked with a chitobiose.

[00161] In certain embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO: 131. In certain embodiments, the immunogenic glycopeptides comprises a glycosylation site at the 7th residue (Asn) of SEQ ID NO: 131 that is linked with a chitobiose.

[00162] Also provided herein is a method of generating an antibody or an antigen-binding fragment thereof that specifically binds to a glycol-protein, comprising immunizing a subject with an immunogenic glycopeptide comprising one or more glycosylation sites, wherein (i) the immunogenic glycopeptide is 10 to 60 amino acid residues, 10 to 30 amino acid residues, 15 to 25 amino acid residues, 15 to 20 amino acid residues, or 15 to 18 amino acid residues in length, (ii) the immunogenic glycopeptide comprises an at least 10 amino acid portion of the amino acid sequence of the glycoprotein, (iii) at least one of the one or more glycosylation sites is linked with a carbohydrate, and (iv) at least one of the one or more glycosylation sites is in said portion of the amino acid sequence. In certain embodiments, the antibody or antigen-binding fragment thereof lacks specific binding to a non-glycosylated form of the glycoprotein. In certain embodiments, the subject is a goat, a sheep, a donkey, a chicken, a guinea pig, a rat, a rabbit, or a mouse. In certain embodiments, the subject is a rat, a rabbit, or a mouse. In certain embodiments, the subject is a mouse. In certain embodiments, the immunogenic glycopeptide comprises one, two, or three glycosylation sites. The method of any of claims 190-195, wherein the immunogenic glycopeptide comprises a glycosylation site that is linked with a carbohydrate. In certain embodiments, the immunogenic glycopeptide comprises two glycosylation sites that are each linked with a carbohydrate. In certain embodiments, the carbohydrate is an N- or O-linked carbohydrate. In certain embodiments, the carbohydrate is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, or a pentasaccharide. In certain embodiments, the carbohydrate is a disaccharide. In certain embodiments, the disaccharide is a chitobiose. In certain embodiments, the N-terminus of the immunogenic glycopeptide is acetylated. In certain embodiments, the C-terminus of the glycopeptide is in the form of an N-methylcarboxamide derivative. In certain embodiments, the immunogenic glycopeptide is conjugated to an immunogenic carrier protein. In certain embodiments, the immunogenic carrier protein is keyhole limpet hemocyanin. In certain embodiments, the immunogenic glycopeptide is 15 to 18 amino acid residues in length. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site that is linked with a chitobiose. In certain embodiments, the

2016233309 22 Oct 2021

immunogenic glycopeptide comprises two glycosylation sites that are each linked with a chitobiose. In certain embodiments, the immunogenic glycopeptide is 18 amino acid residues in length. In certain embodiments, the immunogenic glycopeptide comprises two glycosylation sites that are each linked with a chitobiose. In certain embodiments, the immunogenic glycopeptide is 15 amino acid residues in length. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site that is linked with a chitobiose. In certain embodiments, the glycoprotein comprises the amino acid sequence of SEQ ID NO: 150. In certain embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO:129. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site at the 30th residue (Asn) of SEQ ID NO:129 that is linked with a chitobiose. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site at the 30th residue (Asn) of SEQ ID NO:129 that is linked with a Man3GlcNAc2 moiety. In certain embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO: 130. In certain embodiments, the immunogenic glycopeptide comprises two glycosylation sites at the 4th residue (Asn) and the 10th residue (Asn) of SEQ ID NO:130 that are each linked with a chitobiose. In certain embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO: 131. In certain embodiments, the immunogenic glycopeptide comprises a glycosylation site at the 7th residue (Asn) of SEQ ID NO: 131 that is linked with a chitobiose.

[00163] Also provided herein are antibodies and antigen-binding fragments thereof which immunospecifically bind to MUC16 and which have VH, VL, VH CDR, and/or VL CDR sequences of an antibody described herein (e.g., 10C6, 7B12, 19C11, 16C5, or 18C6), as well as conjugates (e.g., to imaging or cytotoxic agents) thereof.

[00163a] Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

[00163b] Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field

2016233309 22 Oct 2021

relevant to the present disclosure as it existed before the priority date of each of the appended claims.

4. BRIEF DESCRIPTIONS OF FIGURES

[00164] **FIG. 1A-FIG. 1I.** MUC16 constructs. **FIG. 1A:** Schematic illustration of MUC16. **FIG. 1B:** Top: Schematic illustration of MUC16c344. Bottom: Linear representation of the truncated MUC16c344 construct. The amino acid sequence of the N-terminus of the first tandem repeat is as set forth in SEQ ID NO: 155. The amino acid sequence of the C-terminus of the first tandem repeat is as set forth in SEQ ID NO: 156. The amino acid sequence of the N-terminus of the ectodomain is as set forth in SEQ ID NO: 157. The amino acid sequence of the C-terminus of the ectodomain is as set forth in SEQ ID NO: 158. **FIG. 1C:** Top: Schematic illustration of

$MUC16^{c114}$. Bottom: Linear representation of $MUC16^{c114}$. The amino acid sequence of the ectodomain is as set forth in SEQ ID NO: 161. The amino acid sequence of the transmembrane is as set forth in SEQ ID NO: 159. The amino acid sequence for the cytoplasmic tail is as set forth in SEQ ID NO: 160. **FIG. 1D:** Top: Schematic illustration of $MUC16^{c80}$. Bottom: Linear representation of the $MUC16^{c80}$. The amino acid sequence of the ectodomain is as set forth in SEQ ID NO: 162. The amino acid sequence of the transmembrane is as set forth in SEQ ID NO: 159. The amino acid sequence of the cytoplasmic cail is as set forth in SEQ ID NO: 159. **FIG. 1E:** Top: Schematic illustration of $MUC16^{c86}$. Bottom: Linear representation of the $MUC16^{c86}$. The amino acid sequence of the ectodomain is as set forth in SEQ ID NO: 163. The amino acid sequence of the transmembrane domain is as set forth in SEQ NO: 164. The amino acid sequence of the cytoplasmic domain is SEQ ID NO: 165. **FIG. 1F:** Linear representation of the $MUC16^{c114\text{-}N123}$. The amino acid sequence of 3(N→A)Mutated Ectodomain 58 aa is as set forth in SEQ ID NO: 166. The amino acid sequence of the transmembrane domain is as set forth in SEQ ID NO: 159. The amino acid sequence of the cytoplasmic domain is as set forth in SEQ ID NO: 160. **FIG. 1G, FIG. 1H,** and **FIG. 1I** depict the percent of cells detected by 4H11 via FACS analysis, wherein the cell lines express the indicated MUC16 constructs.

[00165] **FIG. 2A-FIG. 2C.** In vitro growth curves for MUC16 transfectants. **FIG. 2A** depicts *in vitro* growth curves for $MUC16^{c114}$ and $MUC16^{c344}$ cell lines, as compared to the control cell line (phrGFP), in 3T3 cells. **FIG. 2B** depicts *in vitro* growth curves for $MUC16^{c114}$ and $MUC16^{c344}$ cell lines, as compared to the control cell line (phrGFP), in A2780 cells. **FIG. 2C** depicts *in vitro* growth curves for $MUC16^{c114}$, $MUC16^{c80}$, and $MUC16^{c86}$ cell lines, as compared to the control cell line (phrGFP), in 3T3 cells.

[00166] **FIG. 3A-FIG. 3E.** Effect of MUC16 in 3T3 cells. **FIG. 3A** depicts soft agar growth of 3T3 transfectants in 60 mm dishes. After 14 days, colonies were counted and plotted. Data shown in the table represent one of three similar experiments (*** $p < 0.0001$) compared to soft agar growth of cells expressing the phrGFP control vector. **FIG. 3B** depicts matrigel invasion assay for 3T3 cell lines following stable transfections with either phrGFP control vector or with $MUC16^{c114}$ or $MUC16^{c344}$ carboxy-terminus constructs. Each assay was performed two or more times in triplicate and counted by hand. Both $MUC16^{c114}$ and $MUC16^{c344}$ cell lines were significantly more invasive (*** $p<0.0001$) compared to invasion of cells expressing the phrGFP vector control and the results with the $MUC16^{c344}$ cell line was significantly different from the

results with the MUC16^{c114} cell line ((# p=0.0354). **FIG. 3C** depicts the expression of metastasis and invasion genes induced by MUC16^{c114} and MUC16^{c344} expression. A SuperArray panel of 80 invasion/metastasis gene transcripts was examined for MUC16-construct-positive and vector only cell lines. The expression of selected chemotactic, adhesion, and invasion transcripts was measured in 3T3 MUC16^{c114} or 3T3-MUC16^{c344} cell lines (each of three triplicates was examined in duplicate and compared to the phr vector only controls by chi square testing). The p value for each transcript, adjusted for repeated measures, is shown in the table. All genes with changes at the $p<0.05$ or below level are included. **FIG. 3D:** Transfected 3T3 cells were examined for activation of the ERK/AKT signaling pathways compared to the vector only controls. Phosphorylation of ERK1/2 (pT202/Y204) and AKT (S473) was increased following expression of the MUC16^{c114} and MUC16^{c344} constructs, as compared to the expression of the phr vector. Activation of both pathways was seen in each of the cell lines. B-actin normalized densitometry quantification values are shown below each western blot in the figure. **FIG. 3E** depicts MUC16-construct-positive tumor growth in athymic nude mice. Two million tumor cells were introduced into the flank of 15 nu/nu mice, and the mice were observed for tumor formation. Tumors were measured by calipers twice weekly. The differences in mean tumor volume were significantly greater for mice bearing MUC16-construct-positive tumors (both lines $p<0.0001$ compared to cells expressing the phrGFP control vector).

[00167] **FIG. 4A-FIG. 4C.** Oncogenic properties of MUC16 fragments. **FIG. 4A** depicts matrigel invasion assay for A2780 cell lines transfected either phrGFP control vector or with MUC16 carboxy-terminus expression vectors, MUC16^{c114} or MUC16^{c344}. Each assay was performed two or more times in triplicate and counted by hand. Results were compared to matrigel invasion of cells expressing phrGFP control vector or MUC16^{c114}. MUC16^{c114} or MUC16^{c34} cell lines showed significant matrigel invasion relative to phrGFP vector control, and the results with the MUC16^{c344} cell line was significantly different from the results with the MUC16^{c114} cell line (##p=0.0018). **FIG. 4B** depicts the effect of MUC16 expression on ERK/AKT signaling. A2780 cells were examined for activation of the ERK/AKT signaling pathways. Phosphorylation of ERK1/2 (pT202/Y204) and AKT (S473) was increased following expression of each of the MUC16 expression constructs. Both pathways were activated in each of the cell lines. β-actin normalized densitometry quantification values are shown below each western blot in the figure. **FIG. 4C** depicts MUC16-construct-positive tumor growth in athymic

nude mice. Two million tumor cells were introduced into the flank of 15 nu/nu mice, and the mice were observed for tumor formation. Tumors were measured by calipers twice weekly. The differences in mean tumor volume were significantly greater for mice bearing any of the $MUC16^{c114}$- or $MUC16^{c344}$-positive tumors at day 28, as indicated in the figure.

[00168] **FIG. 5A-FIG. 5D**: Effects of truncated $MUC16^{c114}$ variants. **FIG. 5A:** Soft agar growth. 3T3 transfectants expressing either internal or external domain portions of $MUC16^{c114}$ were layered on soft agar, as described in Section 6.1.2. Colonies were counted and plotted. The data shown represent one of three experiments. Soft agar growth rates for $MUC16^{c80}$ and $MUC16^{c86}$ were significantly different compared to the growth rate for $MUC16^{c114}$ (# $p = 0.0111$ and ## $p = 0.0258$, respectively), whereas a higher level of significance was seen with the growth rate for $MUC16^{80}$ transfectant compared to the growth rate for $MUC16^{c86}$ transfectant (### $p < 0.0001$). **FIG. 5B** depicts matrigel invasion assay for 3T3 cell lines transfected either phrGFP control vector or with MUC16 carboxy-terminus constructs. Each assay was performed two or more times in triplicate and counted by hand. Invasion of the $MUC16^{c80}$ transfectant cells was significant (# $p = 0.0172$) as compared to invasion of the $MUC16^{c114}$ cell line. **FIG. 5C** depicts the effect of MUC16 expression on ERK/AKT signaling. Transfected 3T3 cells were examined for activation of the ERK/AKT signaling pathways. Phosphorylation of ERK1/2 (pT202/Y204) and AKT (S473) was increased following $MUC16^{c114}$; however, the signals were lower in cells transfected with $MUC16^{c80}$ or $MUC16^{c86}$ constructs. β-Actin normalized densitometry quantification values are shown below each western blot in the figure. **FIG. 5D** depicts MUC16-construct-positive tumor growth in athymic nude mice. Two million tumor cells were introduced into the flank of 20 nu/nu mice, and the mice were observed for tumor formation. Tumors were measured by calipers twice weekly. The differences in mean tumor volume were significantly greater for mice bearing MUC16+ tumors. 3T3 $MUC16^{c114}$ and 3T3 $MUC16^{c86}$ transfectants were significantly different compared to $MUC16^{c80}$ transfectants (### $p < 0.0001$).

[00169] **FIG. 6A- FIG. 6B.** Amino acid sequence for $MUC16^{c114}$ (amino acid residues 1777 to 1890 (SEQ ID NO: 133), **FIG. 6A**) and $MUC16^{c344}$ (amino acid residues 1547 to 1890 (SEQ ID NO: 132), **FIG. 6B**). The N- and O-glycosylation sites are highlighted and the transmembrane domain (amino acid residues 1835 to 1859) is underlined and labeled "Transmembrane Domain." Amino acid residues 1857-1884 represent the 28 amino acid internal domain deletion present in the $MUC16^{c86}$ construct (*see,* FIG. 1). Amino acid residues

1798-1831 represent the 34 amino acid ectodomain deletion present in the $MUC16^{c80}$ construct (*see*, FIG. 1).

[00170] FIG. 7A - FIG. 7H. Effect of *N*-Glycosylation on MUC16 transformation. **FIG. 7A** depicts matrigel invasion assay for 3T3 cell lines transfected with phrGFP control vector or $MUC16^{c114}$ or $MUC16^{c114\text{-}N123}$ and $MUC16^{c114}$ treated with 0.1 µg/mL Tunicamycin. Results with the $MUC16^{c114}$ cell line was significantly different (### $p<0.0001$) than results with the phrGFP vector control cell line. Results with the $MUC16^{c114\text{-}N123}$ cell line were significantly different (** $p=0.007$) compared to results with the phrGFP vector control cell line. Treatment with the *N*-glycosylation inhibitor Tunicamycin significantly inhibited matrigel invasion compared to the untreated $MUC16^{c114}$ ($p=0.004$). **FIG. 7B** depicts matrigel invasion assay for 3T3 transfected cell lines compared to phrGFP control vector. 3T3 cells transfected with $MUC16^{c114}$ were treated with media alone, or treated with 5 µg/mL of control pFUSE hIgG1-Fc2 fusion protein, or with 5 µg/mL of $MUC16^{c57\text{-}c114}$-pFUSE hIgG1-Fc2 fusion protein or with 5 µg/mL of $^{117\text{-}244}$LGALS3-pFUSE hIgG1-Fc2 fusion protein as detailed in FIG. 8. The $MUC16^{c114}$ cell line was much more invasive than the control 3T3 cells (*** $p<0.0001$) expressing phrGFP vector control and this was unaffected by exposure to pFUSE vector only protein. In contrast, the $MUC16^{c114}$ cell line treated with $MUC16^{c57\text{-}c114}$-pFUSE hIgG1-Fc2 fusion protein or $^{117\text{-}244}$LGALS3-pFUSE hIgG1-Fc2 fusion protein demonstrated significant inhibition of matrigel invasion compared to $MUC16^{c114}$ control cells. **FIG. 7C** depicts the effect of MUC16 expression on ERK/AKT signaling. Transfected 3T3 cells were also examined for activation of the ERK/AKT signaling pathways. Phosphorylation of ERK1/2 (pT202/Y204) and AKT (S473) was increased in the 3T3 transfected with $MUC16^{c114}$; however, the effect was diminished in 3T3 cells transfected with the $MUC16^{c114\text{-}N123}$ vector ("$MUC16^{c114\text{-}N123}$" and "$MUC16^{3(N\text{-}\text{-}>A)c114}$" are used herein interchangeably). Despite mutations the 3 asparagine to alanine mutations, western blot with an anti-MUC16 antibody (4H11 mAb) showed a higher signal than either the phrGFP vector control or the native $MUC16^{c114}$-transfected cells, indicating that the high levels of $MUC16^{3(N\text{-}\text{-}>A)c114}$ protein is expressed in the transfected 3T3 cells. As used herein, "4H11" refers to the monoclonal anti-MUC16 antibody designated as 4H11 in Rao et al. Appl. Immunohistochem Mol Morphol, 2010, 18(5):462-72 and in International Patent Application Publication No. WO 2011/119979. **FIG. 7D** depicts MUC16-construct-positive tumor growth in athymic nude mice. Two million tumor cells were introduced into the flank of

20 nu/nu mice, and the mice were observed for tumor formation. Tumors were measured by calipers twice weekly. The differences in mean tumor volume were significantly greater for mice bearing MUC16^{c114} tumors ($p<0.0001$). Results with the 3T3-MUC16^{c114} transfectant were highly significant as compared to results with the phrGFP control vector cell line (*** $p<0.0001$). However, MUC16$^{c114\text{-}N123}$ 3T3 transfectants did not show any significance over phrGFP vector control 3T3 cells indicating that the mutations of *N*-glycosylation dramatically decreased tumor growth and invasion. **FIG. 7E** depicts the linear representation of the MUC16$^{c57\text{-}114}$-pFUSE-human-IgG1-Fc2 construct. The amino acid sequence of the ectodomain is as set forth in SEQ ID NO: 161. **FIG. 7F** depicts protein levels of MUC16$^{c57\text{-}114}$-pFUSE-human-IgG1-Fc2 construct determined by the indicated antibodies. **FIG. 7G** depicts the linear representation of the $^{117\text{-}244}$LGALS3-pFUSE-human-IgG1-Fc2 construct. The amino acid sequence of the sugar binding domain is as set forth in SEQ ID NO: 167. **FIG. 7H** depicts protein levels of $^{17\text{-}244}$LGALS3-pFUSE-human-IgG1-Fc2 construct determined by the indicated antibodies.

[00171] **FIG. 8.** Sequence for the ectodomain-MUC16$^{c57\text{->}c114}$ (SEQ ID NO: 161; amino acid residues 1777-1834 of MUC16) amino acid sequence inserted into the pFUSE-hIgG1-Fc2 vector to construct the MUC16$^{c57\text{-}c114}$pFUSE as a sham receptor and the $^{117\text{-}244}$LGALS3 amino acid sequence (SEQ ID NO: 167) inserted into pFUSE-hIgG1-Fc2, resulting in the $^{117\text{-}244}$LGALS3pFUSE vector.

[00172] **FIG. 9A - FIG. 9E.** MUC16c354 transgenic mice. **FIG. 9A** depicts the strategy for the MUC16^{c354} conditional construct. A CMV early enhancer plus the chicken β actin promoter (CAG) was used to drive the transcription of hrGFP between two loxPs and the downstream MUC16^{c354} sequence. **FIG. 9B:** Southern blot shows 12 candidates of MUC16^{c354} positive founders among 99 animals after microinjection procedure. **FIG. 9C:** Western blot with anti-MUC16 antibody, 4H11, was used to identify founders 9 (~50 copies) and 36 (~10 copies) for MUC16^{c354} mouse colony development; A5 is a positive control from a stable transfected SKOV3 with MUC16^{c354}. **FIG. 9D:** Histological analyses of tumors from double MUC16^{c354}:p53+/-transgenic mice. Multiple sarcomas and lymphomas were identified in the double MUC16^{c354}:p53+/- transgenic mice. Sections were stained with hematoxylin and eosin (H&E). Tumor include histocytic sarcoma in uterus (I, Scale bar:100μm), liver (II, Scale bar:50μm), ovary (III, Scale bar:50μm) and bone marrow (IV, Scale bar:50μm) as well as

lymphoma in ovary (V, Scale bar:50μm), kidney (VI, Scale bar:50μm), and lung (VII, Scale bar:50μm) with carcinoma in the lung (VIII, Scale bar:50μm). **FIG. 9E:** Transgenic mouse cancer specific Kaplan-Meier Survival Curves: the $MUC16^{c354}$ mice showed no spontaneous tumor development over the first 18 months, similar to the wild type (WT). However, when $MUC16^{c354}$ mice were crossed with p53+/- mice, the double transgenic $MUC16^{c354}$:p53+/- mice showed a significantly worse overall survival due to spontaneous tumor development compared to either the p53+/- mice ($p<0.014$) or the $MUC16^{c354}$ mice.

[00173] FIG. 10. Representative tissue histological from 12 months old male and female $MUC16^{c354}$ transgenic mice. Tissue sections were stained with hematoxylin and eosin (H&E, Scale bar: 50μm). Uterine endometrial hyperplasia was observed with similar incidence and severity in both genotypes (here only shown in the transgenic animal). The ovary, lung, colon and liver of transgenic animals (Tg) were similar to the parental line (wild type, WT).

[00174] FIG. 11A- FIG. 11C. Impact of MUC16 in human ovarian cancer. **FIG. 11A** depicts MUC16 transcript numbers. **FIG. 11B:** The quintile of patients with the highest MUC16 expression, combined with the 18 patients with identified MUC16 mutations, have a significantly ($p=0.02117$) worse survival when compared to the patients with lower MUC16 expression in a Kaplan-Meier analysis. **FIG. 11C** depicts the relationship of MUC16 genetic alterations with PI3K mutational events in ovarian cancer.

[00175] FIG. 12A- FIG. 12C. Glycosylation requirements for MUC16 matrigel invasion. **FIG. 12A** depicts matrigel invasion assay for SKOV3 transfected cell lines. phrGFP refers to SKOV3 cells expressing a control vector. $MUC16^{c114}$ refers to SKOV3 cells expressing $MUC16^{c114}$. N3 refers to SKOV3 cells expressing $MUC16^{c114\text{-}N3}$. N1-2 refers to SKOV3 cells expressing $MUC16^{c114\text{-}N12}$. N1-2-3 refers to SKOV3 cells expressing $MUC16^{c114\text{-}N123}$. $MUC16^{c114}$-shControl refers to SKOV-3 cells expressing $MUC16^{c114}$ and a control shRNA. phrGFP shRNA MGAT population #4 refers to SKOV3 cells expressing a control vector and shRNA against MGAT5. phrGFP shRNA LGALS3 population #15 refers to SKOV3 cells expressing a control vector and shRNA against LGALS3. $MUC16^{c114}$-shMGAT5 refers to SKOV3 cells expressing $MUC16^{c114}$ and an shRNA against MGAT5. $MUC16^{c114}$-shLGALS3 refers to SKOV3 cells expressing $MUC16^{c114}$ and an shRNA against LGALS3. **FIG. 12B** depicts matrigel invasion assay for 3T3 cells expressing the control vector, phrGFP, or the

indicated MUC16^{c114} constructs. **FIG. 12C** depicts the tumor growth, as determined by tumor volume, in athymic nude mice implanted with SKOV3 cells expressing the indicated constructs.

[00176] **FIG. 13A- FIG. 13D**. MUC16 glycosylation patterns and peptides. **FIG. 13A** depicts the N-linked profiling of SKOV3 cells expressing MUC16$^{c114\text{-}N12}$. Triangles represent fucose. Squares represent N-acetylglucosamine. Grey circles represent mannose. White circles represent galactose. Diamonds represent N-acethylneuramic acid. **FIG. 13B** depicts the 55-mer (SEQ ID NO:129) immunogen. **FIG. 13C** depicts the 15-mer (SEQ ID NO:131) immunogen. **FIG. 13D** depicts the 18-mer (SEQ ID NO:130) immunogen.

[00177] **FIG. 14** provides a detailed ELISA analysis of the relative reactivity of bioreactive supernatants comprising MUC16 Glycosylation Antibodies with glycosylated and unglycosylated antigens for both the 15 mer and the 18 mer used as immunogens and screening antigen targets.

[00178] **FIG. 15A- FIG. 15B.** MUC16 Glycosylation Antibodies inhibit matrigel invasion. **FIG. 15A** depicts matrigel invasion of SKOV3 cells expressing phrGFP control vector or MUC16^{c114} in the presence or absence of bioreactive supernatants from the generation of MUC16 Glycosylation Antibodies. The line is a reference line for the relative number of 200. **FIG. 15B** depicts matrigel invasion of SKOV3 cells expressing phrGFP control vector or MUC16^{c114} in the presence or absence of purified MUC16 Glycosylation Antibodies. The line is a reference line for the relative number of 90.

[00179] **FIG. 16A- FIG. 16E.** MUC16 Glycosylation Antibodies inhibit matrigel invasion. **FIG. 16A** depicts matrigel invasion of SKOV3 cells expressing phrGFP control vector or the indicated MUC16^{c114} constructs in the presence of (i) control antibody; (ii) 4H11; or (iii) MUC16 Glycosylation Antibody clone 10C6.E4. **FIG. 16B** depicts matrigel invasion of SKOV3 cells stably expressing phrGFP control vector or the indicated MUC16^{c344} constructs after a third FACs sort using 4H11, in the presence of (i) control antibody; (ii) 4H11; or (iii) MUC16 Glycosylation Antibody clone 10C6.E4. **FIG. 16C** depicts matrigel invasion of 3T3 cells expressing phrGFP control vector or the indicated MUC16^{c114} constructs in the presence of (i) control antibody; (ii) 4H11; or (iii) MUC16 Glycosylation Antibody clone 10C6.E4. **FIG. 16D** depicts the tumor growth, as indicated by tumor volume, in athymic nude mice implanted with SKOV3 cells expressing MUC16^{c344} and mock treated (MUC16^{c344}) or treated with the MUC16 Glycosylation Antibody 10C6.E4(MUC16^{c344} +10C6.E4). Arrows indicate days on which 100

μg of the MUC16 Glycosylation Antibody was administered. **FIG. 16E** depicts staining of human ovarian tumor samples with the indicated antibodies.

[00180] **FIG. 17** depicts the percent of cells in which the labeled MUC16 Glycosylation Antibody is internalized at the indicated temperature and timepoints.

[00181] **FIG. 18A** depicts *in vitro* growth curves for MUC16 transfectants. 1000 SKOV3 cells/well in 96 well flat-bottomed plates were cultured with phrGFP vector control, phrGFP vector expressing $MUC16^{c114}$ (SEQ ID NO: 133), or phrGFP vector expressing $MUC16^{c344}$ (SEQ ID NO: 132) and incubated at 37 °C in 5% CO_2 for 5 days. Each day, a plate was stained with Alamar Blue and incubated at 37 °C in 5% CO_2 for 4 hours. Plates were read in a CytoFluor Fluorescent plate reader. No statistical differences were seen among the curves. **FIG. 18B** depicts matrigel invasion assay for SKOV3 phrGFP cells, SKOV3 $MUC16^{c114}$-GFP cells, or SKOV3-$MUC16^{c344}$-GFP cells. Each assay was performed two or more times in triplicate and counted by hand. Results are expressed as the relative number of invasive cells. c114 and c344 were statistically significant as compared with phrGFP. **FIG. 18C** depicts SKOV3 transfectant tumor growth in athymic female nude mice. Two million tumor cells were introduced into the flank of 10 nu/nu mice and the mice were observed for tumor formation. Tumors were measured by calipers twice weekly. The differences in mean tumor volume were statisticcally significantly greater for mice bearing $MUC16^{c344}$ tumors ($p<0.0001$) and $MUC16^{c114}$ tumors ($p=0.002$) when compared to phrGFP tumors. Abbreviations for FIG. 18A-FIG.18C: "SKOV3 phrGFP" and "phrGFP" refer to SKOV3 cells expressing control phrGFP vector; "SKOV3 $MUC16^{c114}$-GFP" and "c114" refer to SKOV3 cells expressing $MUC16^{c114}$ (SEQ ID NO: 133); "SKOV3 $MUC16^{c344}$-GFP" and "c344" refer to SKOV3 cells expressing $MUC16^{c344}$ (SEQ ID NO: 132).

[00182] **FIG. 19A- FIG. 19F** depict the effect of MUC16 Expression on SKOV3 ovarian cancer cells. **FIG. 19A** depicts a matrigel invasion assay for SKOV3 cells expressing control phrGFP control vector ("phrGFP") or the phrGFP vector expressing $MUC16^{c114}$ (SEQ ID NO: 133; "c114") treated with or without the following: (1) 5 μg/mL tunicamycin; (2) 5 μg/mL of control pFUSE protein; (3) 5 μg/mL of $MUC16^{c57\text{-}114}$-pFUSE fusion protein; or (4) 5 μg/mL of $^{117\text{-}244}$LGALS3-pFUSE fusion protein. The results are expressed as number of invasive cells 48 hours-post-treatment. c114 cells were more invasive than phrGFP cells ($p<0.0001$). The invasive properties of the c114 cells were not affected by treatment with the pFUSE vector-only protein. Treatment with tunicamycin (an *N*-glycosylation inhibitor) decreased the invasive

properties of the c114 cells. Treatment with MUC16$^{c57\text{-}114}$-pFUSE fusion protein or $^{117\text{-}244}$LGALS3-pFUSE decreased the invasive properties of the c114 cells ($p<0.0001$). **FIG. 19B** depicts a matrigel invasion assay for SKOV3 cells transfected with phrGFP vector control ("phrGFP") or phrGFP vector expressing MUC16^{c114} (SEQ ID NO: 133) ("c114") in the presence or absence of lamelli control shRNA, MGAT5-specific shRNA, or LGALS3-specific shRNA. c114 cells treated with MGAT5-specific shRNA or LGALS3-specific shRNA had decreased invasion as compared to phrGFP cells treated with the shRNAs. The control shRNA has no impact on c114 cell invasion. Each assay was performed two or more times in triplicate and counted by hand. **FIG. 19C** depicts the glycosylation dependence of SKOV3-MUC16^{c114} matrigel invasion. SKOV3 cells were transfected with phrGFP control vector or phrGFP vector expressing the following MUC16 mutants: c114 (SEQ ID NO: 133), N1 mut c114 (SEQ ID NO: 151), N24 muc c114 (SEQ ID NO: 152), N30 mut c114 (SEQ ID NO:139), N1-N24 mut c114 (SEQ ID NO: 153), N1-N24-N30 mut c114 (SEQ ID NO: 154). The c114-expressing cells displayed increased invasion when compared to the control phrGFP cells. The increased invasive property of the c114-expressing cells was dependent on *N*-glycosylation of the asparagines at amino acid positions 24 and 30 of MUC16^{c114} (SEQ ID NO: 133). While both N24 and N30 sites were important, the N30 position appeared to be more crucial than the N24 site for this effect. Each assay was performed two or more times in triplicate and counted by hand. Results are expressed as % compared to phrGFP vector control. **FIG. 19D** depicts the glycosylation dependence of SKOV3-MUC16^{c344} matrigel invasion. SKOV3 cells were transfected with phrGFP control vector or phrGFP vector expressing the following MUC16 mutants: c344 (SEQ ID NO: 132), N24 mut c344 (SEQ ID NO: 173), N30 mut c344 (SEQ ID NO: 174), or N24-N30 mut c344 (SEQ ID NO: 175). The c344-expressing cells displayed increased invasion when compared to the control phrGFP cells. The increased invasive property of the c344-expressing cells was dependent on *N*-glycosylation of the asparagines corresponding to amino acid positions 24 and 30 of MUC16^{c114} (SEQ ID NO: 133). Each assay was performed two or more times in triplicate and counted by hand. **FIG. 19E** depicts the effect of MUC16-expression on selected signaling pathways. SKOV3 cells transfected with MUC16^{c114} (SEQ ID NO: 133) were treated with or without control shRNA ("shLamelli") or shRNA against MGAT5 ("shMGAT5") or LGALS3 ("shLGALLS3") and compared to SKOV3 cells transfected phrGFP vector control ("phrGFP") or phrGFP vector expressing MUC16$^{c114\text{-}N30mut}$ (SEQ ID NO: 139)

("N30 mut") and the cells were examined for activation of the pAKT, pERK1/2, pSRC, and pEGF receptor (pEGFR) signaling pathways. Phosphorylation of AKT (S473) and ERK1/2 (pT202/Y204) were increased in the MUC16^{c114} cells. Knockdown of MGAT5 (shMGAT5), knockdown of Galectin-3 (shLGALLS3), and the N30A mutation each reduced MUC16^{c114}-induced oncogene activation in the SKOV3 cell lines. **FIG. 19F** depicts SKOV3 transfectant tumor growth in athymic female nude mice. Two million tumor (described below) cells were introduced into the flank of 10 nu/nu mice for each condition, and mice were observed for tumor formation. Tumors were measured by calipers twice per week. *In vivo* growth of c114 tumor cells was much more aggressive ($p<0.0001$) as compared to phrGFP tumor cells. N1-N24-N30-mut c114, c114-sh-MGAT5, and c114-sh-LGALS3 tumor cells did not display growth enhancement when compared to phrGFP tomuor cells. Description of tumor cells: "phrGFP" refers to SKOV3 cells transfected with phrGFP vector control; "c114" refers to SKOV3 cells transfected with phrGFP vector expressing MUC16^{c114} (SEQ ID NO: 133); "N1-N24-N30-mut c114" refers to SKOV3 cells transfected with phrGFP vector expressing MUC16$^{c114\text{-}N1\text{-}N24\text{-}N30\text{-}mut}$ (SEQ ID NO: 154); "c114-sh-MGAT5" refers to SKOV3 cells transfected with phrGFP vector expressing MUC16^{c114} (SEQ ID NO: 133) and treated with shRNA against MGAT5; and "c114-sh-LGALS3" refers to SKOV3 cells transfected with phrGFP vector expressing MUC16^{c114} (SEQ ID NO: 133) and treated with shRNA against LGALS3.

[00183] **FIG. 20A** depicts the effect of MUC16 expression on EGFR surface expression. SKOV3-phrGFP and SKOV3-MUC16^{c114} transfectants were examined in the presence or absence of treatingment with cycloheximide (CHX) for 24 hours. Geometric mean fluorescence of EGFR and MUC16 expression at basal and post-CHX treated levels is shown. EGFR in SKOV3-phrGFP samples was reduced to 58% of untreated levels after 24 hours of treatment with CHX. No significant MUC16 expression was present in these cells. In contrast, in the SKOV3-MUC16^{c114} cells, there was roughly a 25% increase in EGFR geometric mean fluorescence, which decreased to 83% of that of the control after CHX exposure. MUC16^{c114} mean fluorescence was not significantly reduced by CHX. **FIG. 20B** depicts densitometry of the EGFR/β-actin ratio from western blots of total cellular EGFR and illustrates that there was a steady loss of EGFR over time in SKOV3-phrGFP cells treated with CHX. In contrast, the total level of EGFR in SKOV3-MUC16^{c114} cells was maintained, showing EGFR stabilization compared with the MUC16(–) control cell line ("phrGFP (-)"). **FIG. 20C** depicts a matrigel

invasion assay for SKOV3 cells transfected with phrGFP control vector ("stable phrGFP"), SKOV3-MUC16^{c114} and SKOV3-MUC16$^{c114(tet)}$ tetracycline-inducible cell lines, expressed as a fraction of control cell invasion. Tetracycline induction of SKOV3-MUC16$^{c114(tet)}$ cells resulted in an invasive phenotype similar to the stable SKOV3-MUC16^{c114} (SKOV3^{c114}), while un-induced cells matched the MUC16-phrGFP control cells. This MUC16-induced increase in matrigel invasion was completely dependent on EGFR. When a hairpin RNA knockdown of EGFR (shEGFR) was introduced into SKOV3 cells, tetracycline induced expression of MUC16 (4H11 positive protein in western blot) but did not increase matrigel invasion. Each assay was performed in triplicate and counted by hand. **FIG. 20D:** EGFR stability in MUC16^{c114}(+) and MUC16^{c114}(–) cells. Cell extracts of un-induced or tetracycline-induced SKOV3-MUC16c114(tet) cell lines treated with CHX for 24 hours and probed for total cellular EGFR are expressed as densitometry ratios, and normalized with β-Actin. The slope of the EGFR decline in tetracycline-induced SKOV3-MUC16^{c114} cells replicates the EGFR stabilization effect of MUC16^{c114} expression compared with the MUC16^{c114}(–) line. The result is similar to the effect of stable transfection shown above in FIG. 20B).

[00184] **FIG. 21** depicts densitometry for western blot analysis of cell extracts of un-induced or tetracycline-induced SKOV3^{c114} cell lines ("Uninduced MUC16^{c114}" and "Tet-induced MUC16^{c114}", respectively) treated with cycloheximide for 24 hours. The western blots were probed for pEGFR and protein levels were normalized to β-Actin levels. The slopes of the tetracycline-induced SKOV3^{c114} pEGFR signal showed stabilized pEGFR compared with un-induced SKOV3^{c114} cell line.

[00185] **FIG. 22A- FIG. 22C** depict the identification and chemical synthesis of MUC16 ectodomain *N*-glycosylated species. **FIG. 22A:** *N*-glycan profiling of SKOV3 cells transfected with phrGFP expressing N1-N24 mutated MUC16^{c114} (SEQ ID NO: SEQ ID NO: 153). The glycans were detected and characterized by total ion mapping at the Complex Carbohydrate Research Center, University of Georgia. Triangles: fucose; squares: *N*-acetylglucosamin; circles, dark fill: mannose; circles, light fill: galactose; diamonds: *N*-acetylneuraminic acid. **FIG. 22B** depicts the schematic structure of a 55-mer MUC16 antigen with a single chitobiose ($GlcNAc_2$) glycan at the N30 position. This *N*-glycopeptide antigen was used to immunize mice to raise antibodies. The amino acid sequence is as set forth in SEQ ID NO: 129. Squares represent *N*-acetylglucosamin; circles represent mannose. **FIG. 22C** depicts the schematic structure of a

KLH-conjugated, 15-mer MUC16 antigen mono-glycosylated with chitobiose at the N30 position, and KLH-conjugated, 18-mer MUC16 antigen bis-glycosylated with two chitobiose units at the N24 and N30 positions, respectively. These *N*-glycopeptide–KLH constructs were subsequently used to immunize mice to raise monoclonal antibodies against the $GlcNAc_2$-peptide epitope within the MUC16 ectodomain. Sequences of the MUC16-unrelated glycopeptides and the nonglycosylated MUC16 peptide 2 to elicit the 4H11 monoclonal antibody are included as well. The amino acid sequence for KLH-15-mer(chitobiose)[C-G25-V38] is as set forth in SEQ ID NO: 131. The amino acid sequence for KLH-18-mer$(chitobiose)_2$[C-T22-V38] is as set forth in SEQ ID NO: 130. The amino acid sequence for MUC16 Nonglycosylated Peptide2 is as set forth in SEQ ID NO: 168. The amino acid sequence for MUC16 unrelated peptide 18mer and MUC16 unrelated peptide 18mer + GlcNAc2 is as set forth in SEQ ID NO: 169. Squares represent *N*-acetylglucosamin.

[00186] **FIG. 23A-FIG. 23H** depict MUC16 Glycosylation Antibody characterization. **FIG. 23A** depicts the reactivity of 4H11 and four lead $GlcNAc_2$-MUC16-ectodomain monoclonal antibodies (MUC16 Glycosylation Antibodies) to various MUC16 and $GlcNAc_2$-glycosylated peptides by sandwich ELISA. No glycan-MUC16 ectodomain cross reactivity was seen with the nonglycosylated MUC16 peptide 2 (SEQ ID NO: 168), or either of the unrelated peptides (SEQ ID NO: 169). Similarly, 4H11 had essentially no affinity for the $GlcNAc_2$-MUC16 15-mer (SEQ ID NO: 131) or $(GlcNAc_2)_2$-18-mer (SEQ ID NO: 130) *N*-glycopeptides. Squares represent *N*-acetylglusoamin; triangles represent fucose; circles represent mannose. **FIG. 23B, FIG. 23C, and FIG. 23D** depict the effect of MUC16 Glycosylation Antibodies on MUC16-enhanced matrigel invasion. Results are expressed as % compared to control. Matrigel assay of SKOV3 cells transfected with phrGFP expressing $MUC16^{c114}$ (SEQ ID NO: 133) (FIG. 23B), CAOV3 cells (FIG. 23C) and OVCA-433 cells (FIG. 23D) with or without (control) purified 4H11 or the four glycan-MUC16-ectodomain antibodies 18C6, 10C6, 19C22, or 7B12 at 5 μg/mL. Each of the four anti-glycan-MUC16-ectodomain antibodies (MUC16 Glycosylation Antibodies) inhibited the invasion of three different MUC16(+) ovarian cancer cell lines (CAOV3 and OVCA-433), while 4H11 had less effect on inhibiting invasion of the SKOV3-$MUC16^{c114}$ cells. **FIG. 23E** depicts the inhibition of EGFR stabilization by MUC16 Glycosylation Antibody monoclonal antibody ("MAB") 10C6. The densitometry of western blot analysis from cell extracts of un-induced SKOV3-$MUC16^{c114(tet)}$, tetracycline-induced SKOV3-$MUC16^{c114(tet)}$, or

monoclonal MUC16 Glycosylation Antibody 10C6-treated, tetracycline-induced SKOV3-MUC16$^{c114(tet)}$ cell lines treated with CHX and then probed for total EGFR at the indicated hours (hrs) post-treatement with cyclohexamind . As seen in FIG. 20A, the slopes of the densitometry curves indicated that the presence of MUC16^{c114} on the cell surface stabilized EGFR. The MUC16 Glycosylation Antibody 10C6 abrogated the MUC16^{c114} stabilization of total EGFR protein, making it similar to the MUC16(–) un-induced control. **FIG. 23F** depicts human ovarian tissue microarrays stained with 4H11, OC125 (commercial), or monoclonal MUC16 Glycosylation Antibodies (10C6 and 19C11). The expression of MUC16 on the serous ovarian cancer was consistent and overlapped with OC125 and 4H11. **FIG. 23G and FIG. 23H** depict the effect of MUC16 Glycosylation Antibodies on tumor growth in athymic female nude mice. Two million tumor cells (SKOV3 cells transfected with phrGFP vector ("phrGFP") or phrGFP vector expressing MUC16^{c344} (SEQ ID NO: 132; "c344")) were introduced into the flank of 20 nu/nu mice. Ten mice were treated intravenously from day 0 with purified monoclonal MUC16 Glycosylation Antibody 10C6 at 100 µg/mouse twice per week for 4 weeks. All mice were observed for tumor formation. Tumors were measured by calipers twice per week. **FIG. 23G** shows the matrigel invasion assay with the same cells performed in the presence and absence of purified monoclonal MUC16 Glycosylation Antibody 10C6 at 10 µg/mL. **FIG. 23H** demonstratess that differences in mean tumor volume were significantly decreased (p=0.0004) with monoclonal MUC16 Glycosylation Antibody 10C6-treated mice bearing MUC16^{c344} tumors compared with untreated MUC16^{c344} tumors, indicating protection against the effect of MUC16 on tumor growth.

[00187] **FIG. 24A-FIG.24D** depict galectin-mediated MUC16 protein-protein Interactions. **FIG. 24A** depicts immunoblot (IB) and immunoprecipitation (IP) of three glycosylated proteins (EGFR DDK-His; MUC16$^{c57-114}$-pFUSE; and LGALS3Myc-DDK). MUC16$^{c57-114}$-pFUSE glycosylated protein was combined with LGALS3 protein (0.13 µg) and EGFR (0.13 µg) and then rotated at 4 °C for 1 hour. Pre-blocked Protein A/G PLUS Agarose beads were added and were rotated at 4 °C overnight. IP pellets were washed extensively, boiled in loading buffer and separated by 10% SDS-PAGE gel electrophoresis, then transferred onto nitrocellulose membrane. The membrane was probed with anti-EGFR-v3, anti-4H11-HRP, or polyclonal anti-LGALS3 antibodies. As shown, the 4H11 binding showed that MUC16$^{c57-114}$-pFUSE was consistently present. LGALS3 bound in the lane positive for MUC16$^{c57-114}$-pFUSE, but EGFR

was only detected when both LGALS3 and MUC16$^{c57\text{-}114}$-pFUSE were present. The presence of the monoclonal MUC16 Glycosylation Antibody 18C6 prevented the formation of these LGALS3, EGFR, and MUC16 protein complexes (right hand lanes). **FIG. 24B** depicts MUC16 and EGFR protein co-localization. Immunofluorescence staining of wild type OVCAR3 cells or SKOV3 cells transfected with phrGFP expressing MUC16^{c344} (SEQ ID NO: 132; "SKOV3^{c344}") or with phrGFP expressing MUC16^{c114} (SEQ ID NO: 133; "SKOV3^{c114}") with EGFR-A647 and 4H11-PE for MUC16, or a combination of both reagents EGFR-A647 and 4H11-PE for MUC16. Microscopic images (50 μm scale) indicated co-localization of EGFR and MUC16^{c114} in all three cell lines (*see* arrows). **FIG. 24C** depicts immunoblot (IB) and immunoprecipitation (IP) of three glycosylated proteins (Integrin β1Myc-DDK; MUC16$^{c57\text{-}114}$-pFUSE and LGALS3Myc-DDK). Generally the same methods as in FIG. 24A were used. Western blot analysis of immunoblot and all immunoprecipitated samples were run on 10% SDS-PAGE gel, transferred onto nitrocellulose membrane, and probed either with anti-4C5-DDK for Integrin β1, or anti-4H11-HRP or anti-4C5-DDK for LGALS3 antibodies. As with EGFR, all three proteins were required to co-precipitate the Integrin β1 protein. The MUC16 Glycosylation Antibody 18C6 also blocked the combination of MUC16, LGALS3, and Integrin β1, as shown in the three right-hand lanes. **FIG. 24D** depicts MUC16 and Integrin β1 protein co-localization. Immunofluorescence staining of wild ty wild type OVCAR3 cells or SKOV3 cells transfected with phrGFP expressing MUC16^{c344} (SEQ ID NO: 132; "SKOV3^{c344}") or with phrGFP expressing MUC16^{c114} (SEQ ID NO: 133; "SKOV3^{c114}") with Integrin β1-A647 or 4H11-PE for MUC16 or a combination of both reagents Integrin β1-A647 or 4H11-PE for MUC16. Microscopic images (50 μm scale) indicated co-localization of the Integrin β1 and MUC16 in OVCAR3, SKOV3^{c344}, and SKOV3^{c114} cells (*see* arrows).

[00188] **FIG. 25A** depicts immunofluorescence staining of wild type OVCAR3 cells or SKOV3 cells transfected with phrGFP expressing MUC16^{c344} (SEQ ID NO: 132; "SKOV3^{c344}") or with phrGFP expressing MUC16^{c114} (SEQ ID NO: 133; "SKOV3^{c114}") or SKOV3^{c344} or SKOV3^{c114} cell lines with EGFR-A647 or 4H11-PE for MUC16 or a combination of both reagents. Microscopic images (scale 100 μm) clearly indicated co-localization of EGFR and MUC16 (*see* arrows). **FIG. 25 B:** Immunofluorescence staining of wild type OVCAR3 or SKOV3^{c344} or cell lines with Integrin β1-A647 or 4H11-PE for MUC16 or a combination of both

reagents. Microscopic images (scale 100 μm) clearly indicated co-localization of Integrin β1 and MUC16 (*see* arrows).

[00189] **FIG. 26A-FIG. 26D** depicts a model of MUC16 Tumor Promotion. **FIG. 26A** depicts an illustration of EGFR-LGALS3-MUC16 and LGALS3-Integrin β1-MUC16 relationships. Signal transduction of SRC/ERK/AKT by EGFR or of SRC/FAK by Integrin β1 depended on MUC16 and signaling-molecule interaction with LGALS3 pentamers. **FIG. 26B** depicts a model for glycosylation loss: in shMGAT5-transfected cell lines, the *N*-glycosylation at sites on MUC16, EGFR, and Integrin β1 was reduced by loss of the tetra-antennary structures, resulting in no binding to LGALS3. **FIG. 26C** depicts a model for galectin-3 loss: in shLGALS3 transfected cell lines, while the *N*-glycosylation sites on MUC16 were present, the absence of binding to LGALS3 resulted in a loss of MUC16/EGFR or MUC16/Integrin β1 association and reduction of inside-out signals. **FIG. 26D** depicts a model for potential nhibitors for MUC16/LGALS3 interactions. MUC16(+) cells exposed to MUC16 Glycosylation Antibody or "dummy" sham receptors (anti-MUC16$^{c57\text{-}114}$pFUSE or $^{117\text{-}244}$LGALS3-pFUSE) failed to bind to LGALS3 gels and subsequently also to either EGFR or Integrin β1.

[00190] **FIG. 27A** depicts the side-chain protected N-acetylated 55-mer peptide amide (SEQ ID NO: 129). **FIG. 27B** depicts the ESI-MS and UV traces from UPLC analysis for glycopeptide p55-mer[N1-S55]. Calculated for $C_{486}H_{760}N_{84}O_{111}S_8$, 9812.25 (average isotopes) $[M+5H]^{5+}$ *m/z* 1963.45, found 1963.20; $[M+6H]^{6+}$ *m/z* 1636.38, found 1636.24; $[M+7H]^{7+}$ *m/z* 1402.75, found 1402.74. BEH C4 column, gradient: 80-99% acetonitrile/water over 6 minutes at a flow rate of 0.3 mL/min.

[00191] **FIG. 28A** depicts the chitobiose-bearing 55-mer glycopeptide: "55-mer(chitobiose)[N1-S55]" ($GlcNAc_2$-55-mer) (SEQ ID NO: 129). **FIG. 28B** depicts the ESI-MS and UV traces from UPLC analysis for glycopeptide "55 mer(chitobiose) [N1-S55]" ($GlcNAc_2$-55-mer). Calculated for $C_{291}H_{463}N_{87}O_{97}S$, 6764.38 (average isotopes) $[M+4H]^{4+}$ *m/z* 1692.10, found 1692.01; $[M+5H]^{5+}$ *m/z* 1353.88, found 1353.86; $[M+6H]^{6+}$ *m/z* 1128.40, found 1128.41; $[M+7H]^{7+}$ *m/z* 967.34, found 967.45; $[M+8H]^{8+}$ *m/z* 846.55, found 846.27. BEH C4 column, gradient: 20-40% acetonitrile/water over 6 minutes at a flow rate of 0.3 mL/min.

[00192] **FIG. 29A** depicts Man3GlcNAc2-bearing 55-mer glycopeptide: "55-mer($Man_3GlcNAc_2$)[N1-S55]" ($Man_3GlcNAc_2$-55-mer) (SEQ ID NO: 129). **FIG. 29B** depicts the ESI-MS and UV traces from analytical HPLC analysis for glycopeptide "55

mer($Man_3GlcNAc_2$)[N1-S55]" ($Man_3GlcNAc_2$-55-mer). Calculated for $C_{309}H_{493}N_{87}O_{112}S$, 7250.80 (average isotopes) $[M+4H]^{4+}$ *m/z* 1813.70, found 1813.52; $[M+5H]^{5+}$ *m/z* 1451.16, found 1451.02; $[M+6H]^{6+}$ *m/z* 1209.47, found 1209.33; $[M+7H]^{7+}$ *m/z* 1036.83, found 1036.74. Waters X-Bridge C18 column, gradient: 25-35% acetonitrile/water over 30 minutes at a flow rate of 0.2 mL/min.

[00193] **FIG. 30A** depicts side-chain protected 15-mer peptide (p15-mer[C-G25−V38]) (SEQ ID NO: 131). **FIG. 30B** depicts chitobiose-monoglycosylated 15-mer glycopeptide: 15-mer(chitobiose)[C-G25-V38] ($GlcNAc_2$-15-mer) (SEQ ID NO: 132). **FIG. 30C** depicts ESI-MS and UV traces from analytical HPLC analysis for glycopeptide "15 mer(chitobiose)[C-G25-V38]" ($GlcNAc_2$-15-mer). Calculated for $C_{87}H_{142}N_{24}O_{35}S$, 2116.26 (average isotopes) $[2M+3H]^{3+}$ *m/z* 1411.84, found 1412.02; $[M+2H]^{2+}$ *m/z* 1059.13, found 1059.15; $[M+3H]^{3+}$ *m/z* 706.42, found 706.46. Varian Microsorb 300-5 C18 column, gradient: 15-30% acetonitrile/water over 30 minutes at a flow rate of 0.2 mL/min.

[00194] **FIG. 31A** depicts side-chain protected 18-mer peptide (p18-mer[C-G22−V38]) (AF-I-165) (SEQ ID NO: 130). **FIG. 31B** depicts chitobiose-bisglycosylated 18-mer glycopeptide: "18-mer(chitobiose)$_2$[C-T22-V38]" [($GlcNAc_2$)$_2$-18-mer] (SEQ ID NO: 130). **FIG. 31C** depicts the ESI-MS and UV traces from analytical HPLC analysis for glycopeptide "18 mer(chitobiose)$_2$[C-T22-V38]" [($GlcNAc_2$)$_2$-18-mer]. Calculated for $C_{117}H_{193}N_{33}O_{50}S$, 2894.04 (average isotopes) $[2M+3H]^{3+}$ *m/z* 1930.36, found 1930.22; $[M+2H]^{2+}$ *m/z* 1448.02, found 1447.65; $[M+3H]^{3+}$ *m/z* 965.68, found 965.25. Varian Microsorb 300-5 C8 column, gradient: 15-30% acetonitrile/water over 30 minute at a flow rate of 0.2 mL/min.

[00195] **FIG. 32A** depicts glycopeptide "15-mer(chitobiose)[C-G25-V38]", conjugated to KLH (SEQ ID NO: 131). **FIG. 32B** depicts glycopeptide "18-mer(chitobiose)$_2$[C-T22-V38]" conjugated to KLH (SEQ ID NO: 130).

5. DETAILED DESCRIPTION

[00196] Provided are antibodies and antigen-binding fragments thereof, and polypeptides including such antibodies or fragments, such as fusion proteins, conjugates, and/or chimeric antigen receptors, as well as cells expressing the same. Among the antibodies and fragments are those that specifically bind to epitopes of a MUC16 protein. Such antibodies are referred to herein as "MUC16 Glycosylation Antibodies". Such epitopes are typically epitopes within or substantially within an extracellular portion of a MUC16 molecule, generally a non-shed form of

MUC16; in some embodiments, the epitope is not within, or the antibody or fragment does not bind to, a tandem repeat region of MUC16 and/or a secreted form of MUC16. In some embodiments, the epitope is within or includes residues within MUC16c114, and typically includes one or more glycosylated residues or glycosylation sites therein. In some embodiments, the epitope includes one or more glycosylation sites, such as sites for N-glycosylation. In some aspects, the epitope includes an asparagine residue corresponding to Asn1806 or Asn1800 of the MUC16 sequence set forth in SEQ ID NO: 150 (and/or a glycosylated form(s) thereof); in some aspects, the epitope includes an asparagine residue corresponding to Asn1806 of SEQ ID NO: 150, but does not include an asparagine residue corresponding to Asn1800 of SEQ ID NO: 150; in some aspects, the epitope includes an asparagine residue corresponding to Asn1800 of SEQ ID NO: 150, but does not include an asparagine residue corresponding to Asn1806 of of SEQ ID NO: 150. In some of any of such embodiments, such one or more asparagine is glycosylated, such as N-glycosylated. In some embodiments, the antibody or fragment binds to an epitope within or that includes residues within SEQ ID NO: 131; binds to an epitope within or that includes residues within SEQ ID NO: 130, or a combination thereof; in some embodiments, the antibody or fragment does not immunospecifically bind within a region of MUC16 corresponding to SEQ ID NO: 168, or within residues 2-19 of SEQ ID NO: 168.

[00197] In one aspect, provided herein are antibodies (*e.g.,* monoclonal antibodies), and antigen-binding fragments thereof, that (i) immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lack immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibit matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16. In another aspect, provided herein are antibodies (*e.g.,* monoclonal antibodies), and antigen-binding fragments thereof, that (i) immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lack immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO:139; and (iii) inhibit matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16. In a preferred embodiment, MUC16

Glycosylation Antibodies and antigen-binding fragments thereof described herein immunospecifically bind an epitope comprising amino acid residue 1806 (Asn1806) of SEQ ID NO:150, wherein Asn1806 is N-glycosylated (referred to herein as "Asn1806 Glycosylation"). As shown in the examples of Section 6 herein, Asn1806 Glycosylation is essential for MUC16-mediated invasion and growth of tumor cells. Thus, the MUC16 Glycosylation Antibodies and antigen-binding fragments thereof described herein are capable of binding blocking such invasion and growth of tumor cells.

[00198] In one embodiment, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof requires an *N*-glycosylated Asn1800 in addition to an *N*-glycosylated Asn1806 for binding to MUC16 (*i.e.*, both *N*-glycosylated sites are part of the epitope recognized by the MUC16 Glycosylation Antibody or antigen-binding fragment thereof). "Asn1800" refers to amino acid residue 1800 of SEQ ID NO:150. Such a MUC16 Glycosylation Antibody or antigen-binding fragment thereof can be identified by (i) its ability to immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; and (ii) its lack of immunospecific binding to a cell recombinantly expressing a fifth form of MUC16, which fifth form is glycosylated, and wherein the amino acid sequence of the fifth form is SEQ ID NO: 172, wherein the cell recombinantly expressing the first form of MUC16 is the same cell type as the cell recombinantly expressing the fifth form of MUC16.

[00199] In one embodiment, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof requires an *N*-glycosylated Asn1806 but does not require an *N*-glycosylated Asn1800 for binding to MUC16 (*i.e.*, *N*-glycosylated Asn1806 is part of the epitope recognized by the MUC16 Glycosylation Antibody or antigen-binding fragment thereof, but *N*-glycosylated Asn1800 is not part of the epitope recognized by the MUC16 Glycosylation Antibody or antigen-binding fragment thereof). Such a MUC16 Glycosylation Antibody or antigen-binding fragment thereof can be identified by (i) its ability to immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) its lack of immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139; and (iii) its ability to immunospecifically bind to a cell recombinantly expressing a fourth form of MUC16, which

fourth form is glycosylated, and wherein the amino acid sequence of the fourth form is SEQ ID NO: 152; and (iii) wherein the cell recombinantly expressing the first form of MUC16, the cell recombinantly expressing the third form of MUC16, and the cell recombinantly expressing the fourth form of MUC16 are of the same cell type.

[00200] The protein encoded by the amino acid sequence of SEQ ID NO:133 is also referred to herein as $MUC16^{c114}$ and consists of the C-terminal 114 amino acid residues of mature MUC16 (SEQ ID NO: 150 being the sequence of mature MUC16). $MUC16^{c114}$ is capable of being *N*-glycosylated at the asparagine amino acid residues at positions 1, 24, and 30 of SEQ ID NO: 133 (corresponding to amino acid positions Asn1777, Asn1800, and Asn1806 of SEQ ID NO: 150).

[00201] The protein encoded by the amino acid sequence of SEQ ID NO: 139 is also referred to herein as $MUC16^{c114\text{-}N3}$. $MUC16^{c114\text{-}N3}$ consists of the C-terminal 114 amino acid residues of mature MUC16 (SEQ ID NO: 150 being the sequence of mature MUC16), except that the asparagine at amino acid position 30 (corresponding to amino acid position 1806 of SEQ ID NO: 150) has been mutated to an alanine. Thus, $MUC16^{c114\text{-}N3}$ is not capable of being *N*-glycosylated at amino acid position 30 of SEQ ID NO: 139 (corresponding to amino acid position Asn1806 of SEQ ID NO: 150).

[00202] The protein encoded by the amino acid sequence of SEQ ID NO: 152 is also referred to herein as $MUC16^{c114\text{-}N2}$. $MUC16^{c114\text{-}N2}$ consists of the C-terminal 114 amino acid residues of mature MUC16 (SEQ ID NO:150 being the sequence of mature MUC16), except that the asparagine at amino acid position 24 (corresponding to amino acid position Asn1800 of SEQ ID NO: 150) has been mutated to an alanine. Thus, $MUC16^{c114\text{-}N2}$ is not capable of being *N*-glycosylated at amino acid position 24 of SEQ ID NO: 152 (corresponding to amino acid position Asn1800 of SEQ ID NO: 150).

[00203] The protein encoded by the amino acid sequence of SEQ ID NO: 172 is also referred to herein as $MUC16^{c114\text{-}N23}$. $MUC16^{c114\text{-}N23}$ consists of the C-terminal 114 amino acid residues of mature MUC16 (SEQ ID NO:150 being the sequence of mature MUC16), except that the asparagines at amino acid positions 24 and 30 (corresponding to amino acid positions Asn1800 and Asn1806 of SEQ ID NO: 150) have been mutated to alanines. Thus, $MUC16^{c114\text{-}N23}$ is not capable of being *N*-glycosylated at amino acid positions 24 and 30 of SEQ ID NO: 157 (corresponding to amino acid positions Asn1800 and Asn1806 of SEQ ID NO: 150).

[00204] Also provided herein are heavy chains and light chains, wherein a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising said heavy and light chains (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16. Also provided herein are polynucleotides (*e.g.,* isolated polynucleotides) comprising nucleic acid sequences (*e.g.,* complementary DNA (cDNA)), encoding such antibodies, and antigen-binding fragments thereof, heavy chains, or light chains. Further provided are vectors (*e.g.,* expression vectors) and cells (*e.g.,* isolated cells or *ex vivo* cells) comprising polynucleotides (*e.g.,* isolated polynucleotides) comprising nucleic acid sequences (*e.g.,* complementary DNA (cDNA)), encoding such antibodies, and antigen-binding fragments thereof, heavy chains, or light chains. Also provided are methods of making such antibodies, antigen-binding fragments thereof, heavy chains, light chains, vectors, and cells. In other aspects, provided herein are methods and uses for MUC16 activity and/or MUC16-driven tumor growth, or treating or managing certain conditions or disorders described herein, such as treating or managing cancer. Related compositions (*e.g.,* pharmaceutical compositions), kits, and diagnostic methods are also provided.

[00205] As used herein, the term "MUC16" or "MUC16 polypeptide" or "MUC16 peptide" refers to the MUC16 tethered mucin protein as described in Yin BW and Lloyd KO, 2001, J Biol Chem. 276(29):27371-5. GenBank™ accession number NM_024690.2 (SEQ ID NO:137) provides an exemplary human MUC16 nucleic acid sequence. GenBank™ accession number NP_078966.2 (SEQ ID NO:136) provides an exemplary human MUC16 amino acid sequence. Native MUC16 comprises an intracellular domain, a transmembrane domain, an ectodomain proximal to the putative cleavage site, and a large, heavily glycosylated region of 12-20 repeats, each 156 amino acids long (FIG. 1A). "Immature" MUC16 refers to SEQ ID NO:136, which comprises the MUC16 signal sequence (amino acid residues 1-60 of SEQ ID NO:136). "Mature MUC16" refers to native MUC16 as expressed on the cell surface, *i.e.*, where the signal sequence has been removed by cellular processing, for example, SEQ ID NO:150, where the first

60 amino acid residues of SEQ ID NO:136 have been removed (*i.e.*, SEQ ID NO:136 is the "immature" form of MUC16).

[00206] With respect to antibody names, (i) 18C6 and 18C6.D12 are used interchangeably, (ii) 10C6 and 10C6.E4 are used interchangeably, (iii) 19C11 and 19C11.H6 are used interchangeably, and (iv) 7B12 and 7B12.B3 are used interchangeably. The antibody subclones (*i.e.*, 18C6.D12, 10C6.E4, 19C11.H6, and 7B12.B3) were used in the experiments described in Section 6.

5.1 ANTIBODIES

[00207] MUC16 Glycosylation Antibodies or antigen-binding fragments thereof can include, *e.g.,* monoclonal antibodies, polyclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain- antibody heavy chain pair, intrabodies, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain variable fragments (scFv), camelized antibodies, affybodies, and disulfide-linked Fvs (dsFv), or fragments thereof. Such antibodies can be made by methods known in the art.

[00208] A multispecific antibody or fragment thereof refers to an antibody or fragment thereof that can bind simultaneously to at least two targets that are of different structure, *e.g.,* two different antigens, two different epitopes on the same antigen, or a hapten and an antigen or epitope. One specificity could be for, for example, a B-cell, T-cell, myeloid-, plasma-, or mast-cell antigen or epitope, such as, for example CD3. Another specificity could be to a different antigen on the same or different cell type, such as for example, MUC16. Multispecific, multivalent antibodies are constructs that have more than one binding site, and the binding sites are of different specificity, for example, a bispecific diabody, where one binding site reacts with one antigen and the other with another antigen.

[00209] A bispecific antibody is an antibody that can bind simultaneously to two targets which are of different structure. Bispecific antibodies (bsAb) and bispecific antibody fragments (bsFab) have at least one arm that immunospecifically binds to a first target, for example, MUC16, and at least one other arm that immunospecifically binds to a second target, such as, for

example, CD3. A variety of bispecific fusion proteins can be produced using molecular engineering. In one form, the bispecific fusion protein is divalent, consisting of, for example, (i) a scFv with a single binding site for one antigen and (ii) an antibody or a Fab fragment with a single binding site for a second antigen. In another form, the bispecific fusion protein is tetravalent, consisting of, for example, an IgG with two binding sites for one antigen and two identical scFv for a second antigen. See, for example, International Publication No. WO 2011/1160119, which is incorporated by reference in its entirety herein.

[00210] Recent methods for producing bispecific monoclonal antibodies include the use of engineered recombinant monoclonal antibodies which have additional cysteine residues so that they crosslink more strongly than the more common immunoglobulin isotypes. See, *e.g.,* FitzGerald et al., Protein Eng. 10(10):1221-1225, 1997. Another approach is to engineer recombinant fusion proteins linking two or more different single-chain antibody or antibody fragment segments with the needed dual specificities. See, *e.g.,* Coloma et al., Nature Biotech. 15:159-163, 1997. A variety of bispecific fusion proteins can be produced using molecular engineering.

[00211] Bispecific fusion proteins linking two or more different single-chain antibodies or antibody fragments can be produced in similar manner. Recombinant methods can be used to produce a variety of fusion proteins. In certain aspects, a flexible linker connects an scFv (*e.g.,* an scFv targeting CD3) to the constant region of the light chain of a monoclonal antibody (*e.g.,* a MUC16 Glycosylation Antibody described herein; *see* Section 5.1). Appropriate linker sequences necessary for the in-frame connection of the heavy chain Fc to the scFv are introduced into the VL and Vkappa domains through PCR reactions. The DNA fragment encoding the scFv is then ligated into a staging vector containing a DNA sequence encoding the CHI domain. The resulting construct is excised and ligated into a vector containing a DNA sequence encoding the VH region of the antibody (*e.g.,* the MUC16 Glycosylation Antibody). The resulting vector can be used to transfect an appropriate host cell, such as a mammalian cell for the expression of the bispecific fusion protein.

[00212] The MUC16 Glycosylation Antibodies described herein (*see* Section 5.1) and fragments thereof in certain embodiments can also be used to prepare functional bispecific single-chain antibodies (bscAb), also called diabodies, and can be produced in mammalian cells using recombinant methods. See, *e.g.,* Mack et al., Proc. Natl. Acad. Sci., 92: 7021-7025, 1995,

incorporated herein by reference. For example, bscAb can be produced by joining two single-chain Fv fragments via a glycine-serine linker using recombinant methods. The VL and VH domains of two antibodies of interest are isolated using standard PCR methods known in the art. Bispecific single-chain antibodies and bispecific fusion proteins are included within the scope of the present invention.

[00213] In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein refer to scFvs. A scFv is an art-recognized term. An scFv comprises a fusion protein of the variable regions of the heavy (VH) and light (VL) chains of an immunoglobulin, wherein the fusion protein retains the same antigen specificity as the whole immunoglobulin. The VH is fused to the VL via a peptide linker. In certain embodiments, the peptide linker is between 5 and 25, 5 and 15, 10 and 20, 10 and 15, or 15 and 25 amino acid residues in length. In certain embodiments, the scFv peptide linker displays one or more characteristics suitable for a peptide linker known to one of ordinary skill in the art. In certain embodiments, the scFv peptide linker comprises amino acids that allow for scFv peptide linker solubility, such as, for example, serine and threonine. In certain embodiments, the scFv peptide linker comprises amino acids that allow for scFv peptide linker flexibility, such as, for example, glycine. In certain embodiments, the scFv peptide linker connects the N-terminus of the VH to the C-terminus of the VL. In certain embodiments, the scFv peptide linker can connect the C-terminus of the VH to the N-terminus of the VL.

[00214] In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein refer to chimeric antigen receptors (CARs). A CAR is an art-recognized term. A CAR can be targeted to a tumor associated antigen (*e.g.,* MUC16). CARs as provided herein typically are composed of a scFv derived from a MUC16 Glycosylation Antibody, a transmembrane domain, which in some embodiments is a T cell co-stimulatory molecule-derived transmembrane domain (for example, a transmembrane domain derived from CD28, CD8, CD38, OX-40, or 4-1BB), and a primary signaling domain, such as the T cell receptor (TCR) zeta (ζ) chain cytoplasmic signaling domain. In some embodiments, the CAR further includes one or more additional regions or domains such as one or more spacer or linker, including an extracellular spacer, such as one derived from an antibody or other cell-surface molecule, such as a spacer containing gone or more of antibody CH2, CH3, and/or hinge regions, or a spacer derived from a CD28 molecule or a CD8 molecule, or other spacer. Also provided

herein are cells, such as T cells engineered to express such CARs, such as those recombinantly expressing such a CAR. A CAR-expressing T cell, upon recognition of a MUC16 expressing tumor, preferably induces T cell activation, proliferation, and/or lysis of a cell of such a tumor.

[00215] MUC16 Glycosylation Antibodies can be of any type (*e.g.*, IgG, IgE, IgM, IgD, IgA or IgY), any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 or IgA_2), or any subclass (*e.g.*, IgG_{2a} or IgG_{2b}) of immunoglobulin molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class or subclass thereof. In certain embodiments, antibodies described herein are IgG_1 antibodies. In certain embodiments, antibodies described herein are IgG_2 antibodies. In certain embodiments, antibodies described herein are IgG_{2a} antibodies. In certain embodiments, antibodies described herein are IgG_{2b} antibodies. In certain embodiments, antibodies described herein are a mixture of IgG_{2a} and IgG_{2b} antibodies. In a specific embodiment, the antibody is a humanized form of a rodent monoclonal antibody.

[00216] In a specific embodiment, the antigen to which the MUC16 Glycosylation Antibody or antigen-binding fragment thereof binds, is a form of MUC16 which is glycosylated, for example, wherein the amino acid sequence of the form of MUC16 is SEQ ID NO:133. The protein encoded by the amino acid sequence of SEQ ID NO:133 is also referred to herein as $MUC16^{c114}$ and consists of the C-terminal 114 amino acid residues of mature MUC16. $MUC16^{c114}$ is capable of being *N*-glycosylated at the asparagine amino acids of positions 1, 24, and 30 of SEQ ID NO: 133 (corresponding to amino acid positions Asn1777, Asn1800, and Asn1806 of SEQ ID NO: 150). Mature MUC16 (SEQ ID NO:150) refers to full length MUC16 wherein the signal sequence has been removed, and wherein the signal sequence consists of the first 60 amino acid residues of SEQ ID NO:136 (*i.e.*, SEQ ID NO:136 is the "immature" form of MUC16).

[00217] Antigen binding fragments of MUC16 Glycosylation Antibodies can be Fab fragments, $F(ab')_2$ fragments, or a portion of MUC16 Glycosylation Antibody which comprises the amino acid residues that confer on the MUC16 Glycosylation Antibody its specificity for the antigen (*e.g.*, the complementarity determining regions (CDR)). The MUC16 Glycosylation Antibody can be derived from any animal species, such as rodents (*e.g.*, mouse, rat or hamster) and humans.

[00218] As used herein, the terms "variable region" or "variable domain" are used interchangeably and are common in the art. The variable region typically refers to a portion of

an antibody, generally, a portion of a light or heavy chain, typically about the amino-terminal 110 to 120 amino acids in a mature heavy chain and about the amino-terminal 90 to 100 amino acids in a mature light chain, which differs extensively in sequence among antibodies and is used in the binding and specificity of a particular antibody for its particular antigen. The variability in sequence is concentrated in those regions called complementarity determining regions (CDRs) while the more highly conserved regions in the variable domain are called framework regions (FR). CDRs are flanked by FRs. Generally, the spatial orientation of CDRs and FRs are as follows, in an N-terminal to C-terminal direction: FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4. Without wishing to be bound by any particular mechanism or theory, it is believed that the CDRs of the light and heavy chains are primarily responsible for the interaction and specificity of the antibody with antigen. In certain embodiments, the variable region is a rodent (*e.g.,* mouse or rat) variable region. In certain embodiments, the variable region is a human variable region. In certain embodiments, the variable region comprises rodent (*e.g.,* mouse or rat) CDRs and human framework regions (FRs). In particular embodiments, the variable region is a primate (*e.g.,* non-human primate) variable region. In certain embodiments, the variable region comprises rodent or murine CDRs and primate (*e.g.,* non-human primate) framework regions (FRs).

[00219] CDRs are defined in various ways in the art, including the Kabat, Chothia, and IMGT, and Exemplary definitions. The Kabat definition is based on sequence variability (Kabat, Elvin A. *et al.*, Sequences of Proteins of Immunological Interest. Bethesda: National Institutes of Health, 1983). With respect to the Kabat numbering system, (i) the VH CDR1 is typically present at amino acid positions 31 to 35 of the heavy chain, which can optionally include one or two additional amino acids following amino acid position 35 (referred to in the Kabat numbering scheme as 35A and 35B); (ii) the VH CDR2 is typically present at amino acid positions 50 to 65 of the heavy chain; and (iii) the VH CDR2 is typically present at amino acid positions 95 to 102 of the heavy chain (Kabat, Elvin A. *et al.*, Sequences of Proteins of Immunological Interest. Bethesda: National Institutes of Health, 1983). With respect to the Kabat numbering system, (i) the VL CDR1 is typically present at amino acid positions 24 to 34 of the light chain; (ii) the VL CDR2 is typically present at amino acid positions 50 to 56 of the light chain; and (iii) the VL CDR3 is typically present at amino acid positions 89 to 97 of the light chain (Kabat, Elvin A. *et al.*, Sequences of Proteins of Immunological Interest. Bethesda: National Institutes of Health, 1983). As is well known to those of skill in the art, using the Kabat numbering system, the

actual linear amino acid sequence of the antibody variable domain can contain fewer or additional amino acids due to a shortening or lengthening of a FR and/or CDR and, as such, an amino acid's Kabat number is not necessarily the same as its linear amino acid number.

[00220] The Chothia definition is based on the location of the structural loop regions (Chothia *et al.*, (1987) J Mol Biol 196: 901-917; and U.S. Patent No. 7,709,226). The term "Chothia CDRs," and like terms are recognized in the art and refer to antibody CDR sequences as determined according to the method of Chothia and Lesk, 1987, J. Mol. Biol., 196:901-917, which will be referred to herein as the "Chothia CDRs" (see also, *e.g.,* U.S. Patent No. 7,709,226 and Martin, A., "Protein Sequence and Structure Analysis of Antibody Variable Domains," in Antibody Engineering, Kontermann and Dübel, eds., Chapter 31, pp. 422-439, Springer-Verlag, Berlin (2001)). With respect to the Chothia numbering system, using the Kabat numbering system of numbering amino acid residues in the VH region, (i) the VH CDR1 is typically present at amino acid positions 26 to 32 of the heavy chain; (ii) the VH CDR2 is typically present at amino acid positions 53 to 55 of the heavy chain; and (iii) the VH CDR3 is typically present at amino acid positions 96 to 101 of the heavy chain. In a specific embodiment, with respect to the Chothia numbering system, using the Kabat numbering system of numbering amino acid residues in the VH region, (i) the VH CDR1 is typically present at amino acid positions 26 to 32 or 34 of the heavy chain; (ii) the VH CDR2 is typically present at amino acid positions 52 to 56 (in one embodiment, CDR2 is at positions 52A-56, wherein 52A follows position 52) of the heavy chain; and (iii) the VH CDR3 is typically present at amino acid positions 95 to 102 of the heavy chain (in one embodiment, there is no amino acid at positions numbered 96-100). With respect to the Chothia numbering system, using the Kabat numbering system of numbering amino acid residues in the VL region, (i) the VL CDR1 is typically present at amino acid positions 26 to 33 of the light chain; (ii) the VL CDR2 is typically present at amino acid positions 50 to 52 of the light chain; and (iii) the VL CDR3 is typically present at amino acid positions 91 to 96 of the light chain. In a specific embodiment, with respect to the Chothia numbering system, using the Kabat numbering system of numbering amino acid residues in the VL region, (i) the VL CDR1 is typically present at amino acid positions 24 to 34 of the light chain; (ii) the VL CDR2 is typically present at amino acid positions 50 to 56 of the light chain; and (iii) the VL CDR3 is typically present at amino acid positions 89 to 97 of the light chain (in one embodiment, there is no amino acid at positions numbered 96-100). These Chothia CDR

positions may vary depending on the antibody, and may be determined according to methods known in the art.

[00221] The IMGT definition is from the IMGT ("IMGT®, the international ImMunoGeneTics information system® website imgt.org, founder and director: Marie-Paule Lefranc, Montpellier, France; *see*, *e.g.,* Lefranc, M.-P., 1999, The Immunologist, 7:132-136 and Lefranc, M.-P. et al., 1999, Nucleic Acids Res., 27:209-212, both of which are incorporated herein by reference in their entirety). With respect to the IMGT numbering system, (i) the VH CDR1 is typically present at amino acid positions 25 to 35 of the heavy chain; (ii) the VH CDR2 is typically present at amino acid positions 51 to 57 of the heavy chain; and (iii) the VH CDR2 is typically present at amino acid positions 93 to 102 of the heavy chain. With respect to the IMGT numbering system, (i) the VL CDR1 is typically present at amino acid positions 27 to 32 of the light chain; (ii) the VL CDR2 is typically present at amino acid positions 50 to 52 of the light chain; and (iii) the VL CDR3 is typically present at amino acid positions 89 to 97 of the light chain.

5.1.1 SEQUENCES AND STRUCTURES

[00222] In certain embodiments, provided herein is a MUC16 Glycosylation Antibody or antigen-binding fragment thereof which comprises VH CDRs of any of the MUC16 Glycosylation Antibodies provided herein, *e.g.,* as set forth in Tables 1, 3, and 5. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein comprises the VH CDR1 of a MUC16 Glycosylation Antibody as set forth in Table 1, 3, or 5. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein comprises the VH CDR2 of a MUC16 Glycosylation Antibody as set forth in Table 1, 3, or 5. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein comprises the VH CDR3 of a MUC16 Glycosylation Antibody as set forth in Table 1, 3, or 5. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein comprises one, two or all three of VH CDRs of a MUC16 Glycosylation Antibody as set forth in Table 1, 3, or 5 (*e.g.,* the VL CDRs in row two of Table 1, *e.g.,* all of the VH CDRs for antibody 10C6)

[00223] In certain embodiments, provided herein is a MUC16 Glycosylation Antibody or antigen-binding fragment thereof which comprises VL CDRs of any of the anti-MUC16 antibodies provided herein, *e.g.,* as set forth in Tables 2, 4, and 6. In certain embodiments, a

MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein comprises the VH CDR1 of a MUC16 Glycosylation Antibody as set forth in Table 2, 4, or 6. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein comprises the VH CDR2 of a MUC16 Glycosylation Antibody as set forth in Table 2, 4, or 6. In certain embodiments, an anti-MUC16 antibody or antigen-binding fragment thereof provided herein comprises the VH CDR3 of a MUC16 Glycosylation Antibody as set forth in Table 2, 4, or 6. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein comprises one, two or all three of VL CDRs of a MUC16 Glycosylation Antibody in Table 2, 4, or 6 (*e.g.*, the VL CDRs in row two of Table 2, *e.g.*, all of the VH CDRs for antibody 10C6)

[00224] **Table 1.** VH CDR Amino Acid Sequences (Kabat).

Antibody	**VH CDR1 (SEQ ID NO)**	**VH CDR2 (SEQ ID NO)**	**VH CDR3 (SEQ ID NO)**
10C6	TLGMGVG (SEQ ID NO:3)	HIWWDDDKYYNPALKS (SEQ ID NO:4)	IGTAQATDALDY (SEQ ID NO:5)
7B12	TVGMGVG (SEQ ID NO:23)	HIWWDDEDKYYNPALKS (SEQ ID NO:24)	IGTAQATDALDY (SEQ ID NO:25)
19C11	TLGMGVG (SEQ ID NO:43)	HIWWDDDKYYNPALKS (SEQ ID NO:44)	IGTAQATDALDY (SEQ ID NO:45)
16C5	TLGMGVG (SEQ ID NO:63)	HIWWDDDKYYYPALKS (SEQ ID NO:64)	IGTAQATDALDY (SEQ ID NO:65)
18C6	TVGMGVG (SEQ ID NO:83)	HIWWDDEDKYYNPALKS (SEQ ID NO:84)	IGTAQATDALDY (SEQ ID NO:85)
10C6, 7B12, 19C11, 16C5, and 18C6 Consensus	TX_1GMGVG (SEQ ID NO:103) wherein X_1 is L or V	HIWWDDX_2DKYYX$_3$PALKS (SEQ ID NO:104) wherein X_2 is E or absent and wherein X_3 is Y or N	IGTAQATDALDY (SEQ ID NO:105)

[00225] **Table 2.** VL CDR Amino Acid Sequences (Kabat).

Antibody	**VL CDR1 (SEQ ID NO)**	**VL CDR2 (SEQ ID NO)**	**VL CDR3 (SEQ ID NO)**
10C6	RASKSVSTSGYSYMH (SEQ ID NO:6)	LVSNLES (SEQ ID NO:7)	QHIRELTRS (SEQ ID NO:8)
7B12	RSSKSLRKSNGNTYL (SEQ ID NO:26)	YMSNLAS (SEQ ID NO:27)	MQSLEYPLT (SEQ ID NO:28)
19C11	RSSKSLLHSNGNTYLY (SEQ ID NO:46)	YMSNLAS (SEQ ID NO:47)	MQGLEHPLT (SEQ ID NO:48)
16C5	LASEDIYSGIS (SEQ ID NO:66)	GASNLES (SEQ ID NO:67)	LGGYSYSSTLT (SEQ ID NO:68)

18C6	RSSKSLLHSNGNTYLY (SEQ ID NO:86)	YMSNLAS (SEQ ID NO:87)	MQSLEYPLT (SEQ ID NO:88)
7B12, 19C11, and 18C6 Consensus	RSSKSLX$_4$X$_5$SNGNTYLY (SEQ ID NO:106) wherein X$_4$ is R or L, and wherein X$_5$ is K or H	YMSNLAS (SEQ ID NO:107)	MQX$_6$LEX$_7$PLT (SEQ ID NO:108) wherein X$_6$ is G or S and wherein X$_7$ is H or Y

[00226] **Table 3.** VH CDR Amino Acid Sequences (Chothia).

Antibody	**VH CDR1 (SEQ ID NO)**	**VH CDR2 (SEQ ID NO)**	**VH CDR3 (SEQ ID NO)**
10C6	GFSLNTLGM (SEQ ID NO:9)	WDD (SEQ ID NO:10)	GTAQATDALD (SEQ ID NO:11)
7B12	GFSLSTVGM (SEQ ID NO:29)	WDDE (SEQ ID NO:30)	GTAQATDALD (SEQ ID NO:31)
19C11	GFSLSTLGM (SEQ ID NO:49)	WDD (SEQ ID NO:50)	GTAQATDALD (SEQ ID NO:51)
16C5	GFSLNTLGM (SEQ ID NO:69)	WDD (SEQ ID NO:70)	GTAQATDALD (SEQ ID NO:71)
18C6	GFSLSTVGM (SEQ ID NO:89)	WDDE (SEQ ID NO:90)	GTAQATDALD (SEQ ID NO:91)
10C6, 7B12, 19C11, 16C5, and 18C6 Consensus	GFSLX$_8$TX$_9$GM (SEQ ID NO:109) wherein X$_8$ is N or S, and wherein X$_9$ is L or V	WDDX$_{10}$ (SEQ ID NO:110) wherein X$_{10}$ is E or absent	GTAQATDALD (SEQ ID NO:111)

[00227] **Table 4.** VL CDR Amino Acid Sequences (Chothia).

Antibody	**VL CDR1 (SEQ ID NO)**	**VL CDR2 (SEQ ID NO)**	**VL CDR3 (SEQ ID NO)**
10C6	SKSVSTSGYSY (SEQ ID NO:12)	LVS (SEQ ID NO:13)	IRELTR (SEQ ID NO:14)
7B12	SKSLRKSNGNTY (SEQ ID NO:32)	YMS (SEQ ID NO:33)	SLEYPL (SEQ ID NO:34)
19C11	SKSLLHSNGNTY (SEQ ID NO:52)	YMS (SEQ ID NO:53)	GLEHPL (SEQ ID NO:54)
16C5	SEDIYSG (SEQ ID NO:72)	GAS (SEQ ID NO:73)	GYSYSSTL (SEQ ID NO:74)
18C6	SKSLLHSNGNTY (SEQ ID NO:92)	YMS (SEQ ID NO:93)	SLEYPL (SEQ ID NO:94)
7B12, 19C11, and 18C6 Consensus	SKSLX$_{11}$X$_{12}$SNGNTY (SEQ ID NO:112)	YMS (SEQ ID NO:113)	X$_{13}$LEX$_{14}$PL (SEQ ID NO:114)

	wherein X_{11} is L or R, and wherein X_{12} is H or K		wherein X_{13} is G or S, and wherein X_{14} is H or Y

[00228] **Table 5.** VH CDR Amino Acid Sequences (IMGT).

Antibody	**VH CDR1 (SEQ ID NO)**	**VH CDR2 (SEQ ID NO)**	**VH CDR3 (SEQ ID NO)**
10C6	GFSLNTLGMG (SEQ ID NO:15)	IWWDDDK (SEQ ID NO:16)	SRIGTAQATDALDY (SEQ ID NO:17)
7B12	GFSLSTVGMG (SEQ ID NO:35)	IWWDDEDK (SEQ ID NO:36)	TRIGTAQATDALDY (SEQ ID NO:37)
19C11	GFSLSTLGMG (SEQ ID NO:55)	IWWDDDK (SEQ ID NO:56)	ARIGTAQATDALDY (SEQ ID NO:57)
16C5	GFSLNTLGMG (SEQ ID NO:75)	IWWDDDK (SEQ ID NO:76)	ARIGTAQATDALDY (SEQ ID NO:77)
18C6	GFSLSTVGMG (SEQ ID NO:95)	IWWDDEDK (SEQ ID NO:96)	TRIGTAQATDALDY (SEQ ID NO:97)
10C6, 7B12, 19C11, 16C5, and 18C6 Consensus	GFSLX_{15}TX_{16}GMG (SEQ ID NO:115) wherein X_{15} is N or S, and wherein X_{16} is V or L	IWWDDX_{17}DK (SEQ ID NO:116) wherein X_{17} is E or absent	X_{18}RIGTAQATDALDY (SEQ ID NO:117) wherein X_{18} is T, A, or S

[00229] **Table 6.** VL CDR Amino Acid Sequences (IMGT).

Antibody	**VL CDR1 (SEQ ID NO)**	**VL CDR2 (SEQ ID NO)**	**VL CDR3 (SEQ ID NO)**
10C6	KSVSTSGYSY (SEQ ID NO:18)	LVS (SEQ ID NO:19)	QHIRELTRS (SEQ ID NO:20)
7B12	KSLRKSNGNTY (SEQ ID NO:38)	YMS (SEQ ID NO:39)	MQSLEYPLT (SEQ ID NO:4)
19C11	KSLLHSNGNTY (SEQ ID NO:58)	YMS (SEQ ID NO:59)	MQGLEHPLT (SEQ ID NO:60)
16C5	EDIYSG (SEQ ID NO:78)	GAS (SEQ ID NO:79)	LGGYSYSSTLT (SEQ ID NO:80)
18C6	KSLLHSNGNTY (SEQ ID NO:98)	YMS (SEQ ID NO:99)	MQSLEYPLT (SEQ ID NO:100)
7B12, 19C11, and 18C6 Consensus	KSL$X_{19}X_{20}$SNGNTY (SEQ ID NO:118) wherein X_{19} is V or L, and wherein X_{20} is H or K	YMS (SEQ ID NO:119)	MQSLEYPLT (SEQ ID NO:120)

[00230] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein, comprises a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V;

(b) a VH CDR2 comprising the amino acid sequence $HIWWDDX_2DKYYX_3PALKS$ (SEQ ID NO:104), wherein X_2 is E or absent, and X_3 is Y or N; and

(c) a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105).

[00231] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence $GFSLX_8TX_9GM$ (SEQ ID NO:109), wherein X_8 is N or S, and X_9 is L or V;

(b) a VH CDR2 comprising the amino acid sequence $WDDX_{10}$ (SEQ ID NO:110), wherein X_{10} is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111).

[00232] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence $GFSLX_{15}TX_{16}GMG$ (SEQ ID NO:115), wherein X_{15} is N or S, and X_{16} is V or L;

(b) a VH CDR2 comprising the amino acid sequence $IWWDDX_{17}DK$ (SEQ ID NO:116), wherein X_{17} is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence $X_{18}RIGTAQATDALDY$ (SEQ ID NO:117), wherein X_{18} is T, A, or S.

[00233] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a VH

CDR3 comprising the amino acid sequence of SEQ ID NO:11. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:16, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17.

[00234] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:25. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:31. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37.

[00235] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:45. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:50, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:51. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:55, a VH CDR2 comprising the

amino acid sequence of SEQ ID NO:56, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:57.

[00236] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:63, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:64, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:65. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:69, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:70, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:71. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:75, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:76, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:77.

[00237] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:97.

[00238] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence $RSSKSLX_4X_5SNGNTYLY$

(SEQ ID NO:106), wherein X_4 is R or L, and X_5 is K or H;

(b) a VL CDR2 comprising the amino acid sequence YMSNLAS (SEQ ID NO:107); and

(c) a VL CDR3 comprising the amino acid sequence MQX_6LEX_7PLT (SEQ ID NO:108), wherein X_6 is G or S, and X_7 is H or Y.

[00239] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence $SKSLX_{11}X_{12}SNGNTY$ (SEQ ID NO:112), wherein X_{11} is L or R, and X_{12} is H or K;

(b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:113); and

(c) a VL CDR3 comprising the amino acid sequence $X_{13}LEX_{14}PL$ (SEQ ID NO:114), wherein X_{13} is G or S, and X_{14} is H or Y.

[00240] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises:

(a) a VL complementarity determining region (CDR)1 comprising the amino acid sequence $KSLX_{19}X_{20}SNGNTY$ (SEQ ID NO:118), wherein X_{19} is V or L, and X_{20} is H or K;

(b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:119); and

(c) a VL CDR3 comprising the amino acid sequence MQSLEYPLT (SEQ ID NO:120).

[00241] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20.

[00242] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:38, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:39, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40.

[00243] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:48. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:52, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:53, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:54. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60.

[00244] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:66, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:67, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:68. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof

described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:72, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:73, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:74. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:80.

[00245] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100.

[00246] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises:

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V;

(b) a VH CDR2 comprising the amino acid sequence $HIWWDDX_2DKYYX_3PALKS$ (SEQ ID NO:104), wherein X_2 is E or absent and wherein X_3 is Y or N; and

(c) a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105); and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence $RSSKSLX_4X_5SNGNTYLY$ (SEQ ID NO:106), wherein X_4 is R or L, and wherein X_5 is K or H;

(b) a VL CDR2 comprising the amino acid sequence YMSNLAS (SEQ ID NO:107); and

(c) a VL CDR3 comprising the amino acid sequence MQX_6LEX_7PLT (SEQ ID NO:108), wherein X_6 is G or S and wherein X_7 is H or Y.

[00247] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence $GFSLX_8TX_9GM$ (SEQ ID NO:109), wherein X_8 is N or S, and wherein X_9 is L or V;

(b) a VH CDR2 comprising the amino acid sequence $WDDX_{10}$ (SEQ ID NO:110), wherein X_{10} is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111); and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence $SKSLX_{11}X_{12}SNGNTY$ (SEQ ID NO:112), wherein X_{11} is L or R, and wherein X_{12} is H or K;

(b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:113); and

(c) a VL CDR3 comprising the amino acid sequence $X_{13}LEX_{14}PL$ (SEQ ID NO:114), wherein X_{13} is G or S, and wherein X_{14} is H or Y.

[00248] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence $GFSLX_{15}TX_{16}GMG$ (SEQ ID NO:115), wherein X_{15} is N or S, and wherein X_{16} is V or L;

(b) a VH CDR2 comprising the amino acid sequence $IWWDDX_{17}DK$ (SEQ ID NO:116), wherein X_{17} is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence $X_{18}RIGTAQATDALDY$ (SEQ ID NO:117), wherein X_{18} is T, A, or S; and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence $KSLX_{19}X_{20}SNGNTY$ (SEQ ID NO:118), wherein X_{19} is V or L, and wherein X_{20} is H or K;

(b) a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:119); and

(c) a VL CDR3 comprising the amino acid sequence MQSLEYPLT (SEQ ID NO:120).

[00249] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises:

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence TX_1GMGVG (SEQ ID NO:103), wherein X_1 is L or V;

(b) a VH CDR2 comprising the amino acid sequence $HIWWDDX_2DKYYX_3PALKS$ (SEQ ID NO:104), wherein X_2 is E or absent and wherein X_3 is Y or N; and

(c) a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105); and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence SEQ ID NO:6;

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7; and

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8.

[00250] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence $GFSLX_8TX_9GM$ (SEQ ID NO:109), wherein X_8 is N or S, and wherein X_9 is L or V;

(b) a VH CDR2 comprising the amino acid sequence $WDDX_{10}$ (SEQ ID NO:110), wherein X_{10} is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111); and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence SEQ ID NO:12;

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13; and

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14.

[00251] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence GFSLX$_{15}$TX$_{16}$GMG (SEQ ID NO:115), wherein X$_{15}$ is N or S, and wherein X$_{16}$ is V or L;

(b) a VH CDR2 comprising the amino acid sequence IWWDDX$_{17}$DK (SEQ ID NO:116), wherein X$_{17}$ is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence X$_{18}$RIGTAQATDALDY (SEQ ID NO:117), wherein X$_{18}$ is T, A, or S; and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence SEQ ID NO:18;

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19; and

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20.

[00252] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence TX$_1$GMGVG (SEQ ID NO:103), wherein X$_1$ is L or V;

(b) a VH CDR2 comprising the amino acid sequence HIWWDDX$_2$DKYYX$_3$PALKS (SEQ ID NO:104), wherein X$_2$ is E or absent and wherein X$_3$ is Y or N; and

(c) a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105); and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence SEQ ID NO:26;

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27; and

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28.

[00253] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises:

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence GFSLX$_8$TX$_9$GM (SEQ ID NO:109), wherein X$_8$ is N or S, and wherein X$_9$ is L or V;

(b) a VH CDR2 comprising the amino acid sequence WDDX$_{10}$ (SEQ ID NO:110), wherein X$_{10}$ is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID

NO:111) ; and

(ii) a VL which comprises:

(a) a VL CDR1 comprising the amino acid sequence SEQ ID NO:32;

(b) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33; and

(c) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34.

[00254] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises:

(i) a VH which comprises:

(a) a VH CDR1 comprising the amino acid sequence GFSLX$_{15}$TX$_{16}$GMG (SEQ ID NO:115), wherein X$_{15}$ is N or S, and wherein X$_{16}$ is V or L;

(b) a VH CDR2 comprising the amino acid sequence IWWDDX$_{17}$DK (SEQ ID NO:116), wherein X$_{17}$ is E or absent; and

(c) a VH CDR3 comprising the amino acid sequence X$_{18}$RIGTAQATDALDY (SEQ ID NO:117), wherein X$_{18}$ is T, A, or S; and

(ii) a VL which comprises:

(d) a VL CDR1 comprising the amino acid sequence SEQ ID NO:38;

(e) a VL CDR2 comprising the amino acid sequence of SEQ ID NO:39; and

(f) a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40.

[00255] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and (b) a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14. In a particular embodiment, a

MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:16, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17; and (b) a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20.

[00256] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:25; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:31; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37; and (b) a VL CDR1 comprising the amino acid sequence of SEQ ID NO:38, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:39, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40.

[00257] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:45; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VL

CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:48. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:50, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:51; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:52, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:53, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:54. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:56, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:57; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60.

[00258] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:63, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:64, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:65; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:66, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:67, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:68. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:69, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:70, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:71; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:72, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:73, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:74. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:75, a VH CDR2 comprising the amino acid sequence of SEQ ID

NO:76, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:77; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:80.

[00259] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94. In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH which comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:97; and (b) a VL which comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100.

[00260] **Table 7.** VH Domain Amino Acid Sequences

Antibody	**VH (SEQ ID NO)**
10C6	QVTLKESGPGILQPSQTLSLTCSFSGFSLNTLGMGVGWIRQPSGKGLEWLA HIWWDDDKYYNPALKSRLTISKDSSKNQVFLKIANVDTADIATYYCSRIGT AQATDALDYWGQGTSVTVSS (SEQ ID NO:1)
7B12	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTVGMGVGWSRQPSGKGLEWLA HIWWDDEDKYYNPALKSRLTISKDTSKNQVFLKIANVDTADSATYYCTRI GTAQATDALDYWGQGTSVTVSS (SEQ ID NO:21)
19C11	QVNLKESGPGKLQPSQTLSLTCSFSGFSLSTLGMGVGWIRQSSGKGLEWL AHIWWDDDKYYNPALKSRLTISRATSKNQVFLKIVNVGTADTATYYCARI

	GTAQATDALDYWGQGTSVTVSS (SEQ ID NO:41)
16C5	QVTLKESGPGILQPSQTLSLTCSFSGFSLNTLGMGVGWIRQPSGKGLEWLA HIWWDDDKYYYPALKSRLTISRDTSKNQVFLKIANVDTADTATYYCARIG TAQATDALDYWGQGTSVTVSS (SEQ ID NO:61)
18C6	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTVGMGVGWSRQPSGKGLEWLA HIWWDDEDKYYNPALKSRLTISKDTSKNQVFLKIANVDTADTATYYCTRI GTAQATDALDYWGQGTSVTVSS (SEQ ID NO:81)
10C6, 7B12, 19C11, 16C5, and 18C6 VH Consensus	QVX_{21}LKESGPGX_{22}LQPSQTLSLTCSFSGFSLX_{23}TX_{24}GMGVGWX_{25}RQX_{26}SG KGLEWLAHIWWDDX_{27}DKYYX_{28}PALKSRLTIS$X_{29}X_{30}X_{31}$SKNQVFLKIX_{32}N VX_{33}TADX34ATYYCX35RIGTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101) wherein X_{21} is T or N, X_{22} is I or K, X_{23} is N or S, X_{24} is V or L, X_{25} is S or I, X_{26} is P or S, X_{27} is E or absent, X_{28} is N or Y, X_{29} is K or R, X_{30} is A or D, X_{31} is T or S, X_{32} is V or A, X_{33} is G or D, X_{34} is T, I, or S, and X_{35} is T, S, or A

[00261] **Table 8.** VL Domain Amino Acid Sequences

Antibody	**VL (SEQ ID NO)**
10C6	DIVLTQSPASLAVSLGQRATISYRASKSVSTSGYSYMHWNQQKPGQPPRLL IYLVSNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHIRELTRSEG GPSWKN (SEQ ID NO:2)
7B12	DIVMTQAAPSVSVTPGESVSISCRSSKSLRKSNGNTYLYWFLQRPGQSPQR LIYYMSNLASGVPDRFSGRGSGTDFTLRISRVEAEDVGVYYCMQSLEYPLT FGGGTKLKIK (SEQ ID NO:22)
19C11	DIVMTQAAPSIPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPQRL IYYMSNLASGVPDRFSGRGSGTDFTLKISRVEAGDVGVYYCMQGLEHPLT FGGGTKLEIK (SEQ ID NO:42)
16C5	ELDMTQTPPSLSASVGETVRIRCLASEDIYSGISWYQQKPGKPPTLLIYGAS NLESGVPPRFSGSGSGTDYTLTIGGVQAEDAATYYCLGGYSYSSTLTFGAG TNVEIK (SEQ ID NO:62)
18C6	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQRPGQSPQR LIYYMSNLASGVPDRFSGRGSGTDFTLRISRVEAEDVGVYYCMQSLEYPLT FGGGTKLEIK (SEQ ID NO:82)
7B12, 19C11, and 18C6 VH Consensus	DIVMTQAAPS$X_{36}X_{37}$VTPGESVSISCRSSKSLX$_{38}$X$_{39}$SNGNTYLYWFLQRPGQ SPQRLIYYMSNLASGVPDRFSGRGSGTDFTLX$_{40}$ISRVEAX$_{41}$DVGVYYCMQ X$_{42}$LEX$_{43}$PLTFGGGTKLEIK (SEQ ID NO:102) wherein X_{36} is I or V, X_{37} is P or S, X_{38} is R or L, X_{39} is K or H, X_{40} is R or K, X_{41} is E or G, X_{42} is S or G, and X_{43} is Y or H

[00262] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH region comprising QVX_{21}LKESGPGX_{22}LQPSQTLSLTCSFSGFSLX_{23}TX_{24}GMGVGWX_{25}RQX_{26}SGKGLEWLAH IWWDDX_{27}DKYYX_{28}PALKSRLTIS$X_{29}X_{30}X_{31}$SKNQVFLKIX_{32}NVX_{33}TADX$_{34}$ATYYCX$_{35}$RI

GTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X_{21} is T or N, X_{22} is I or K, X_{23} is N or S, X_{24} is V or L, X_{25} is S or I, X_{26} is P or S, X_{27} is E or absent, X_{28} is N or Y, X_{29} is K or R, X_{30} is A or D, X_{31} is T or S, X_{32} is V or A, X_{33} is G or D, X_{34} is T, I, or S, and X_{35} is T, S, or A.

[00263] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL region comprising DIVMTQAAPS$X_{36}X_{37}$VTPGESVSISCRSSKSL$X_{38}X_{39}$SNGNTYLYWFLQRPGQSPQRLIYY MSNLASGVPDRFSGRGSGTDFTLX_{40}ISRVEAX_{41}DVGVYYCMQX_{42}LEX_{43}PLTFGGGTKL EIK (SEQ ID NO:102), wherein X_{36} is I or V, X_{37} is P or S, X_{38} is R or L, X_{39} is K or H, X_{40} is R or K, X_{41} is E or G, X_{42} is S or G, and X_{43} is Y or H.

[00264] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises

(a) VH region comprising QVX_{21}LKESGPGX_{22}LQPSQTLSLTCSFSGFSLX_{23}TX_{24}GMGVGWX_{25}RQX_{26}SGK GLEWLAHIWWDDX_{27}DKYYX_{28}PALKSRLTIS$X_{29}X_{30}X_{31}$SKNQVFLKIX_{32}NVX_{33} TADX_{34}ATYYCX_{35}RIGTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X_{21} is T or N, X_{22} is I or K, X_{23} is N or S, X_{24} is V or L, X_{25} is S or I, X_{26} is P or S, X_{27} is E or absent, X_{28} is N or Y, X_{29} is K or R, X_{30} is A or D, X_{31} is T or S, X_{32} is V or A, X_{33} is G or D, X_{34} is T, I, or S, and X_{35} is T, S, or A; and

(b) a VL region comprising DIVMTQAAPS$X_{36}X_{37}$VTPGESVSISCRSSKSL$X_{38}X_{39}$SNGNTYLYWFLQRPGQSP QRLIYYMSNLASGVPDRFSGRGSGTDFTLX_{40}ISRVEAX_{41}DVGVYYCMQX_{42}LE X_{43}PLTFGGGTKLEIK (SEQ ID NO:102), wherein X_{36} is I or V, X_{37} is P or S, X_{38} is R or L, X_{39} is K or H, X_{40} is R or K, X_{41} is E or G, X_{42} is S or G, and X_{43} is Y or H.

[00265] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises

(a) VH region comprising QVX_{21}LKESGPGX_{22}LQPSQTLSLTCSFSGFSLX_{23}TX_{24}GMGVGWX_{25}RQX_{26}SGK GLEWLAHIWWDDX_{27}DKYYX_{28}PALKSRLTIS$X_{29}X_{30}X_{31}$SKNQVFLKIX_{32}NVX_{33} TADX_{34}ATYYCX_{35}RIGTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X_{21} is T or N, X_{22} is I or K, X_{23} is N or S, X_{24} is V or L, X_{25} is S or I, X_{26} is P

or S, X_{27} is E or absent, X_{28} is N or Y, X_{29} is K or R, X_{30} is A or D, X_{31} is T or S, X_{32} is V or A, X_{33} is G or D, X_{34} is T, I, or S, and X_{35} is T, S, or A; and

(b) a VL region comprising the amino acid sequence of SEQ ID NO:2.

[00266] In a particular embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises

(a) VH region comprising

QVX_{21}LKESGPGX_{22}LQPSQTLSLTCSFSGFSLX_{23}TX_{24}GMGVGWX_{25}RQX_{26}SGK GLEWLAHIWWDDX_{27}DKYYX_{28}PALKSRLTIS$X_{29}X_{30}X_{31}$SKNQVFLKIX_{32}NVX_{33} TADX_{34}ATYYCX_{35}RIGTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X_{21} is T or N, X_{22} is I or K, X_{23} is N or S, X_{24} is V or L, X_{25} is S or I, X_{26} is P or S, X_{27} is E or absent, X_{28} is N or Y, X_{29} is K or R, X_{30} is A or D, X_{31} is T or S, X_{32} is V or A, X_{33} is G or D, X_{34} is T, I, or S, and X_{35} is T, S, or A; and

(b) a VL region comprising the amino acid sequence of SEQ ID NO:62.

[00267] In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH comprising an amino acid sequence as set forth in Table 7. In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:1 (Table 7) (*e.g.*, the VH of antibody 10C6). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:21 (Table 7) (*e.g.*, the VH of antibody 7B12). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:41 (Table 7) (*e.g.*, the VH of antibody 19C11). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:61 (Table 7) (*e.g.*, the VH of antibody 16C5). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:81 (Table 7) (*e.g.*, the VH of antibody 18C6).

[00268] In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VL comprising an amino acid sequence as set forth in Table 8. In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:2 (Table 8) (*e.g.*, the VL of antibody 10C6). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:22 (Table 8) (*e.g.*, the VL of antibody 7B12). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:42 (Table 8) (*e.g.*, the VL of antibody 19C11). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:62 (Table 8) (*e.g.*, the VL of antibody 16C5). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:82 (Table 8) (*e.g.*, the VL of antibody 18C6).

[00269] In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a VH comprising an amino acid sequence as set forth in Table 7; and (b) a VL comprising an amino acid sequence as set forth in Table 8. In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:1 (Table 7) (*e.g.*, the VH of antibody 10C6); and (b) a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:2 (Table 8) (*e.g.*, the VL of antibody 10C6). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:21 (Table 7) (*e.g.*, the VH of antibody 7B12); and (b) a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:22 (Table 8) (*e.g.*, the VL of antibody 7B12). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a heavy chain variable region sequence comprising the amino acid sequence

of SEQ ID NO:41 (Table 7) (*e.g.*, the VH of antibody 19C11); and (b) a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:42 (Table 8) (*e.g.*, the VL of antibody 19C11). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:61 (Table 7) (*e.g.*, the VH of antibody 16C5); and (b) a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:62 (Table 8) (*e.g.*, the VL of antibody 16C5). In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises (a) a heavy chain variable region sequence comprising the amino acid sequence of SEQ ID NO:81 (Table 7) (*e.g.*, the VH of antibody 18C6); and (b) a light chain variable region sequence comprising the amino acid sequence of SEQ ID NO:82 (Table 8) (*e.g.*, the VL of antibody 18C6).

[00270] In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises VH CDRs (*e.g.*, as set forth in Table 1, 3, or 5) of a VH comprising the amino acid sequence as set forth in Table 7 and VL CDRs (*e.g.*, as set forth in Table 2, 4, or 6) of a VL comprising the amino acid sequence as set forth in Table 8.

[00271] In certain embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein may be described by its VH domain alone, or its VL domain alone, or by its three VH CDRs alone, or by its three VL CDRs alone. *See*, *e.g.*, Rader C *et al.*, (1998) PNAS 95: 8910-8915, which is incorporated herein by reference in its entirety, which describes the humanization of the mouse anti-αvβ3 antibody by identifying a complementing light chain or heavy chain, respectively, from a human light chain or heavy chain library, resulting in humanized antibody variants having affinities as high or higher than the affinity of the original antibody. See also, Clackson T *et al.*, (1991) Nature 352: 624-628, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VH domain (or VL domain) and screening a library for the complementary variable domains. See also, Kim SJ & Hong HJ, (2007) J Microbiol 45: 572-577, which is incorporated herein by reference in its entirety, describing methods of producing antibodies that bind a specific antigen by using a specific VH domain and screening a library (*e.g.*, human VL library) for complementary VL domains; the selected VL domains in turn could be used to guide selection of additional complementary (*e.g.*, human) VH domains.

[00272] In certain embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein may be a humanized antibody, for example, a humanized form of a rodent antibody. Humanized antibodies can be produced using a variety of techniques known in the art, including but not limited to, CDR-grafting (European Patent No. EP 239,400; International publication No. WO 91/09967; and U.S. Patent Nos. 5,225,539, 5,530,101, and 5,585,089), chain shuffling (U.S. Patent No. 5,565,332), veneering or resurfacing (European Patent Nos. EP 592,106 and EP 519,596; Padlan, 1991, Molecular Immunology 28(4/5):489-498; Studnicka *et al.*, 1994, Protein Engineering 7(6):805-814; and Roguska *et al.*, 1994, PNAS 91:969-973), and techniques disclosed in, *e.g.,* U.S. Pat. No. 6,407,213, U.S. Pat. No. 5,766,886, WO 9317105, Sandhu JS, Gene 150(2):409-10 (1994), Pedersen *et al.*, J. Mol. Biol. 235(3):959-73 (1994), Couto *et al.*, Cancer Res. 55(8):1717-22 (1995), Roguska *et al.*, Protein Eng. 9(10):895 904 (1996), Baca *et al.*, J. Biol. Chem. 272(16):10678-84 (1997), Couto *et al.*, Cancer Res. 55 (23 Supp):5973s- 5977s (1995), Caldas *et al.*, Protein Eng. 13(5):353-60 (2000), Morea *et al.*, Methods 20(3):267 79 (2000), and Tan *et al.*, J. Immunol. 169:1119 25 (2002). *See* also U.S. Patent Pub. No. US 2005/0042664 A1 (Feb. 24, 2005), each of which is incorporated by reference herein in its entirety.

[00273] In certain embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein may be a composite human antibody. A composite human antibody can be generated by, *e.g.,* designing variable region sequences from fragments of multiple human antibody variable region sequences in a manner that avoids T cell epitopes, thereby minimizing the immunogenicity of the resulting antibody (see, *e.g.,* Baker *et al.*, 2010, Self Nonself., 1(4):314-322; Bryson *et al.*, 2010, BioDrugs, 24(1):1-8; and Jones *et al.*, 2009, Methods Mol Biol., 525:405-23). Such antibodies can comprise human constant region sequences, *e.g.,* human light chain and/or heavy chain constant regions.

[00274] In certain embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein may be a deimmunized antibody. A deimmunized antibody is an antibody in which T-cell epitopes have been removed. Methods for making deimmunized antibodies have been described. *See*, *e.g.,* Jones *et al.,* Methods Mol Biol. 2009;525:405-23, xiv, and De Groot *et al.*, Cell. Immunol. 244:148-153(2006)).

[00275] In specific embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein is a humanized immunoglobulin that comprises the 3 VH

CDRs and the 3 VL CDRs (*i.e.*, VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and VL CDR3) of any of the antibodies in Table 1, Table 2, and Table 3, and Table 4, Table 5, and Table 6, respectively, human-derived framework regions, and human derived constant regions. Non-limiting examples of human framework regions are described in the art, *e.g.,* see Kabat *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242). In certain embodiment, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein comprises framework regions (*e.g.,* framework regions of the VL domain and/or VH domain) that are human framework regions or derived from human framework regions. In certain embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein comprises framework regions (*e.g.,* framework regions of the VL domain and/or VH domain) that are primate (*e.g.,* non-human primate) framework regions or derived from primate (*e.g.,* non-human primate) framework regions. For example, CDRs from antigen-specific non-human antibodies, typically of rodent origin (*e.g.,* mouse or rat), are grafted onto homologous human or non-human primate (*e.g.,* Old World apes, *e.g.,* Pan troglodytes, Pan paniscus or Gorilla gorilla, Pan troglodytes, Old World monkeys, *e.g.,* from the genus Macaca, or the cynomolgus monkey Macaca cynomolgus). Non-human primate framework sequences are described in U.S. Patent Application Publication No. US 2005/0208625.

[00276] In a specific embodiment, the position of VH CDR1, VH CDR2, and/or VH CDR3 in the VH region and/or the position of VL CDR1, VL CDR2, and/or VL CDR2 in the VL region of a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein may vary by 1, 2, 3, 4, 5, 6, or more amino acid positions so long as (i) immunospecific binding to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133 is maintained; (ii) lack of immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139 is maintained; and (iii) inhibition of matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16 is maintained (*e.g.,* substantially maintained, *e.g.,* at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In another embodiment, the length of VH CDR1, VH CDR2, and/or VH CDR3 in the VH region and/or the length of VL CDR1, VL CDR2, and/or VL CDR2 in the VL region of a MUC16 Glycosylation

Antibody or antigen binding fragment thereof described herein may vary (*e.g.,* be shorter or longer) by 1, 2, 3, 4, 5, 6, or more amino acids, so long as (i) immunospecific binding to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133 is maintained; (ii) lack of immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139 is maintained; and (iii) inhibition of matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16 is maintained (*e.g.,* substantially maintained, *e.g.,* at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). In another embodiment, the amino terminus and/or the carboxy terminus of a VH CDR1, VH CDR2, VH CDR3, VL CDR1, VL CDR2, and/or VL CDR3 described herein may be extended or shortened by 1, 2, 3, 4, 5, 6, or more amino acids compared to one or more of the CDRs described herein so long as (i) immunospecific binding to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133 is maintained; (ii) lack of immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139 is maintained; and (iii) inhibition of matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16 is maintained (*e.g.,* substantially maintained, *e.g.,* at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%). As used herein, the terms "immunospecifically binds," "immunospecifically recognizes," "specifically binds," and "specifically recognizes" are analogous terms in the context of antibodies and refer to antibodies and antigen-binding fragments thereof that bind to an antigen (*e.g.,* epitope or immune complex) via the antigen-binding sites as understood by one skilled in the art, and does not exclude cross-reactivity of the antibody or antigen-binding fragment with other antigens. Any method known in the art can be used to ascertain whether (i) immunospecific binding to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133 is maintained; (ii) lack of immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139 is maintained; and (iii) inhibition of matrigel invasion *in*

vitro of cells recombinantly expressing said first form of MUC16 is maintained, *e.g.,* ELISA binding assays or FACs analysis as described in Section 6, below.

[00277] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprising an antibody heavy chain and/or light chain, *e.g.,* a heavy chain alone, a light chain alone, or both a heavy chain and a light chain. With respect to the heavy chain, in a specific embodiment, the heavy chain of a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein can be an alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain. In another specific embodiment, the heavy chain of a MUC16 Glycosylation Antibody or antigen binding fragment thereof described can comprise a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain.

[00278] In a particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein, which (i) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and (iii) inhibits matrigel invasion *in vitro* of cells recombinantly expressing said first form of MUC16, comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy chain comprises a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO:103, SEQ ID NO:104, and SEQ ID NO:105, respectively, SEQ ID NO:109, SEQ ID NO:110, and SEQ ID NO:111, respectively, or SEQ ID NO:115, SEQ ID NO:116, and SEQ ID NO:117, respectively, and wherein the constant region of the heavy chain is a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain constant region. As used herein, the term "constant region" or "constant domain" is interchangeable and has its meaning common in the art. The constant region is an antibody portion, *e.g.,* a carboxyl terminal portion of a light and/or heavy chain which is not directly involved in binding of an antibody to antigen but which can exhibit various effector functions, such as interaction with the Fc receptor. The constant region of an immunoglobulin molecule generally has a more conserved amino acid sequence relative to an immunoglobulin variable domain. In a particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy chain comprises a VH

CDR1, VH CDR2, and VH CDR3 of antibody 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.*, those listed in Table 1, Table 3, or Table 5) and wherein the constant region of the heavy chain is a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain constant region.

[00279] In another particular embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy chain comprises the amino acid sequence of SEQ ID NO:101, and wherein the constant region of the heavy chain is a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain constant region. In another particular embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy chain comprises the amino acid sequence of SEQ ID NO:1, SEQ ID NO:21, SEQ ID NO:41, SEQ ID NO:61, or SEQ ID NO:81, and wherein the constant region of the heavy chain is a human alpha (α), delta (δ), epsilon (ε), gamma (γ) or mu (μ) heavy chain constant region.

[00280] In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy chain comprises a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO:103, SEQ ID NO:104, and SEQ ID NO:105, respectively, or SEQ ID NO:109, SEQ ID NO:110; or SEQ ID NO:111, respectively, or SEQ ID NO:115, SEQ ID NO:116, or SEQ ID NO:117, respectively, and wherein the constant region of the heavy chain is a human heavy chain constant region. In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy chain comprises a VH CDR1, VH CDR2, and VH CDR3 of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 VH CDRs (*i.e.*, those listed in Table 1, Table 3, and Table 5), and wherein the constant region of the heavy chain is a human heavy chain constant region. In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy chain comprises the amino acid sequence of SEQ ID NO:101, and wherein the constant region of the heavy chain is a human heavy chain constant region. In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain wherein the amino acid sequence of the variable region of the heavy

chain comprises the amino acid sequence of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 VH CDRs (*i.e.*, those listed in Table 7), and wherein the constant region of the heavy chain is a human heavy chain constant region. Non-limiting examples of human constant region sequences have been described in the art, *e.g.,* see Kabat EA *et al.,* (1991) *supra.*

[00281] With respect to the light chain, in a specific embodiment, the light chain of a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein is a kappa light chain. In another specific embodiment, the light chain of a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein is a lambda light chain. In yet another specific embodiment, the light chain of a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein is a human kappa light chain or a human lambda light chain.

[00282] In a particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of antibody SEQ ID NO:106, SEQ ID NO:107, and SEQ ID NO:108, respectively, or SEQ ID NO:112, SEQ ID NO:113, and SEQ ID NO:114, respectively, or SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120, respectively, and wherein the constant region of the light chain is a kappa or lambda light chain constant region. In a particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises a VL CDR1, VL CDR2, and VL CDR3 of antibody 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.*, those listed in Table 2, Table 4, or Table 6) and wherein the constant region of the light chain is a kappa or lambda light chain constant region.

[00283] In another particular embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises the amino acid sequence of SEQ ID NO:102, and wherein the constant region of the light chain is a kappa or lambda light chain constant region. In another particular embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises the amino acid sequence of SEQ ID NO:2, SEQ ID NO:22, SEQ ID NO:42, SEQ ID NO:62, or SEQ ID NO:82, and wherein the constant region of the light chain is a kappa or lambda light chain constant region.

[00284] In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO:106, SEQ ID NO:107, and SEQ ID NO:108, respectively, or SEQ ID NO:112, SEQ ID NO:113, and SEQ ID NO:114, respectively, or SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120, respectively, and wherein the constant region of the light chain comprises the amino acid of a human light chain constant region. In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 VL CDRs (*i.e.*, those listed in Table 2, Table 4, and Table 6), and wherein the constant region of the light chain is a human light chain constant region. In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises the amino acid sequence of SEQ ID NO:102, and wherein the constant region of the light chain is a human light chain constant region. In a specific embodiment, a MUC16 Glycosylated Antibody or an antigen-binding fragment thereof described herein comprises a light chain wherein the amino acid sequence of the variable region of the light chain comprises the amino acid sequence of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 VL CDRs (*i.e.*, those listed in Table 8), and wherein the constant region of the light chain is a human light chain constant region. Non-limiting examples of human constant region sequences have been described in the art, *e.g.,* see Kabat EA *et al.,* (1991) *supra.*

[00285] In a specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a heavy chain variable region (VH) and a light chain variable region (VL) as described herein, and wherein the constant regions are of the type found in an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, or a human IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule. In another specific embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein comprises a VH and a VL comprising any amino acid sequences described herein, and wherein the constant regions are of the type found in an IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule,

any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 and IgA_2), or any subclass (*e.g.*, IgG_{2a} and IgG_{2b}) of immunoglobulin molecule. In a particular embodiment, the constant regions are of the type found in a human IgG, IgE, IgM, IgD, IgA or IgY immunoglobulin molecule, any class (*e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1 and IgA_2), or any subclass (*e.g.*, IgG_{2a} and IgG_{2b}) of immunoglobulin molecule.

[00286] In another particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain and/or a light chain, wherein (i) the heavy chain comprises (a) a variable region comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of SEQ ID NO:103, SEQ ID NO:104, and SEQ ID NO:105, respectively, SEQ ID NO:109, SEQ ID NO:110, and SEQ ID NO:111, respectively, or SEQ ID NO:115, SEQ ID NO:116, and SEQ ID NO:117, respectively, and (b) comprises a constant heavy chain domain which is the constant domain of a human IgG heavy chain; and/or (ii) the light chain comprises (a) a variable region comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of SEQ ID NO:106, SEQ ID NO:107, and SEQ ID NO:108, respectively, or SEQ ID NO:112, SEQ ID NO:113, and SEQ ID NO:114, respectively, or SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120, respectively, and (b) a constant light chain domain which is the constant domain of a human IgG. In another particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain and/or a light chain, wherein (i) the heavy chain comprises (a) a variable region comprising a VH CDR1, VH CDR2, and VH CDR3 having the amino acid sequences of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 VH CDRs (*i.e.*, those listed in Table 1, Table 3, and Table 5), and (b) comprises a constant heavy chain domain which is the constant domain of a human IgG heavy chain; and/or (ii) the light chain comprises (a) a variable region comprising a VL CDR1, VL CDR2, and VL CDR3 having the amino acid sequences of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 VL CDRs (*i.e.*, those listed in Table 2, Table 4, and Table 6), and (b) a constant light chain domain which is the constant domain of a human IgG.

[00287] In another particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain and/or a light chain, wherein (i) the heavy chain comprises (a) a variable region comprising the amino acid sequence of SEQ ID NO:101, and (b) a constant heavy chain domain which is the constant domain of a human

IgG; and/or (ii) the light chain comprises (a) a variable region comprising the amino acid sequence of SEQ ID NO:102, and (b) a constant light chain domain is the constant domain of a human kappa light chain. In another particular embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein comprises a heavy chain and/or a light chain, wherein (i) the heavy chain comprises (a) a variable region comprising the amino acid sequence of the VH of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.*, those listed in Table 7), and (b) a constant heavy chain domain which is the constant domain of a human IgG; and/or (ii) the light chain comprises (a) a variable region comprising the amino acid sequence of the VL of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.*, those listed in Table 8), and (b) a constant light chain domain is the constant domain of a human kappa light chain.

[00288] In certain embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein or an antigen-binding fragment thereof comprises amino acid sequences with the percent identity described below relative to any one of SEQ ID NOs:1-100. Mathematical algorithms can be utilized to determine percent identity between two sequences (*e.g.,* amino acid sequences or nucleic acid sequences). A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul, 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2264 2268, modified as in Karlin and Altschul, 1993, Proc. Natl. Acad. Sci. U.S.A. 90:5873 5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.*, 1990, J. Mol. Biol. 215:403. BLAST nucleotide searches can be performed with the NBLAST nucleotide program parameters set, *e.g.,* for score=100, wordlength=12 to obtain nucleotide sequences homologous to a nucleic acid molecules described herein. BLAST protein searches can be performed with the XBLAST program parameters set, *e.g.,* to score 50, wordlength=3 to obtain amino acid sequences homologous to a protein molecule described herein. Gapped BLAST can be utilized as described in Altschul *et al.*, 1997, Nucleic Acids Res. 25:3389 3402, to obtain gapped alignments for comparison purposes. Alternatively, an iterated search which detects distant relationships between molecules can be performed by PSI BLAST (*Id.*). The default parameters of the respective programs (*e.g.,* of XBLAST and NBLAST) can be used (see, *e.g.,* National Center for Biotechnology Information (NCBI) on the worldwide web, ncbi.nlm.nih.gov) when utilizing BLAST, Gapped BLAST, and PSI Blast programs. Another preferred, non limiting

example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, 1988, CABIOS 4:11 17. Such an algorithm is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Moreover, the percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. Typically only exact matches are counted when calculating percent identity.

[00289] In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VH having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:101. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VH having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 1B5 (*i.e.,* those listed in Table 7). In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:101, wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.,* VH CDRs and/or VL CDRs) that are identical to the CDRs (*e.g.,* VH CDRs and/or VL CDRs) set forth in Table 1, Table 2, Table 3, Table 4, Table 5, or Table 6. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.,* those listed in Table 7), wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.,* VH CDRs and/or VL CDRs) that are identical to the CDRs (*e.g.,* VH CDRs and/or VL CDRs) set forth in Table 1, Table 2, Table 3, Table 4, Table 5, or Table 6.

[00290] In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VL having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:102. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises

a VL having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 1B5 (*i.e.,* those listed in Table 8). In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:102, wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.,* VH CDRs and/or VL CDRs) that are identical to the CDRs (*e.g.,* VH CDRs and/or VL CDRs) set forth in Table 1, Table 2, Table 3, Table 4, Table 5, or Table 6. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.,* those listed in Table 7), wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.,* VH CDRs and/or VL CDRs) that are identical to the CDRs (*e.g.,* VH CDRs and/or VL CDRs) set forth in Table 1, Table 2, Table 3, Table 4, Table 5, or Table 6.

[00291] In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises: (i) a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:101; and (ii) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:102. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises: (i) a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.,* those listed in Table 8); and (ii) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.,* those listed in Table 7), respectively. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises: (i) a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:101; and (ii) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of SEQ ID NO:102, wherein the antibody or

antigen-binding fragment comprises CDRs (*e.g.,* VH CDRs and/or VL CDRs) that are identical to the CDRs (*e.g.,* VH CDRs and/or VL CDRs) set forth in Table 1, Table 2, Table 3, Table 4, Table 5, or Table 6. In certain embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof comprises: (i) a VH domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VH of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.,* those listed in Table 8); and (ii) a VL domain having at least 80%, at least 85%, at least 90%, at least 95%, or at least 98% sequence identity to the amino acid sequence of the VL of any one of antibodies 10C6, 7B12, 19C11, 16C5, or 18C6 (*i.e.,* those listed in Table 7), respectively, wherein the antibody or antigen-binding fragment comprises CDRs (*e.g.,* VH CDRs and/or VL CDRs) that are identical to the CDRs (*e.g.,* VH CDRs and/or VL CDRs) set forth in Table 1, Table 2, Table 3, Table 4, Table 5, or Table 6.

[00292] In another aspect, provided herein are antibodies that bind the same or an overlapping epitope of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*e.g.,* 10C6, 7B12, 19C11, 16C5, and/or 16C5). As used herein, an "epitope" is a term in the art and can refer to a localized region of an antigen to which an antibody can immunospecifically bind. An epitope can be, *e.g.,* contiguous amino acids of a polypeptide (linear or contiguous epitope) or an epitope can, *e.g.,* come together from two or more non-contiguous regions of a polypeptide or polypeptides (conformational, non-linear, discontinuous, or non-contiguous epitope). In certain embodiments, the epitope of an antibody can be determined by, *e.g.,* NMR spectroscopy, X-ray diffraction crystallography studies, ELISA assays, hydrogen/deuterium exchange coupled with mass spectrometry (*e.g.,* MALDI mass spectrometry), array-based oligo-peptide scanning assays, and/or mutagenesis mapping (*e.g.,* site-directed mutagenesis mapping). For X-ray crystallography, crystallization may be accomplished using any of the known methods in the art (*e.g.,* Giegé R *et al.,* (1994) Acta Crystallogr D Biol Crystallogr 50(Pt 4): 339-350; McPherson A (1990) Eur J Biochem 189: 1-23; Chayen NE (1997) Structure 5: 1269-1274; McPherson A (1976) J Biol Chem 251: 6300-6303). Antibody:antigen crystals may be studied using well known X-ray diffraction techniques and may be refined using computer software such as X-PLOR (Yale University, 1992, distributed by Molecular Simulations, Inc.; see *e.g.* Meth Enzymol (1985) volumes 114 & 115, eds Wyckoff HW *et al.,*; U.S. Patent Application No. 2004/0014194), and BUSTER (Bricogne G

(1993) Acta Crystallogr D Biol Crystallogr 49(Pt 1): 37-60; Bricogne G (1997) Meth Enzymol 276A: 361-423, ed Carter CW; Roversi P *et al.,* (2000) Acta Crystallogr D Biol Crystallogr 56(Pt 10): 1316-1323). Mutagenesis mapping studies may be accomplished using any method known to one of skill in the art. *See, e.g.,* Champe M *et al.,* (1995) and Cunningham BC & Wells JA (1989) for a description of mutagenesis techniques, including alanine scanning mutagenesis techniques. In addition, antibodies that recognize and bind to the same or overlapping epitopes can be identified using routine techniques such as an immunoassay, *e.g.,* by showing the ability of one antibody to block the binding of another antibody to a target antigen, *i.e.*, a competitive binding assay. Competition binding assays also can be used to determine whether two antibodies have similar binding specificity for an epitope. Competitive binding can be determined in an assay in which the immunoglobulin under test inhibits immunospecific binding of a reference antibody to a common antigen. Numerous types of competitive binding assays are known, e.g.: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli C *et al.,* (1983) Methods Enzymol 9: 242-253); solid phase direct biotin-avidin EIA (see Kirkland TN *et al.,* (1986) J Immunol 137: 3614-9); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow E & Lane D, (1988) Antibodies: A Laboratory Manual, Cold Spring Harbor Press); solid phase direct label RIA using I-125 label (see Morel GA *et al.,* (1988) Mol Immunol 25(1): 7-15); solid phase direct biotin-avidin EIA (Cheung RC *et al.,* (1990) Virology 176: 546-52); and direct labeled RIA. (Moldenhauer G *et al.,* (1990) Scand J Immunol 32: 77-82). 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 can be 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. Usually, when a competing antibody is present in excess, it will inhibit immunospecific binding of a reference antibody to a common antigen by at least 50-55%, 55-60%, 60-65%, 65-70% 70-75% or more. A competition binding assay can be configured in a large number of different formats using either labeled antigen or labeled antibody. In a common version of this assay, the antigen is immobilized on a 96-well plate. The ability of unlabeled antibodies to block the binding of labeled antibodies to the antigen is then measured using radioactive or enzyme labels. For further details see, *e.g.,* Wagener C *et al.,* (1983) J Immunol 130: 2308-2315; Wagener C *et*

al., (1984) J Immunol Methods 68: 269-274; Kuroki M *et al.,* (1990) Cancer Res 50: 4872-4879; Kuroki M *et al.,* (1992) Immunol Invest 21: 523-538; Kuroki M *et al.,* (1992) Hybridoma 11: 391-407 and Antibodies: A Laboratory Manual, Ed Harlow E & Lane D editors *supra*, pp. 386-389.

[00293] In certain aspects, competition binding assays can be used to determine whether an antibody is competitively blocked, *e.g.,* in a dose dependent manner, by another antibody *e.g.,* an antibody binds essentially the same epitope, or overlapping epitopes, as a reference antibody, when the two antibodies recognize identical or sterically overlapping epitopes in competition binding assays such as competition ELISA assays, which can be configured in all number of different formats, using either labeled antigen or labeled antibody. In a particular embodiment, an antibody can be tested in competition binding assays with a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein (*e.g.,* a murine IgG antibody containing the variable region of 10C6, 7B12, 19C11, 16C5, or 16C5).

[00294] In another aspect, provided herein are antibodies that compete (*e.g.,* in a dose dependent manner) for binding to MUC16 with a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein (*e.g.,* a murine IgG antibody containing the variable region of 10C6, 7B12, 19C11, 16C5, or 16C5), as determined using assays known to one of skill in the art or described herein (*e.g.,* ELISA). In another aspect, provided herein are antibodies that competitively inhibit (*e.g.,* in a dose dependent manner) a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein (*e.g.,* a murine IgG antibody containing the variable region of 10C6, 7B12, 19C11, 16C5, or 16C5) from binding to MUC16, as determined using assays known to one of skill in the art or described herein (*e.g.,* ELISA).

[00295] In certain embodiments, provided herein is an antibody that competes with an antibody described herein for binding to the same extent that a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein self-competes for binding to MUC16. In certain embodiments, provided herein is a first antibody that competes with a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein for binding to MUC16, wherein the competition is exhibited as reduced binding of the first antibody to the epitope by more than 80% (*e.g.,* 85%, 90%, 95%, or 98%, or between 80% to 85%, 80% to 90%, 85% to 90%, or 85% to 95%).

[00296] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VH comprising a VH CDR1, a VH CDR2, and/or a VH CDR3 comprising amino acid sequences as described in Table 1, Table 3, or Table 5. In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VH CDRS of 10C6 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VH CDRS of 7B12 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VH CDRS of 19C11 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VH CDRS of 16C5 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VH CDRS of 18C6 (*see*, Table 1, Table 3, and Table 5).

[00297] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VL comprising a VL CDR1, a VL CDR2, and/or a VL CDR3 comprising amino acid sequences as described in Table 2, Table 4, or Table 6. In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a

MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VL CDRS of 10C6 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VL CDRS of 7B12 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VL CDRS of 19C11 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VL CDRS of 16C5 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VL CDRS of 18C6 (*see*, Table 2, Table 4, and Table 6).

[00298] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) a VH comprising a VH CDR1, a VH CDR2, and/or a VH CDR3 comprising amino acid sequences as described in Table 1, Table 3, or Table 5; and (b) a VL comprising a VL CDR1, a VL CDR2, and/or a VL CDR3 comprising amino acid sequences as described in Table 2, Table 4, or Table 6. In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) the VH CDRS of 10C6 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 10C6 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof

comprising (a) the VH CDRS of 7B12 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 7B12 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) the VH CDRS of 19C11 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 19C11 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) the VH CDRS of 16C5 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 16C5 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.,* in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) the VH CDRS of 18C6 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 18C6 (*see*, Table 2, Table 4, and Table 6).

[00299] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VH domain having an amino acid sequence as described in Table 7. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VH domain having the amino acid sequence of SEQ ID NO:1. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VH domain having the amino acid sequence of SEQ ID NO:21. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VH domain having the amino acid

sequence of SEQ ID NO:41. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VH domain having the amino acid sequence of SEQ ID NO:61. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VH domain having the amino acid sequence of SEQ ID NO:81.

[00300] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VL domain having an amino acid sequence as described in Table 8. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VL domain having the amino acid sequence of SEQ ID NO:2. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VL domain having the amino acid sequence of SEQ ID NO:22. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VL domain having the amino acid sequence of SEQ ID NO:42. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VL domain having the amino acid sequence of SEQ ID NO:62. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a VL domain having the amino acid sequence of SEQ ID NO:82.

[00301] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) a VH domain having an amino acid sequence as described in Table 7; and (b) a VL domain having an amino acid sequence as described in Table 8. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:1; and (b) a VL domain having the amino acid sequence of SEQ ID NO:2. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:21; and (b) a VL domain having the amino acid sequence of SEQ ID NO:22. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:41; and (b) a VL domain having the amino acid sequence of SEQ ID NO:42. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:61; and (b) a VL domain having the amino acid sequence of SEQ ID NO:62. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which competes (*e.g.,* in a dose dependent manner) for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:81; and (b) a VL domain having the amino acid sequence of SEQ ID NO:82.

[00302] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof which binds to the same or an overlapping epitope of antibody comprising a VH comprising a VH CDR1, a VH CDR2, and/or a VH CDR3 comprising amino

acid sequences as described in Table 1, Table 3, or Table 5. In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VH CDRS of 10C6 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VH CDRS of 7B12 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that competes (*e.g.*, in a dose-dependent manner), for immunospecific binding to MUC16, with a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising the VH CDRS of 19C11 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VH CDRS of 16C5 (*see*, Table 1, Table 3, and Table 5). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VH CDRS of 18C6 (*see*, Table 1, Table 3, and Table 5).

[00303] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof binds to the same or an overlapping epitope of antibody comprising a VL comprising a VL CDR1, a VL CDR2, and/or a VL CDR3 comprising amino acid sequences as described in Table 2, Table 4, or Table 6. In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VL CDRS of 10C6 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VL CDRS of 7B12 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VL CDRS of 19C11 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VL CDRS of 16C5 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or

antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising the VL CDRS of 18C6 (*see*, Table 2, Table 4, and Table 6).

[00304] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) a VH comprising a VH CDR1, a VH CDR2, and/or a VH CDR3 comprising amino acid sequences as described in Table 1, Table 3, or Table 5; and (b) a VL comprising a VL CDR1, a VL CDR2, and/or a VL CDR3 comprising amino acid sequences as described in Table 2, Table 4, or Table 6. In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) the VH CDRS of 10C6 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 10C6 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) the VH CDRS of 7B12 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 7B12 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) the VH CDRS of 19C11 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 19C11 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) the VH CDRS of 16C5 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 16C5 (*see*, Table 2, Table 4, and Table 6). In a particular embodiment, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) the VH CDRS of 18C6 (*see*, Table 1, Table 3, and Table 5); and (b) the VL CDRS of 18C6 (*see*, Table 2, Table 4, and Table 6).

[00305] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VH domain having an amino acid sequence as described in Table 7. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VH domain having the amino acid sequence of SEQ ID NO:1. In specific aspects, provided herein is a

MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VH domain having the amino acid sequence of SEQ ID NO:21. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VH domain having the amino acid sequence of SEQ ID NO:41. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VH domain having the amino acid sequence of SEQ ID NO:61. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VH domain having the amino acid sequence of SEQ ID NO:81.

[00306] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VL domain having an amino acid sequence as described in Table 8. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VL domain having the amino acid sequence of SEQ ID NO:2. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VL domain having the amino acid sequence of SEQ ID NO:22. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VL domain having the amino acid sequence of SEQ ID NO:42. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VL domain having the amino acid sequence of SEQ ID NO:62. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising a VL domain having the amino acid sequence of SEQ ID NO:82.

[00307] In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) a VH domain having an amino acid sequence as described in Table 7; and (b) a

VL domain having an amino acid sequence as described in Table 8. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:1; and (b) a VL domain having the amino acid sequence of SEQ ID NO:2. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:21; and (b) a VL domain having the amino acid sequence of SEQ ID NO:22. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:41; and (b) a VL domain having the amino acid sequence of SEQ ID NO:42. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:61; and (b) a VL domain having the amino acid sequence of SEQ ID NO:62. In specific aspects, provided herein is a MUC16 Glycosylation Antibody or antigen binding fragment thereof that binds to the same or an overlapping epitope of antibody comprising (a) a VH domain having the amino acid sequence of SEQ ID NO:81; and (b) a VL domain having the amino acid sequence of SEQ ID NO:82.

[00308] Assays known to one of skill in the art or described herein (*e.g.,* X-ray crystallography, ELISA assays, etc.) can be used to determine if two antibodies bind to the same epitope. Affinity can be measured and/or expressed in a number of ways known in the art, including, but not limited to, equilibrium dissociation constant (K_D), and equilibrium association constant (K_A). The K_D can be determined by techniques known to one of ordinary skill in the art, such as biolayer interferometry.

[00309] In certain embodiments, the epitope of a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein is used as an immunogen to produce antibodies. *See, e.g.,* Section 5.3 and Section 6.2 for methods for producing antibodies.

5.1.2 FUNCTIONAL CHARACTERISTICS

[00310] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of less than $0.5x10^{-3}$/s, $1x10^{-3}$/s,

$1.5x10^{-3}$/s, $2x10^{-3}$/s, $2.5x10^{-3}$/s, $3x10^{-3}$/s, $4x10^{-3}$/s, $5x10^{-3}$/s, $6x10^{-3}$/s, $7x10^{-3}$/s, $8x10^{-3}$/s, $9x10^{-3}$/s, $1x10^{-4}$/s, $2x10^{-4}$/s, $3x10^{-4}$/s, $4x10^{-4}$/s, $5x10^{-4}$/s, $6x10^{-4}$/s, $7x10^{-4}$/s, or $8x10^{-4}$/s. In some embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of about $0.5x10^{-3}$/s, $1x10^{-3}$/s, $1.5x10^{-3}$/s, $2x10^{-3}$/s, $2.5x10^{-3}$/s, $3x10^{-3}$/s, $4x10^{-3}$/s, $5x10^{-3}$/s, $6x10^{-3}$/s, $7x10^{-3}$/s, $8x10^{-3}$/s, $9x10^{-3}$/s, $1x10^{-4}$/s, $2x10^{-4}$/s, $3x10^{-4}$/s, $4x10^{-4}$/s, $5x10^{-4}$/s, $6x10^{-4}$/s, $7x10^{-4}$/s, or $8x10^{-4}$/s. In some embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of about $0.5x10^{-3}$/s to $8x10^{-4}$/s. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of about $1x10^{-3}$/s. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of about $1.5x10^{-3}$/s. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of about $2x10^{-3}$/s. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of about $2x10^{-4}$/s. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_d of about $7x10^{-4}$/s.

[00311] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_a of at least $2.5x10^4$/s, $3x10^4$/s, $3.5x10^4$/s, $4x10^4$/s, $4.5x10^4$/s, $5x10^4$/s, $5.5x10^4$/s, $6x10^4$/s, $6.5x10^4$/s, $7x10^4$/s, $7.5x10^4$/s, $8x10^4$/s, $9x10^4$/s, or $9x10^5$/s. In some embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_a of about $2.5x10^4$/s, $3x10^4$/s, $3.5x10^4$/s, $4x10^4$/s, $4.5x10^4$/s, $5x10^4$/s, $5.5x10^4$/s, $6x10^4$/s, $6.5x10^4$/s, $7x10^4$/s, $7.5x10^4$/s, $8x10^4$/s, $9x10^4$/s, or $9x10^5$/s. In some embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein, binds to MUC16 with a k_a of about $4x10^4$/s. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_a of about $6x10^4$/s. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a k_a of about $7.5x10^4$/s.

[00312] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of less than 1000 nM, 500 nM,

100 nM, 50 nM, 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, or 0.05 nM. In some embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 1000 nM, 500 nM, 100 nM, 50 nM, 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, or 0.05 nM. In some embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 500 nM to 1000 nM. In some embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 5 nM to 75 nM. In a specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 7 nM. In another specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 10 pM. In another specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 15 pM. In another specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 20 pM. In another specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 25 pM. In another specific embodiment, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to MUC16 with a K_D of about 65 pM. As used herein, the terms "about" when used to modify a numeric value or numeric range, indicate that deviations of 5% to 10% above and 5% to 10% below the value or range remain within the intended meaning of the recited value or range.

[00313] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133. In certain embodiments, the cell is a cancer cell (*e.g.,* an ovarian cancer cell, a lung cancer cell, a pancreatic cancer cell, a breast cancer cell, a fallopian tube cancer cell, a uterine (*e.g.,* endometrial) cancer cell, or a primary peritoneum cancer cell). In certain embodiments, the cell is an ovarian cancer cell. In certain embodiments, the cell is a lung cancer cell. In certain embodiments, the cell is a pancreatic cancer cell. In certain embodiments, the cell is a breast cancer cell. In certain embodiments, the cell is a uterine (*e.g.,* endometrial) cancer

cell. In certain embodiments, the cell is a fallopian tube cancer cell. In certain embodiments, the cell is a primary peritoneum cancer cell. In certain embodiments, the cell is a SKOV3 cell. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133 at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 250, 500, or 1000 fold more than an isotype control antibody binds to the cells. An isotype control antibody is an art-recognized term. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133 about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 250, 500, or 1000 fold more than an isotype control antibody binds to the cell. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133 between 10 and 50, 50 and 100, 100 and 250, 250 and 500, or 500 and 1000 fold more than an isotype control antibody binds to the cell.

[00314] The protein encoded by the amino acid sequence of SEQ ID NO:133 is also referred to herein as $MUC16^{c114}$ and consists of the C-terminal 114 amino acid residues of mature MUC16 (SEQ ID NO: 150 being the sequence of mature MUC16). $MUC16^{c114}$ is capable of being *N*-glycosylated at the asparagine amino acids of positions 1, 24, and 30 of SEQ ID NO: 133 (corresponding to amino acid positions Asn1777, Asn1800, and Asn1806 of SEQ ID NO: 150).

[00315] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139. In certain embodiments, the cells are ovarian cancer cells. In certain embodiments, the cells are lung cancer cells. In certain embodiments, the cells are pancreatic cancer cells. In certain embodiments, the cells are breast cancer cells. In certain embodiments, the cells are uterine (*e.g.,* endometrial) cancer cells. In certain embodiments, the cells are fallopian tube cancer cells. In certain embodiments, the cells are primary peritoneum cancer cells. In certain embodiments, the cells are SKOV3 cells. In

certain embodiments, the second form of MUC16 is fused to a detectable protein, such as, for example, green fluorescent protein or red fluorescent protein. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139, at most 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, or 5 fold more than an isotype control antibody binds to the cells. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139, about 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, or 5 fold more than an isotype control antibody binds to the cells. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139, between 0 and 1.1, 1.1 and 1.5, 1.5 and 3, or 3 and 5 fold more than an isotype control antibody binds to the cells.

[00316] The protein encoded by the amino acid sequence of SEQ ID NO: 139 is also referred to herein as $MUC16^{c114\text{-}N3}$. $MUC16^{c114\text{-}N3}$ consists of the C-terminal 114 amino acid residues of mature MUC16 (SEQ ID NO: 150 being the sequence of mature MUC16), except that the asparagine at amino acid position 30 (corresponding to amino acid position 1806 of SEQ ID NO: 150) has been mutated to an alanine. Thus, $MUC16^{c114\text{-}N3}$ is not capable of being *N*-glycosylated at amino acid position 30 of SEQ ID NO: 139 (corresponding to amino acid position Asn1806 of SEQ ID NO: 150).

[00317] In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139, at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 30, or 40 fold less than 4H11 binds to the cells. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139, about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 20, 30, or 40 fold less than 4H11 binds to the cells. In certain embodiments, the

MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139, between 3 and 5, 5 and 10, 10 and 20, or 20 and 40 fold less than 4H11 binds to the cell.

[00318] Assays to determine binding of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein to a cell, such as, for example, FACs, are known to a person skilled in the art. *See*, for example, the methods described in Section 6.2.

[00319] As used herein, "4H11" refers to the monoclonal anti-MUC16 antibody designated as 4H11 in Rao et al. Appl. Immunohistochem Mol Morphol, 2010, 18(5):462-72 and in International Patent Application Publication No. WO 2011/119979.

[00320] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein, binds to a peptide comprising the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are glycosylated. In certain embodiments, the peptide consists of the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are glycosylated. In certain embodiments, the glycosylation consists of an N-linked chitobiose. In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof binds to a peptide comprising the amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated. In certain embodiments, the peptide consists of the amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated. In certain embodiments, the glycosylation consists of an N-linked chitobiose. In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof binds to a mixture of peptides, wherein the mixture of peptides comprises (a) a first peptide comprising the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are glycosylated, and (b) a second peptide comprising of the amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of

CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated. In certain embodiments, the first peptide consists of the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are glycosylated. In certain embodiments, the second peptide consists of amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated. In certain embodiments, the glycosylation consists of an N-linked chitobiose.

[00321] Assays to determine binding of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein to a cell, such as, for example, ELISA, are known to a person skilled in the art. *See*, for example, the methods described in Section 6.2. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 30 fold more than binding of anti-MUC16 monoclonal antibody 4H11 to the peptide. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) at about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or 30 fold more than binding of anti-MUC16 monoclonal antibody 4H11 to the peptide.

[00322] In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a k_d of less than $0.5x10^{-3}$/s, $1x10^{-3}$/s, $1.5x10^{-3}$/s, $2x10^{-3}$/s, $2.5x10^{-3}$/s, $3x10^{-3}$/s, $4x10^{-3}$/s, $5x10^{-3}$/s, $6x10^{-3}$/s, $7x10^{-3}$/s, $8x10^{-3}$/s, $9x10^{-3}$/s, $1x10^{-4}$/s, $2x10^{-4}$/s, $3x10^{-4}$/s, $4x10^{-4}$/s, $5x10^{-4}$/s, $6x10^{-4}$/s, $7x10^{-4}$/s, or $8x10^{-4}$/s. In some embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a k_d of about $0.5x10^{-3}$/s, $1x10^{-3}$/s, $1.5x10^{-3}$/s, $2x10^{-3}$/s, $2.5x10^{-3}$/s, $3x10^{-3}$/s, $4x10^{-3}$/s, $5x10^{-3}$/s, $6x10^{-3}$/s, $7x10^{-3}$/s, $8x10^{-3}$/s, $9x10^{-3}$/s, $1x10^{-4}$/s, $2x10^{-4}$/s, $3x10^{-4}$/s, $4x10^{-4}$/s, $5x10^{-4}$/s, $6x10^{-4}$/s, $7x10^{-4}$/s, or $8x10^{-4}$/s. In some embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a k_d of about $0.5x10^{-3}$/s to $8x10^{-4}$/s.

[00323] In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a k_a of at least $2.5x10^{4}$/s, $3x10^{4}$/s, $3.5x10^{4}$/s, $4x10^{4}$/s, $4.5x10^{4}$/s, $5x10^{4}$/s, $5.5x10^{4}$/s, $6x10^{4}$/s, $6.5x10^{4}$/s, $7x10^{4}$/s, $7.5x10^{4}$/s, $8x10^{4}$/s, $9x10^{4}$/s, or $9x10^{5}$/s. In some embodiments, the MUC16 Glycosylation Antibody or antigen-

binding fragment thereof provided herein binds to the peptide(s) with a k_a of about $2.5x10^4$/s, $3x10^4$/s, $3.5x10^4$/s, $4x10^4$/s, $4.5x10^4$/s, $5x10^4$/s, $5.5x10^4$/s, $6x10^4$/s, $6.5x10^4$/s, $7x10^4$/s, $7.5x10^4$/s, $8x10^4$/s, $9x10^4$/s, or $9x10^5$/s. In some embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a k_a of about $2.5x10^4$/s to $9x10^5$/s.

[00324] In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a K_D of less than 1000 nM, 500 nM, 100 nM, 50 nM, 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, or 0.05 nM. In some embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a K_D of about 1000 nM, 500 nM, 100 nM, 50 nM, 25 nM, 20 nM, 15 nM, 10 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.1 nM, or 0.05 nM. In some embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein binds to the peptide(s) with a K_D of about 500 nM to 1000 nM.

[00325] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment lacks immunospecific binding to the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are not glycosylated. In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof lacks immunospecific binding to the amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated. In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein, lacks immunospecific binding to a mixture of peptides, wherein the mixture of peptides comprises (a) a first peptide consisting of the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are glycosylated and (b) a second peptide consisting of the amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated.

[00326] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein inhibits matrigel invasion *in vitro* of cells recombinantly

expressing a form of MUC16 which is glycosylated and wherein the amino acid sequence of the form of MUC16 is SEQ ID NO:133 ($MUC16^{c114}$). In certain embodiments, the cells recombinantly expressing glycosylated $MUC16^{c114}$ are SKOV3 cells. In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated. In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated at amino acid residue Asn30 (corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150)). In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated at amino acid residues Asn 24 and Asn30 (corresponding to Asn1800 and Asn1806, respectively, of mature MUC16 (SEQ ID NO:150)). In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated at amino acid residues Asn1, Asn24, and Asn30 (corresponding to Asn1777, Asn1800, and Asn1806, respectively, of mature MUC16 (SEQ ID NO:150)). In certain embodiments, the glycosylation comprises N-linked chitobiose. In certain embodiments, the glycosylation consists of an N-linked chitobiose. In certain embodiments, matrigel invasion is inhibited by at least 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold as compared to matrigel invasion *in vitro* of the cells wherein the cells are treated with a control antibody (*e.g.,* an antibody that does not target MUC16) or with 4H11. In certain embodiments, matrigel invasion is inhibited by about 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 7, 8, 9, or 10 fold as compared to matrigel invasion *in vitro* of the cells wherein the cells are treated with a control antibody (*e.g.,* an antibody that does not target MUC16) or with 4H11.

[00327] Assays to determine the MUC16 Glycosylation Antibody- or antigen-binding fragment-mediated inhibition of matrigel invasion are known to a person skilled in the art. *See*, for example, the methods described in Section 6.2. For example, BD BioCoat™ Matrigel™ Invasion Inserts or Chambers (catalog # 354480 in 24 well plate) and Control Inserts (catalog # 354578 in 24 well plate) can be purchased from BD Biosciences, MA. Matrigel Invasion assay can be performed as per manufacturer's protocol. Briefly, the matrigel chambers in 24 well plates (stored at -20°C) and control inserts (stored at 4°C) are allowed to come to room temperature. Both inserts are rehydrated with 0.5 mL of serum free medium in the insert as well as in the outside well of the 24 well plate, for 2 hrs at 37°C 5% CO_2 humidified incubator. Cultured SKOV3 cells are trypsinized and washed with culture medium. A million cells are separated into another centrifuge tube and washed 3 times with serum free medium. These cells are later adjusted to give 5,000 cells in 0.5 mL serum free medium. The medium in the rehydrated inserts are removed and the insert was transferred into a new 24 well plate containing

0.75 mL of 10% Foetal Bovine Serum (FBS) containing culture medium in the well which serves as a chemo attractant. Immediately, 0.5 mL of the cells (5,000 cells) in serum free medium is added to the insert. Proper care is taken to see that there is no air bubble is trapped in the insert and the outside well. The 24 well plate is incubated at 37°C 5% CO_2 humidified incubator for 48 hrs. After incubation, the non-invading cells are removed from the upper surface of the membrane by "scrubbing" by inserting a cotton tipped swab into matrigel or control insert and gently applied pressure while moving the tip of the swab over the membrane surface. The scrubbing is repeated with a second swab moistened with medium. Then the inserts are stained in a new 24 well plate containing 0.5 mL of 0.5% crystal violet stain in distilled water for 30 minutes. Following staining the inserts are rinsed in 3 beakers of distilled water to remove excess stain. The inserts are air dried for in a new 24 well plate. The invaded cells are hand counted under an inverted microscope at 200X magnification. Several fields of triplicate membranes were counted and recorded in the figure.

[00328] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein is capable of inhibiting or reducing metastasis, inhibiting tumor growth or inducing tumor regression in mouse model studies. For example, tumor cell lines can be introduced into athymic nude mice, and the athymic mice can be administered MUC16 Glycosylation Antibodies described herein one or more times, and tumor progression of the injected tumor cells can be monitored over a period of weeks and/or months. In some cases, administration of the MUC16 Glycosylation Antibodies or antigen-binding fragments thereof to the athymic nude mice can occur prior to introduction of the tumor cell lines. In a certain embodiment, SKOV3 cells expressing $MUC16^{c114}$ are utilized for the mouse xenograft models described herein. *See*, *e.g.,* Section 6.2 and Section 6.3.

[00329] In specific embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein inhibit tumor growth or induce tumor regression in a mouse model by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or 100% as assessed by methods described herein or known to one of skill in the art, as compared to mock treated mice. In specific embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein inhibit tumor growth or induce tumor regression in a mouse model by at least about 25% or 35%, optionally to about 75%, as assessed by methods described herein or known to one of

skill in the art, as compared to mock-treated mice. In specific embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein inhibit tumor growth or induce tumor regression in a mouse model by at least about 1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10 fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein or known to one of skill in the art, as compared to mock-treated mice. Mock-treated mice can, for example, be treated with phosphate buffered saline or a control (*e.g.*, anti-IgG antibody).

[00330] Determining tumor growth inhibition or tumor regression can be assessed, for example, by monitoring tumor size over a period of time, such as by physical measurement of palpable tumors, or other visual detection methods. For example, tumor cell lines can be generated to recombinantly express a visualization agent, such as green fluorescent protein (GFP) or luciferase, then *in vivo* visualization of GFP can be carried out by microscopy, and *in vivo* visualization of luciferase can be carried out by administering luciferase substrate to the xenograft mice and detecting luminescent due to the luciferase enzyme processing the luciferase substrate. The degree or level of detection of GFP or luciferase correlates to the size of the tumor in the xenograft mice.

[00331] In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein can increase survival of animals in tumor xenograft models as compared to mock-treated mice. In specific embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein increase survival of mice in tumor xenograft models by at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% as assessed by methods described herein or known to one of skill in the art, as compared to mock-treated mice. In specific embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein increase survival of mice in tumor xenograft models by at least about 25% or 35%, optionally to about 75%, as assessed by methods described herein or known to one of skill in the art, as compared to mock-treated mice in tumor xenograft models. In specific embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein increase survival of mice in tumor xenograft models by at least about 1 fold, 1.2 fold, 1.3 fold, 1.4 fold, 1.5 fold, 2 fold, 2.5 fold, 3 fold, 3.5 fold, 4 fold, 4.5 fold, 5 fold, 6 fold, 7 fold, 8 fold, 9 fold, 10

fold, 15 fold, 20 fold, 30 fold, 40 fold, 50 fold, 60 fold, 70 fold, 80 fold, 90 fold, or 100 fold as assessed by methods described herein or known to one of skill in the art, as compared to mock-treated mice in tumor xenograft models. Survival can, for example, be determined by plotting a survival curve of number of surviving mice against time (*e.g.*, days or weeks) after tumor cell line injection. Mock-treated mice can, for example, be treated with phosphate buffered saline or a control (*e.g.*, anti-IgG antibody).

[00332] In certain embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein is internalized into a cell expressing a form of MUC16, which is glycosylated, and wherein the amino acid sequence of the form of MUC16 is SEQ ID NO:133 ($MUC16^{c114}$) upon contacting the cell with the MUC16 Glycosylation Antibody or antigen-binding fragment thereof. "Internalized" or "internalization," when in reference to a molecule that is internalized by a cell, refers to passage of the molecule that is in contact with the extracellular surface of a cell membrane across the cell membrane to the intracellular surface of the cell membrane and/or into the cell cytoplasm. In certain embodiments, the cells recombinantly expressing glycosylated $MUC16^{c114}$ are SKOV3 cells. In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated. In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated at amino acid residue Asn30 (corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150)). In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated at amino acid residues Asn 24 and Asn30 (corresponding to Asn1800 and Asn1806, respectively, of mature MUC16 (SEQ ID NO:150)). In certain embodiments, the glycosylated form of $MUC16^{c114}$ is N-glycosylated at amino acid residues Asn1, Asn24, and Asn30 (corresponding to Asn1777, Asn1800, and Asn1806, respectively, of mature MUC16 (SEQ ID NO:150)). In certain embodiments, the glycosylation comprises N-linked chitobiose. In certain embodiments, the glycosylation consists of an N-linked chitobiose.

[00333] Assays to determine internalization of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein to a cell, such as, for example, using radiolabeled antibodies, are known to a person skilled in the art. *See*, for example, the methods described in Section 6.2. For example, internalization of ^{89}Zr-labled antibody can be investigated on SKOV3 cells expressing $MUC16^{c114}$. Briefly, approximately 1×10^5 cells are seeded in a 12-well plate and incubated overnight at 37°C 5% CO_2 incubator. A volume of radiolabeled protein is added to each well and the plates are incubated at 37°C and 4°C for 1, 5, 12, and 24 hours. Following

each incubation period, the medium is collected and the cells are rinsed with 1 mL of phosphate buffered saline (PBS). Surface-bound activity is collected by washing the cells in 1 mL of 100 mM acetic acid with 100 mM glycine (1:1, pH 3.5) at 4°C. The adherent cells are then lysed with 1 mL of 1 M NaOH. Each wash is collected and counted for activity. The ratio of activity of the final wash to the total activity of all the washes is used to determine the % internalized. In certain embodiments, the assay is performed at 37°C. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is internalized in at least 1, 2, 3, 5, 6, 7, 8, 9, or 10 percent of cells incubated with the MUC16 Glycosylation Antibody or antigen-binding fragment thereof. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is internalized in about 1, 2, 3, 5, 6, 7, 8, 9, or 10 percent of cells incubated with the MUC16 Glycosylation Antibody or antigen-binding fragment thereof. In certain embodiments, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is internalized within 1, 2, 3, 4, 8, 12, 16, 20, or 24 hours of contacting the cells with the MUC16 Glycosylation Antibody or antigen-binding fragment thereof.

5.2 ANTIBODY CONJUGATES

[00334] In preferred embodiments, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see*, Section 5.1) provided herein is not conjugated to any other molecule, such as an organic moiety, a detectable label, or an isotope. In alternative embodiments, MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see*, Section 5.1) provided herein is conjugated to one or more organic moieties. In alternative embodiments, MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein is conjugated to one or more detectable labels. In alternative embodiments, MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein is conjugated to one or more isotopes.

5.2.1 DETECTABLE LABELS AND ISOTOPES

[00335] In certain embodiments, provided herein are MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see*, Section 5.1) conjugates, wherein said MUC16 Glycosylation Antibody or antigen-binding fragment thereof is conjugated to one or more agent, *e.g.*, an imaging agent or a cytotoxic agent. Also provided herein are bispecific antibody conjugates, wherein said bispecific antibody is conjugated to one or more agent, *e.g.*, an imaging agent or a cytotoxic agent. Also provided herein are antibody heavy chain conjugates, wherein said antibody heavy chain is conjugated to one or more agent, *e.g.*, an imaging agent or a

cytotoxic agent. Also provided herein are antibody light chain conjugates, wherein said antibody light chain is conjugated to one or more agent, *e.g.*, an imaging agent or a cytotoxic agent. Also provided herein are fusion protein conjugates, wherein said fusion protein is conjugated to an agent, *e.g.*, an imaging agent or a cytotoxic agent. In certain embodiments, the agent is conjugated covalently or non-covalently.

[00336] In certain embodiments, the imaging agent is a detectable label, such as, a chromogenic, enzymatic, radioisotopic, isotopic, fluorescent, toxic, chemiluminescent, nuclear magnetic resonance contrast agent or other label.

[00337] Non-limiting examples of suitable chromogenic labels include diaminobenzidine and 4-hydroxyazo-benzene-2-carboxylic acid.

[00338] Non-limiting examples of suitable enzyme labels include malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast-alcohol dehydrogenase, alpha-glycerol phosphate dehydrogenase, triose phosphate isomerase, peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase, and acetylcholine esterase.

[00339] Non-limiting examples of suitable radioisotopic labels include ^{3}H, ^{111}In, ^{125}I, ^{131}I, ^{32}P, ^{35}S, ^{14}C, ^{51}Cr, ^{57}To, ^{58}Co, ^{59}Fe, ^{75}Se, ^{152}Eu, ^{90}Y, ^{67}Cu, ^{217}Ci, ^{211}At, ^{212}Pb, ^{47}Sc, ^{223}Ra, ^{223}Ra, ^{89}Zr, ^{177}Lu, and ^{109}Pd. In certain embodiments, ^{111}In is a preferred isotope for *in vivo* imaging as it avoids the problem of dehalogenation of ^{125}I or ^{131}I-labeled MUC16 Glycosylation Antibodies or antigen-binding fragments thereof in the liver. In addition, ^{111}In has a more favorable gamma emission energy for imaging (Perkins et al, Eur. J. Nucl. Med. 70:296-301 (1985); Carasquillo et ah, J. Nucl. Med. 25:281-287 (1987)). For example, ^{111}In coupled to monoclonal antibodies with 1-(P-isothiocyanatobenzyl)-DPTA has shown little uptake in non-tumorous tissues, particularly the liver, and therefore enhances specificity of tumor localization (Esteban et al., J. Nucl. Med. 28:861-870 (1987)).

[00340] Non-limiting examples of suitable non-radioactive isotopic labels include ^{157}Gd, ^{55}Mn, ^{162}Dy, ^{52}Tr, and ^{56}Fe.

[00341] Non-limiting examples of suitable fluorescent labels include a ^{152}Eu label, a fluorescein label, an isothiocyanate label, a rhodamine label, a phycoerythrin label, a phycocyanin label, an allophycocyanin label, a Green Fluorescent Protein (GFP) label, an o-phthaldehyde label, and a fluorescamine label.

[00342] Non-limiting examples of chemiluminescent labels include a luminol label, an isoluminol label, an aromatic acridinium ester label, an imidazole label, an acridinium salt label, an oxalate ester label, a luciferin label, a luciferase label, and an aequorin label.

[00343] Non-limiting examples of nuclear magnetic resonance contrasting agents include heavy metal nuclei such as Gd, Mn, and iron.

[00344] Techniques known to one of ordinary skill in the art for conjugating the above-described labels to said MUC16 Glycosylation Antibodies or antigen-binding fragments thereof, bispecific antibodies, antibody heavy chains, antibody light chains, and fusion proteins are described in, for example, Kennedy et at., Clin. CMm. Acta 70:1-31 (1976), and Schurs et al, Clin. CMm. Acta 81:1-40 (1977). Coupling techniques mentioned in the latter are the glutaraldehyde method, the periodate method, the dimaleimide method, the m-maleimidobenzyl-N-hydroxy-succinimide ester method, all of which methods are incorporated by reference herein.

[00345] Nonlimiting examples of cytotoxic agents include a cytostatic or cytocidal agent, a radioactive metal ion, *e.g.,* alpha-emitters, and toxins, *e.g.,* pseudomonas exotoxin, abrin, cholera toxin, ricin A, and diphtheria toxin.

[00346] In certain embodiments, the agent is a diagnostic agent. A diagnostic agent is an agent useful in diagnosing or detecting a disease by locating the cells containing the antigen. Useful diagnostic agents include, but are not limited to, radioisotopes, dyes (such as with the biotin-streptavidin complex), contrast agents, fluorescent compounds or molecules and enhancing agents (*e.g.,* paramagnetic ions) for magnetic resonance imaging (MRI). U.S. Pat. No. 6,331,175 describes MRI technique and the preparation of antibodies conjugated to a MRI enhancing agent and is incorporated in its entirety by reference. Preferably, the diagnostic agents are selected from the group consisting of radioisotopes, enhancing agents for use in magnetic resonance imaging, and fluorescent compounds. In order to load a MUC16 Glycosylation Antibody or antigen-binding fragment thereof with radioactive metals or paramagnetic ions, it may be necessary to react it with a reagent having a long tail to which are attached a multiplicity of chelating groups for binding the ions. Such a tail can be a polymer such as a polylysine, polysaccharide, or other derivatized or derivatizable chain having pendant groups to which can be bound chelating groups such as, for example, ethylenediaminetetraacetic acid (EDTA), diethylenetriaminepentaacetic acid (DTPA), porphyrins, polyamines, crown ethers, bis-thiosemicarbazones, polyoximes, and like groups known to be useful for this purpose. Chelates

are coupled to the antibodies using standard chemistries. The chelate is normally linked to the antibody by a group which enables formation of a bond to the molecule with minimal loss of immunoreactivity and minimal aggregation and/or internal cross-linking other, more unusual, methods and reagents for conjugating chelates to antibodies are disclosed in U.S. Pat. No. 4,824,659 to Hawthorne, entitled "Antibody Conjugates," issued Apr. 25, 1989, the disclosure of which is incorporated herein in its entirety by reference. Particularly useful metal-chelate combinations include 2-benzyl-DTPA and its monomethyl and cyclohexyl analogs, used with diagnostic isotopes for radio-imaging. The same chelates, when complexed with non-radioactive metals, such as manganese, iron and gadolinium are useful for MRI, when used along with a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein. Macrocyclic chelates such as NOTA, DOTA, and TETA are of use with a variety of metals and radiometals, most particularly with radionuclides of gallium, yttrium and copper, respectively. Such metal-chelate complexes can be made very stable by tailoring the ring size to the metal of interest. Other ring-type chelates such as macrocyclic polyethers, which are of interest for stably binding nuclides, such as ^{223}Ra for RAIT are encompassed herein.

[00347] In certain embodiments, the agent is an organic agent. Such organic agents can produce a conjugate with improved pharmacokinetic properties (*e.g.,* increased *in vivo* serum half-life). The organic moiety can be a hydrophilic polymeric group, fatty acid group, or fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. As used herein, a "hydrophilic polymeric group" refers to an organic polymer that is more soluble in water than in octane, *e.g.,* polylysine. Hydrophilic polymers suitable for modifying a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein can be linear or branched and include, for example, polyalkane glycols (*e.g.,* polyethylene glycol, (PEG), monomethoxy-polyethylene glycol, and polypropylene glycol), carbohydrates (*e.g.,* dextran, cellulose, oligosaccharides, and polysaccharides), polymers of hydrophilic amino acids (*e.g.,* polylysine, polyarginine, and polyaspartate), polyalkane oxides (*e.g.,* polyethylene oxide and polypropylene oxide) and polyvinyl pyrolidone. In certain embodiments, the hydrophilic polymer that modifies a MUC16 Glycosylation Antibody or antigen-binding fragment thereof, a bispecific antibody, an antibody heavy chain, an antibody light chain, or a fusion protein provided herein has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example PEG_{5000} and $PEG_{20,000}$, wherein the

subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (*e.g.,* activated with N,N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

[00348] Fatty acids and fatty acid esters suitable for modifying a MUC16 Glycosylation Antibody or antigen-binding fragment thereof, a bispecific antibody, an antibody heavy chain, an antibody light chain, or a fusion protein provided herein can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying a MUC16 Glycosylation Antibody or antigen-binding fragment thereof, a bispecific antibody, an antibody heavy chain, an antibody light chain, or a fusion protein provided herein include, for example, n-dodecanoate, n-tetradecanoate, n-octadecanoate, n-eicosanoate, n-docosanoate, n-triacontanoate, n-tetracontanoate, cis-delta-9-octadecanoate, all cis-delta-5,8,11,14-eicosatetraenoate, octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.

[00349] The conjugates provided herein can be prepared using suitable methods, such as by reaction with one or more modifying agents. As used herein, an "activating group" is a chemical moiety or functional group that can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as, for example, tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acrylolyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see, for example, Hernanson, G. T., Bioconjugate

Techniques, Academic Press: San Diego, Calif. (1996)). An activating group can be bonded directly to the organic group (*e.g.*, hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C_1-C_{12} group, wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, $(CH_2)_3$, and NH. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (*e.g.*, mono-Boc-ethylenediamine or mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, et al., WO 92/16221 the entire teachings of which are incorporated herein by reference.)

[00350] A "modifying agent" can refer to a suitable organic group (*e.g.*, hydrophilic polymer, a fatty acid, and a fatty acid ester) that comprises an activating group. For example, the organic moieties can be bonded to the MUC16 Glycosylation Antibody or antigen-binding fragment thereof in a non-site specific manner by employing an amine-reactive modifying agent, for example, an N-hydroxysuccinimide ester of PEG. Modified MUC16 Glycosylation Antibody or antigen-binding fragment thereof can also be prepared by reducing disulfide bonds (*e.g.*, intra-chain disulfide bonds) of the MUC16 Glycosylation Antibody or antigen-binding fragment thereof, bispecific antibody, antibody heavy chain, antibody light chain, or fusion protein. The reduced MUC16 Glycosylation Antibody or antigen-binding fragment thereof, bispecific antibody, antibody heavy chain, antibody light chain, or fusion protein can then be reacted with a thiol-reactive modifying agent to produce the conjugates provided herein. Conjugates comprising an organic moiety that is bonded to specific sites of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein can be prepared using suitable methods, such as reverse proteolysis (Fisch et al., Bioconjugate Chem., 3:147-153 (1992); Werlen et al., Bioconjugate Chem., 5:411-417 (1994); Kumaran et al., Protein Sci. 6(10):2233-2241 (1997); Itoh et al., Bioorg. Chem., 24(1): 59-68 (1996); Capellas et al., Biotechnol.

Bioeng., 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., Bioconjugate Techniques, Academic Press: San Diego, Calif. (1996).

5.3 ANTIBODY PRODUCTION

5.3.1 PRODUCING AND SCREENING ANTIBODIES

[00351] In another aspect, provided herein are methods of producing MUC16 Glycosylation Antibodies or antigen-binding fragments thereof (*see*, Section 5.1 and Section 5.2).

[00352] The antibodies or antigen-binding fragments thereof described herein can be produced by any method known in the art for the synthesis of antibodies, *e.g.,* by chemical synthesis or by recombinant expression techniques. The methods described herein employs, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, *e.g.,* in the references cited herein and are fully explained in the literature. See, *e.g.,* Maniatis T *et al.,* (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook J *et al.,* (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook J *et al.,* (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel FM *et al.,* Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren B *et al.,* (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[00353] In a specific embodiment, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein is an antibody (*e.g.,* recombinant antibody) prepared, expressed, created or isolated by any means that involves creation, *e.g.,* via synthesis, genetic engineering of DNA sequences. In certain embodiments, such antibody comprises sequences that are encoded by DNA sequences that do not naturally exist within the antibody germline repertoire of an animal or mammal (*e.g.,* human) *in vivo*. In a specific embodiment, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein is made by a

method comprising using a glycosylated form of SEQ ID NO:129, SEQ ID NO:130, and/or SEQ ID NO:131. In a specific embodiment, the glycosylated form of SEQ ID NO:129, SEQ ID NO:130, and/or SEQ ID NO:131 is glycosylated with one or more chitobiose. *See, e.g.,* Section 6.2, Section 6.3, and Section 6.4 for a detailed description of how to produce antibodies described herein.

[00354] In a certain aspect, provided herein is an immunogenic glycopeptide comprising one or more glycosylation sites, wherein (i) the immunogenic glycopeptide is 10 to 60 amino acid residues, 10 to 30 amino acid residues, 15 to 25 amino acid residues, 15 to 20 amino acid residues, or 15 to 18 amino acid residues in length, and (ii) at least one of the one or more glycosylation sites is linked with a carbohydrate.

[00355] In some embodiments, the immunogenic glycopeptide comprises one, two, or three glycosylation sites. In a specific embodiment, the immunogenic glycopeptide comprises one glycosylation site. In another specific embodiment, the immunogenic glycopeptide comprises two glycosylation sites.

[00356] In specific embodiments, the immunogenic glycopeptide comprises one glycosylation site that is linked with a carbohydrate. In specific embodiments, the immunogenic glycopeptide comprises two glycosylation sites that are each linked with a carbohydrate.

[00357] Carbohydrate linked to the one or more glycosylation sites of the immunogenic glycopeptide can be an N-linked carbohydrate, an O-linked carbohydrate, or a C-linked carbohydrate. N-linked carbohydrate is attached to an asparagine residue, and is the most common form found in nature. The majority of N-linked carbohydrates are linked to peptides in the form of GlcNAc-β-Asn. O-linked carbohydrate is attached to an amino acid hydroxyl side chain (usually from serine or threonine). The majority of O-linked carbohydrates are linked to peptides in the form of GlcNAc-β-Ser/Thr or GlcNAc-α-Ser/Thr. C-linked carbohydrate refers to a mannose attached to a tryptophan residue, and is the least common form found in nature. In one embodiment, the carbohydrate in the immunogenic glycopeptide is an N- or O-linked carbohydrate. In a specific embodiment, the carbohydrate in the immunogenic glycopeptide is an N-linked carbohydrate.

[00358] Carbohydrate linked to the one or more glycosylation sites of the immunogenic glycopeptide can be a monosaccharide, a disaccharide, an oligosaccharide (*e.g.,* a trisaccharide, a tetrasaccharide, or a pentasaccharide), or a polysaccharide. In certain embodiments, the

carbohydrate is a monosaccharide, a disaccharide, a trisaccharide, a tetrasaccharide, or a pentasaccharide. In a specific embodiment, the carbohydrate is a disaccharide. In a particular embodiment, the disaccharide is a chitobiose. In another specific embodiment, the carbohydrate is $Man_3GlcNAc_2$. In specific embodiments, the N-terminus of the immunogenic glycopeptide is acetylated. In specific embodiments, the C-terminus of the immunogenic glycopeptide is in the form of an N-methylcarboxamide derivative.

[00359] In certain embodiments, the immunogenic glycopeptide is conjugated to an immunogenic carrier protein. In most cases, small antigens (*e.g.,* short peptides or small haptens) are not sufficiently complex to elicit the production of antibodies. The immunogenic carrier proteins, because of their large size and complex structure, may confer immunogenicity to conjugated small antigens, resulting in antibodies being produced against epitopes on the small antigens and the immunogenic carrier proteins. Therefore, small antigens are always chemically conjugated with immunogenic carrier proteins to intensify the immune response for successful production of antibodies. Commonly used immunogenic carrier proteins include, but are not limited to, keyhole limpet hemocyanin (KLH), concholepas concholepas hemocyanin (CCH), bovine serum albumin (BSA), and ovalbumin (OVA). In a specific embodiment, the immunogenic glycopeptide is conjugated to KLH. KLH is a copper-containing polypeptide that belongs to a group of non-heme proteins called hemocyanins, which are found in arthropods and mollusks. KLH is isolated from keyhole limpets (*Megathura crenulata*). Because of its evolutionary distance from mammals, high molecular weight, complex structure, and a large surface containing several hundred lysine groups that provide primary amines as targets for conjugation, KLH is an extremely immunogenic and effective carrier protein in mammals.

[00360] In certain embodiments, the immunogenic glycopeptide is 10 to 60 amino acid residues in length. In some embodiments, the immunogenic glycopeptide is 10 to 30 amino acid residues in length. In some embodiments, the immunogenic glycopeptide is 15 to 25 amino acid residues in length. In some embodiments, the immunogenic glycopeptide is 15 to 20 amino acid residues in length. In specific embodiments, the immunogenic glycopeptide is 15 to 18 amino acid residues in length. In a particular aspect of such specific embodiments wherein the immunogenic glycopeptide is 15 to 18 amino acid residues in length, the immunogenic glycopeptide comprises a glycosylation site that is linked with a chitobiose. In another particular aspect of such specific embodiments wherein the immunogenic glycopeptide is 15 to 18 amino

acid residues in length, the immunogenic glycopeptide comprises two glycosylation sites that are each linked with a chitobiose. In a specific embodiment, the immunogenic glycopeptide is 55 amino acid residues in length. In a particular aspect of such specific embodiment wherein the immunogenic glycopeptide is 55 amino acid residues in length, the immunogenic glycopeptide comprises a glycosylation site that is linked with a chitobiose. In a specific embodiment, the immunogenic glycopeptide is 18 amino acid residues in length. In a particular aspect of such specific embodiment wherein the immunogenic glycopeptide is 18 amino acid residues in length, the immunogenic glycopeptide comprises two glycosylation sites that are each linked with a chitobiose. In another specific embodiment, the immunogenic glycopeptide is 15 amino acid residues in length. In a particular aspect of such specific embodiment wherein the immunogenic glycopeptide is 15 amino acid residues in length, the immunogenic glycopeptide comprises a glycosylation site that is linked with a chitobiose.

[00361] In certain embodiments, the immunogenic glycopeptide comprises an at least 10 amino acid portion of the amino acid sequence of SEQ ID NO:150, and at least one of the one or more glycosylation sites of the immunogenic glycopeptide is in said portion of the amino sequence. In certain other embodiments, the immunogenic glycopeptide comprises an at least 15, 20, 25, or 30 amino acid portion of the amino acid sequence of SEQ ID NO:150, and at least one of the one or more glycosylation sites of the immunogenic glycopeptide is in said portion of the amino sequence. In specific embodiments, the immunogenic glycopeptide is 15 to 18 amino acid residues in length. In specific embodiments, the immunogenic glycopeptide is 55 amino acid residues in length. In specific embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO:129. In a specific embodiment, the immunogenic glycopeptide is 55 amino acid residues in length and comprises the amino acid sequence of SEQ ID NO:129. In a particular embodiment, the immunogenic glycopeptide comprising the amino acid sequence of SEQ ID NO:129 comprises a glycosylation site at the 30^{th} residue (Asn) that is linked with a chitobiose. In another particular embodiment, the immunogenic glycopeptide comprising the amino acid sequence of SEQ ID NO:129 comprises a glycosylation site at the 30^{th} residue (Asn) of SEQ ID NO: 129 that is linked with a $Man_3GlcNAc_2$ moiety. In specific embodiments, the immunogenic glycopeptide is 18 amino acid residues in length. In specific embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO:130. In a specific embodiment, the immunogenic glycopeptide is 18 amino acid residues in

length and comprises the amino acid sequence of SEQ ID NO:130. In a particular embodiment, the immunogenic glycopeptide comprising the amino acid sequence of SEQ ID NO:130 comprises the two glycosylation sites at the 4th residue (Asn) and the 10th residue (Asn) that are each linked with a chitobiose. In specific embodiments, the immunogenic glycopeptide is 15 amino acid residues in length. In specific embodiments, the immunogenic glycopeptide comprises the amino acid sequence of SEQ ID NO:131. In a specific embodiment, the immunogenic glycopeptide is 15 amino acid residues in length and comprises the amino acid sequence of SEQ ID NO:131. In a particular embodiment, the immunogenic glycopeptide comprising the amino acid sequence of SEQ ID NO:131 comprises a glycosylation site at the 7th residue (Asn) that is linked with a chitobiose.

[00362] In another aspect, provided herein is a method of generating an antibody or an antigen-binding fragment thereof that specifically binds to a glycoprotein, comprising immunizing a subject with an immunogenic glycopeptide comprising one or more glycosylation sites as described above. In certain embodiments, the immunogenic glycopeptide comprises an at least 10 amino acid portion of the amino acid sequence of the glycoprotein, and at least one of the one or more glycosylation sites of the immunogenic glycopeptide is in said portion of the amino acid sequence. In other certain embodiments, the immunogenic glycopeptide comprises an at least 15, 20, 25 or 30 amino acid portion of the amino acid sequence of the glycoprotein, and at least one of the one or more glycosylation sites of the immunogenic glycopeptide is in said portion of the amino acid sequence. In a particular embodiment, the glycoprotein comprises the amino acid sequence of SEQ ID NO: 150. In a specific embodiment, the antibody or antigen-binding fragment thereof lacks specific binding to a non-glycosylated form of the glycoprotein. The subject immunized in accordance with the methods described herein can be, but is not limited to, a goat, a sheep, a donkey, a chicken, a guinea pig, a rat, a rabbit, or a mouse. In some embodiments, the subject immunized in accordance with the methods described herein is a rat, a rabbit, or a mouse. In a specific embodiment, the subject immunized in accordance with the methods described herein is a mouse. Immunization of the subject can be performed by any method known in the art, for example, by administering the immunogenic glycopeptide and an adjuvant to the subject as described in Example 2 and Example 3 (*see*, Section 6.2 and Section 6.3).

[00363] In another aspect, also provided herein is a method of preparing an immunogenic glycopeptide described herein. In certain embodiments, the method of preparing the immunogenic glycopeptide comprises linking one or more glycosylation sites of the immunogenic glycopeptide described herein with a carbohydrate (*e.g.*, a chitobiose). In certain embodiments, the method of preparing the immunogenic glycopeptide also comprises synthesizing the peptide moiety. The peptide moiety of the immunogenic glycopeptide can be synthesized by any method known in the art, for example, by Fmoc solid-phase peptide synthesis as described in Example 2 (*see*, Section 6.2). In certain embodiments, the amino acid (*e.g.*, asparagine) at the one or more glycosylation sites is protected by a protecting group during the synthesis of the immunogenic glycopeptide. In a specific embodiment, only one asparagine residue of the peptide moiety is linked with a carbohydrate (*e.g.*, a chitobiose), and the protecting group on the asparagine is an allyl group. In another specific embodiment, more than one (*e.g.*, two) asparagine residues of the peptide moiety are each linked with a carbohydrate (*e.g.*, a chitobiose), and the protecting group on the asparagine residues is *O*-2-phenylisopropyl ester (*O*-2-Ph*i* Pr, OPp). The linking step can be performed by any method known in the art. In a preferred embodiment, the carbohydrate moiety is linked with the peptide moiety using a one-flask aspartylation/deprotection procedure as described in Example 2 (*see* Section 6.2.2.1).

[00364] Methods to produce MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein are known to one of ordinary skill in the art, for example, by chemical synthesis, by purification from biological sources, or by recombinant expression techniques, including, for example, from mammalian cell or transgenic preparations. The methods described herein employs, unless otherwise indicated, conventional techniques in molecular biology, microbiology, genetic analysis, recombinant DNA, organic chemistry, biochemistry, PCR, oligonucleotide synthesis and modification, nucleic acid hybridization, and related fields within the skill of the art. These techniques are described, for example, in the references cited herein and are fully explained in the literature. See, for example, Maniatis et al. (1982) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press; Sambrook et al. (1989), Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor Laboratory Press; Sambrook et al. (2001) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY; Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons (1987 and annual updates); Current Protocols in Immunology, John

Wiley & Sons (1987 and annual updates) Gait (ed.) (1984) Oligonucleotide Synthesis: A Practical Approach, IRL Press; Eckstein (ed.) (1991) Oligonucleotides and Analogues: A Practical Approach, IRL Press; Birren et al. (eds.) (1999) Genome Analysis: A Laboratory Manual, Cold Spring Harbor Laboratory Press.

[00365] A variety of methods exist in the art for the production of MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein (*see*, Section 5.1 and Section 5.2). For example, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof may be made by recombinant DNA methods, such as those described in U.S. Pat. No. 4,816,567. The one or more DNAs encoding a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein can be readily isolated and sequenced using conventional procedures (*e.g.,* by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies, or such chains from human, humanized, or other sources). Once isolated, the DNA may be placed into expression vectors, which are then transformed into host cells such as NS0 cells, Simian COS cells, Chinese hamster ovary (CHO) cells, yeast cells, algae cells, eggs, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of the MUC16 Glycosylation Antibody or antigen-binding fragment thereof in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains of a desired species in place of the homologous human sequences (U.S. Pat. No. 4,816,567; Morrison et al, supra) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof provided herein. In certain embodiments, the DNA is as described in Section 5.3.2.

[00366] MUC16 Glycosylation Antibodies or antigen-binding fragments thereof provided herein can also be prepared using at least one MUC16 Glycosylation Antibody- or antigen-binding fragment thereof-encoding polynucleotide to provide transgenic animals or mammals, such as goats, cows, horses, sheep, and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, for example, but not limited to, U.S. Pat. Nos. 5,827,690; 5,849,992; 4,873,316; 5,849,992; 5,994,616, 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

[00367] In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof provided herein can additionally be prepared using at least one MUC16 Glycosylation Antibody- or antigen-binding fragment thereof-encoding polynucleotide provided herein to provide transgenic plants and cultured plant cells (for example, but not limited to tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured there from. As a non-limiting example, transgenic tobacco leaves expressing recombinant proteins have been successfully used to provide large amounts of recombinant proteins, for example, using an inducible promoter. See, for example, Cramer et al., Curr. Top. Microbol. Immunol. 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian proteins at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, for example, Hood et al., Adv. Exp. Med. Biol. 464:127-147 (1999) and references cited therein. Antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as scFvs, including tobacco seeds and potato tubers. See, for example, Conrad et al., Plant Mol. Biol. 38:101-109 (1998) and references cited therein. Thus, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof can also be produced using transgenic plants, according to known methods. See also, for example, Fischer et al., Biotechnol. Appl. Biochem. 30:99-108 (October, 1999), Ma et al., Trends Biotechnol. 13:522-7 (1995); Ma et al., Plant Physiol. 109:341-6 (1995); Whitelam et al., Biochem Soc. Trans. 22:940-944 (1994); and references cited therein. Each of the above references is entirely incorporated herein by reference.

[00368] In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof provided herein can be prepared using at least one MUC16 Glycosylation Antibody- or antigen-binding fragment thereof-encoding polynucleotide provided herein to provide bacteria that produce such MUC16 Glycosylation Antibodies or antigen-binding fragments. As a non-limiting example, *E. coli* expressing recombinant proteins has been successfully used to provide large amounts of recombinant proteins. See, for example, Verma et al., 1998, 216(1-2): 165-181 and references cited therein.

[00369] Methods for making multispecific (*e.g.,* bispecific antibodies) have been described, see, *e.g.,* U.S. Patent Nos. 7,951,917; 7,183,076; 8,227,577; 5,837,242; 5,989,830; 5,869,620; 6,132,992 and 8,586,713.

[00370] In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof provided herein (see, Section 5.1 and Section 5.2) are utilized in the generation of bispecific antibodies. Bispecific antibodies can be made by fusing two hybridomas to create hybrid immunoglobulin molecules with two binding sites. Bispecific antibodies not only handcuff tumors to T-cells; they cross-link CD3 on T-cells and initiate the activation cascade. This way, T cell receptor-based cytotoxicity is redirected to desired tumor targets bypassing MHC restrictions. Arming of polyclonally activated T cells (ATC) with an anti-CD3-anti-MUC16 bispecific binding molecule combines the targeting specificity of the MUC16 Glycosylation Antibody with the non-MHC-restricted perforin/granzyme mediated cytotoxicity of T cells. Bispecific binding molecules BsAb or BiTE can arm ex vivo expanded activated T cells before infusion into a patient. This strategy converts every ATC into a specific CTL (Thakur and Lum, 2010, Curr Opin Mol Ther 12, 340-349; Grabert et al., 2006, Clin Cancer Res 12, 569-576).

[00371] Bispecific binding molecules may be comprised of a MUC16 Glycosylation Antibody, wherein the MUC16 Glycosylation Antibody is an immunoglobulin, wherein each light chain of the immunoglobulin is a fusion protein, wherein the fusion protein is the immunoglobulin light chain linked via a peptide linker to a scFv targeting CD3. A N297A mutation in the CH2 domain results in aglycosylation leading to no FcR or Clq binding.

[00372] A MUC16 Glycosylation Antibody or antigen-binding fragment thereof may be utilized to generate a CAR. CARs are most commonly composed of a single chain variable fragment length antibody (scFv), such as one derived from a monoclonal antibody targeting a given tumor associated antigen and/or variant thereof, a transmembrane domain (for example, a transmembrane domain derived from a T Cell surface molecule such as a costimulatory molecule such as CD8, CD28, OX-40, and 4-1BB), a signaling portion of a TCR complex, such as an intracellular domain and/or additional portion(s) of a TCR zeta (ζ) chain, such as a cytoplasmic signaling domain thereof. In a specific embodiment, the heavy and light chain variable regions of a monoclonal MUC16 Glycosylation Antibody described herein are isolated from a hybridoma cell line which generates a monoclonal MUC16 Glycosylation Antibody. For example, RNA is extracted from the hybridoma cell line and cDNA is generated from the RNA by reverse transcription PCR. The VH and VL chain variable regions are cloned by standard PCR utilizing primers specific for such variable regions. The resulting VH and VL fragments

are subcloned into a shuttle vector, such as, for example TopoTA PCR 2.1 cloning vector (Invitrogen), and sequenced. The VH and VL fragments are subsequently ligated to a $(Gly_4Ser)_3$ spacer domain, generating a MUC16 Glycosylation Antibody scFv and fused to the human CD8 leader peptide (CD8L) (CD8L-MUC16 Glycosylation Antibody scFv) by overlapping PCR (*see, e.g.,* Maher J, et al. Nat Biotechnol 2002;20(1):70-5.; and Gong MC et al., Neoplasia 1999;1(2):123-7). The coding region of the CD8L-MUC16 Glycosylation Antibody scFv is fused to the human CD8 hinge and transmembrane domains, or alternatively to the CD28 transmembrane and cytoplasmic signaling domains, fused to the T cell receptor CD3-ζ signaling domain (*see, e.g.,* Maher J, et al. Nat Biotechnol 2002;20(1):70-5.; Brentjens RJ, et al. Nat Med 2003;9(3):279-86; and Brentjens RJ, et al., Clin Cancer Res 2007;13(18 Pt 1):5426-35).

[00373] Also provided herein is a T cell expressing a CAR described herein. Methods for the generation of a T cell expressing a CAR are known in the art. For example, a CAR construct can be sub-cloned into a modified MMLV retroviral vector SFG (*see, e.g.,* Riviere I, et al., Proc Natl Acad Sci USA 1995;92(15):6733-7) or other suitable retroviral vectors. In some embodiments, the retroviral vector is a lentiviral vector, for example, an HIV-based vector. VSV-G pseudotyped retroviral supernatants derived from transduced gpg29 fibroblasts can be used to construct stable PG13 gibbon ape leukemia virus (GaLV) envelope-pseudotyped retroviral producing cell lines (*see, e.g.,* Gong MC, et al. Neoplasia 1999;1(2):123-7). Isolated healthy donor peripheral blood mononuclear cells (PBMCs) can be activated with phytohemagglutinin (PHA) at 2μg/m1 (Sigma. St. Louis, MO) and retrovirally transduced on retronectin coated non-tissue culture plates (Quintas-Cardama A, et al., Hum Gene Ther 2007;18(12):1253-60) to generate the T cell recombinantly expressing the CAR. Gene transfer of the CAR into the T cell can be assessed by FACS.

[00374] Single domain antibodies, *e.g.,* antibodies lacking the light chains, can be produced by methods well known in the art. See Riechmann L & Muyldermans S (1999) J Immunol 231: 25-38; Nuttall SD *et al.,* (2000) Curr Pharm Biotechnol 1(3): 253-263; Muyldermans S, (2001) J Biotechnol 74(4): 277-302; U.S. Patent No. 6,005,079; and International Publication Nos. WO 94/04678, WO 94/25591 and WO 01/44301.

[00375] In particular embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein, which binds to the same or an overlapping epitope as a MUC16 Glycosylation Antibody described herein, is a human MUC16 Glycosylation Antibody

or antigen-binding fragment thereof. In particular embodiments, a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein, which competitively blocks (*e.g.*, in a dose-dependent manner) any one of the antibodies described herein, from binding to MUC16, is a human MUC16 Glycosylation Antibody or antigen-binding fragment thereof. Human antibodies can be produced using any method known in the art. For example, transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes, can be used. In particular, the human heavy and light chain immunoglobulin gene complexes can be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region can be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes can be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the J_H region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of an antigen. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see, *e.g.*, Lonberg N & Huszar D (1995) Int Rev Immunol 13:65-93. For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, International Publication Nos. WO 98/24893, WO 96/34096 and WO 96/33735; and U.S. Patent Nos. 5,413,923, 5,625,126, 5,633,425, 5,569,825, 5,661,016, 5,545,806, 5,814,318 and 5,939,598. Examples of mice capable of producing human antibodies include the Xenomouse™ (Abgenix, Inc.; U.S. Patent Nos. 6,075,181 and 6,150,184), the HuAb-Mouse™ (Mederex, Inc./Gen Pharm; U.S. Patent Nos. 5,545,806 and 5,569, 825), the Trans Chromo Mouse™ (Kirin) and the KM Mouse™ (Medarex/Kirin).

[00376] Human antibodies which immunospecifically bind to MUC16 can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. *See* also U.S. Patent Nos. 4,444,887, 4,716,111, and 5,885,793; and International Publication Nos. WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741.

[00377] In some embodiments, human antibodies can be produced using mouse–human hybridomas. For example, human peripheral blood lymphocytes transformed with Epstein-Barr virus (EBV) can be fused with mouse myeloma cells to produce mouse–human hybridomas secreting human monoclonal antibodies, and these mouse–human hybridomas can be screened to determine ones which secrete human monoclonal antibodies that immunospecifically bind to a target antigen . Such methods are known and are described in the art, see, *e.g.,* Shinmoto H *et al.,* (2004) Cytotechnology 46: 19-23; Naganawa Y *et al.,* (2005) Human Antibodies 14: 27-31.

[00378] In specific embodiments, the methods of producing antibodies or antigen-binding fragments thereof that immunospecifically bind to MUC16 are as described in Section 6.2, *infra*.

[00379] In specific embodiments, the methods of screening and selecting antibodies or antigen-binding fragments thereof that immunospecifically bind to MUC16 are as described in Section 6.2, *infra*.

[00380] Once a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein has been produced, it can be purified by any method known in the art for purification of an immunoglobulin molecule, *e.g.,* by chromatography (*e.g.,* ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. Further, the antibodies described herein can be fused to heterologous polypeptide sequences described herein or otherwise known in the art to facilitate purification.

[00381] In specific embodiments, a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein is isolated or purified. Generally, an isolated antibody is one that is substantially free of other antibodies with different antigenic specificities than the isolated antibody. For example, in a particular embodiment, a preparation of a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein is substantially free of cellular material and/or chemical precursors. The language "substantially free of cellular material" includes preparations of a MUC16 Glycosylation Antibody or antigen binding fragment thereof

in which the antibody is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, a MUC16 Glycosylation Antibody or antigen binding fragment thereof that is substantially free of cellular material includes preparations of antibody having less than about 30%, 20%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein") and/or variants of a MUC16 Glycosylation Antibody or antigen binding fragment thereof, *e.g.,* different post-translational modified forms of a MUC16 Glycosylation Antibody or antigen binding fragment thereof or other different versions of a MUC16 Glycosylation Antibody or antigen binding fragment thereof (*e.g.,* antibody fragments). When the antibody is recombinantly produced, it is also generally substantially free of culture medium, *i.e.,* culture medium represents less than about 20%, 10%, 2%, 1%, 0.5%, or 0.1% of the volume of the protein preparation. When the antibody is produced by chemical synthesis, it is generally substantially free of chemical precursors or other chemicals, *i.e.,* it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly, such preparations of the antibody have less than about 30%, 20%, 10%, or 5% (by dry weight) of chemical precursors or compounds other than the antibody of interest. In a specific embodiment, antibodies described herein are isolated or purified.

5.3.2 POLYNUCLEOTIDES

[00382] In certain embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see*, Section 5.1 and Section 5.2). Also provided herein are vectors comprising such polynucleotides (*see*, Section 5.3.3). Also provided herein are polynucleotides encoding antigens of the MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2). Also provided herein are polynucleotides that hybridize under stringent or lower stringency hybridization conditions to polynucleotides that encode a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein.

[00383] The language "purified" includes preparations of polynucleotide or nucleic acid molecule having less than about 15%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% (in particular less than about 10%) of other material, *e.g.,* cellular material, culture medium, other nucleic acid molecules, chemical precursors and/or other chemicals. In a specific embodiment, a nucleic acid

molecule(s) encoding a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2) is isolated or purified.

[00384] Nucleic acid molecules provided herein can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as the anti-sense strand.

[00385] In certain embodiments, provided herein is a polynucleotide comprising nucleotide sequences encoding MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2).

[00386] In particular aspects, also provided herein are polynucleotides comprising nucleotide sequences encoding MUC16 Glycosylation Antibodies or antigen-binding fragments thereof (*see*, Section 5.1 and Section 5.2), which immunospecifically bind to MUC16, and comprise an amino acid sequence as described herein, as well as antibodies which compete with such MUC16 Glycosylation Antibody or antigen-binding fragment thereof for binding to MUC16, or which binds to the same epitope as that of such antibodies.

[00387] The polynucleotides provided herein can be obtained by any method known in the art. For example, if the nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see*, Section 5.1 and Section 5.2) described herein is known, a polynucleotide encoding the MUC16 Glycosylation Antibody or antigen-binding fragment thereof can be may be assembled from chemically synthesized oligonucleotides (*e.g.*, as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[00388] Alternatively, a polynucleotide encoding a MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see*, Section 5.1 and Section 5.2) may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular MUC16 Glycosylation Antibody or antigen-binding fragment thereof is not available, but the sequence of the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is known,

a nucleic acid encoding the MUC16 Glycosylation Antibody or antigen-binding fragment thereof may be chemically synthesized or obtained from a suitable source (*e.g.,* an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express a MUC16 Glycosylation Antibody or antigen binding fragment thereof provided herein) by PCR amplification using synthetic primers that hybridize to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, for example, a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art (*see*, for example, Section 5.3.3).

[00389] In such embodiments, a polynucleotide encoding such a MUC16 Glycosylation Antibody or antigen-binding fragment thereof may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, *e.g.,* recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y. and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, N.Y., which are both incorporated by reference herein in their entireties), to generate MUC16 Glycosylation Antibodies or antigen-binding fragments thereof having a different amino acid sequence, for example, to create amino acid substitutions, deletions, and/or insertions. For example, such manipulations can be performed to render the encoded amino acid aglycosylated, or to destroy the antibody's ability to bind to C1q, Fc receptor, or to activate the complement system.

[00390] Isolated nucleic acid molecules provided herein can include nucleic acid molecules comprising an open reading frame (ORF), optionally with one or more introns, for example, but not limited to, at least one specified portion of at least one complementarity determining region (CDR), as CDR1, CDR2 and/or CDR3 of at least one heavy chain or light chain; nucleic acid molecules comprising the coding sequence for a MUC16 Glycosylation Antibody or variable region; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof as described herein.

[00391] Also provided herein are isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides provided herein can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

[00392] The nucleic acids can conveniently comprise sequences in addition to a polynucleotide provided herein. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. In addition, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide provided herein. For example, a hexa-histidine marker sequence provides a convenient means to purify the polypeptides provided herein. The nucleic acid provided herein—excluding the coding sequence—is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide provided herein.

[00393] Additional sequences can also be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, *e.g.,* Ausubel, supra; or Sambrook, supra).

[00394] In a specific embodiment, using routine recombinant DNA techniques, one or more of the CDRs of a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein may be inserted within known framework regions. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, *e.g.,* Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes a MUC16 Glycosylation Antibody or antigen binding fragment thereof that immunospecifically binds MUC16. One or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an

intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are provided herein and within the skill of the art.

[00395] In certain embodiments, the isolated or purified nucleic acid molecule, or fragment thereof, upon linkage with another nucleic acid molecule, can encode a fusion protein. The generation of fusion proteins is within the ordinary skill in the art and can involve the use of restriction enzyme or recombinational cloning techniques (see, for example, Gateway.TM.. (Invitrogen)). See, also, U.S. Pat. No. 5,314,995.

[00396] In certain embodiments, a polynucleotide provided herein is in the form of a vector (*e.g.,* expression vector) as described in Section 5.3.3.

[00397] In certain aspects, provided herein are polynucleotides comprising a nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein or an antigen-binding fragment thereof (*e.g.,* a variable light chain region and/or variable heavy chain region) that immunospecifically binds to MUC16, and vectors, *e.g.,* vectors comprising such polynucleotides for their efficient expression in host cells (*e.g., E. coli* and mammalian cells). In some embodiments, a polynucleotide is isolated or purified.

[00398] As used herein, an "isolated" polynucleotide or nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source (*e.g.,* in a mouse or a human) of the nucleic acid molecule. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized. For example, the language "substantially free" includes preparations of polynucleotide or nucleic acid molecule having less than about 15%, 10%, 5%, 2%, 1%, 0.5%, or 0.1% of other material, *e.g.,* cellular material, culture medium, other nucleic acid molecules, chemical precursors and/or other chemicals.

[00399] In particular aspects, provided herein are polynucleotides comprising nucleotide sequences encoding MUC16 Glycosylation Antibodies or antigen binding fragments thereof and comprise an amino acid sequence as described herein, as well as antibodies which compete with such antibodies for binding to MUC16 (*e.g.,* in a dose-dependent manner), or which binds to the same or an overlapping epitope as that of such antibodies.

[00400] In certain aspects, provided herein are polynucleotides comprising a nucleic acid sequence encoding the light chain or heavy chain of a MUC16 Glycosylation Antibody or

antigen binding fragment thereof described herein. The polynucleotides can comprise nucleotide sequences encoding a heavy chain comprising the VH CDRs described herein (see, *e.g.,* Table 1, Table 3, and Table 5). The polynucleotides can comprise nucleotide sequences encoding a light chain comprising the VL CDRs described herein (see, *e.g.,* Table 2, Table 4, and Table 6).

[00401] In particular embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding a MUC16 Glycosylation Antibody comprising three VH CDRs, *e.g.,* containing VH CDR1, VH CDR2, and VH CDR3 as described in Table 1, Table 3, or Table 5. In specific embodiments, a polynucleotide described herein encodes a VH CDR1, a VH CDR2, and a VH CDR3 of the 10C6, 7B12, 19C11, 16C5, and 18C6 consensus VH CDRs (*i.e.*, SEQ ID NO:103, SEQ ID NO:104, and SEQ ID NO:105, respectively, or SEQ ID NO:109, SEQ ID NO:110, and SEQ ID NO:111, respectively, or SEQ ID NO:115, SEQ ID NO:116, and SEQ ID NO:117). In specific embodiments, a polynucleotide described herein encodes a VH CDR1, a VH CDR2, and a VH CDR3 of 10C6 (*i.e.*, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5, respectively, or SEQ ID NO:9, SEQ ID NO:10, and SEQ ID NO:11, respectively, or SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively). In specific embodiments, a polynucleotide described herein encodes a VH CDR1, a VH CDR2, and a VH CDR3 of 7B12 (*i.e.*, SEQ ID NO:23, SEQ ID NO:24, and SEQ ID NO:25, respectively, or SEQ ID NO:29, SEQ ID NO:30, and SEQ ID NO:31, respectively, or SEQ ID NO:35, SEQ ID NO:36, and SEQ ID NO:37, respectively). In specific embodiments, a polynucleotide described herein encodes a VH CDR1, a VH CDR2, and a VH CDR3 of 19C11 (*i.e.*, SEQ ID NO:43, SEQ ID NO:44, and SEQ ID NO:45, respectively, or SEQ ID NO:49, SEQ ID NO:50, and SEQ ID NO:51, respectively, or SEQ ID NO:55, SEQ ID NO:56, and SEQ ID NO:57, respectively). In specific embodiments, a polynucleotide described herein encodes a VH CDR1, a VH CDR2, and a VH CDR3 of 16C5 (*i.e.*, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, respectively, or SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, respectively, or SEQ ID NO:75, SEQ ID NO:76, and SEQ ID NO:77, respectively). In specific embodiments, a polynucleotide described herein encodes a VH CDR1, a VH CDR2, and a VH CDR3 of 18C6 (*i.e.*, SEQ ID NO:83, SEQ ID NO:84, and SEQ ID NO:85, respectively, or SEQ ID NO:89, SEQ ID NO:90, and SEQ ID NO:91, respectively, or SEQ ID NO:95, SEQ ID NO:96, and SEQ ID NO:97, respectively).

[00402] In specific embodiments, provided herein are polynucleotides comprising a nucleotide sequence encoding MUC16 Glycosylation Antibody comprising (a) three VH CDRs,

e.g., containing VH CDR1, VH CDR2, and VH CDR3 as described in Table 1, Table 3, or Table 5, and (b) three VL chain CDRs, *e.g.,* containing VL CDR1, VL CDR2, and VL CDR3 as described in Table 2, Table 4, or Table 6. In specific embodiments, a polynucleotide described herein encodes (a) a VH CDR1, a VH CDR2, and a VH CDR3 of the 10C6, 7B12, 19C11, 16C5, and 18C6 consensus VH CDRs (*i.e.*, SEQ ID NO:103, SEQ ID NO:104, and SEQ ID NO:105, respectively, or SEQ ID NO:109, SEQ ID NO:110, and SEQ ID NO:111, respectively, or SEQ ID NO:115, SEQ ID NO:116, and SEQ ID NO:117), and (b) a VL CDR1, a VL CDR2, and a VL CDR3 of the 10C6, 7B12, 19C11, 16C5, and 18C6 consensus VL CDRs (*i.e.*, SEQ ID NO:106, SEQ ID NO:107, and SEQ ID NO:108, respectively, or SEQ ID NO:112, SEQ ID NO:113, and SEQ ID NO:114, respectively, or SEQ ID NO:118, SEQ ID NO:119, and SEQ ID NO:120). In specific embodiments, a polynucleotide described herein encodes (a) a VH CDR1, a VH CDR2, and a VH CDR3 of 10C6 (*i.e.*, SEQ ID NO:3, SEQ ID NO:4, and SEQ ID NO:5, respectively, or SEQ ID NO:9, SEQ ID NO:10, and SEQ ID NO:11, respectively, or SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively), and (b) a VL CDR1, a VL CDR2, and a VL CDR3 of 10C6 (*i.e.*, SEQ ID NO:6, SEQ ID NO:7, and SEQ ID NO:8, respectively, or SEQ ID NO:12, SEQ ID NO:13, and SEQ ID NO:14, respectively, or SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively). In specific embodiments, a polynucleotide described herein encodes (a) a VH CDR1, a VH CDR2, and a VH CDR3 of 7B12 (*i.e.*, SEQ ID NO:23, SEQ ID NO:24, and SEQ ID NO:25, respectively, or SEQ ID NO:29, SEQ ID NO:30, and SEQ ID NO:31, respectively, or SEQ ID NO:35, SEQ ID NO:36, and SEQ ID NO:37, respectively), and (b) a VL CDR1, a VL CDR2, and a VL CDR3 of 7B12 (*i.e.*, SEQ ID NO:26, SEQ ID NO:27, and SEQ ID NO:28, respectively, or SEQ ID NO:32, SEQ ID NO:33, and SEQ ID NO:34, respectively, or SEQ ID NO:38, SEQ ID NO:39, and SEQ ID NO:40, respectively). In specific embodiments, a polynucleotide described herein encodes (a) a VH CDR1, a VH CDR2, and a VH CDR3 of 19C11 (*i.e.*, SEQ ID NO:43, SEQ ID NO:44, and SEQ ID NO:45, respectively, or SEQ ID NO:49, SEQ ID NO:50, and SEQ ID NO:51, respectively, or SEQ ID NO:55, SEQ ID NO:56, and SEQ ID NO:57, respectively), and (b) a VL CDR1, a VL CDR2, and a VL CDR3 of 19C11 (*i.e.*, SEQ ID NO:46, SEQ ID NO:47, and SEQ ID NO:48, respectively, or SEQ ID NO:52, SEQ ID NO:53, and SEQ ID NO:54, respectively, or SEQ ID NO:58, SEQ ID NO:59, and SEQ ID NO:60, respectively). In specific embodiments, a polynucleotide described herein encodes (a) a VH CDR1, a VH CDR2, and a VH CDR3 of 16C5

(*i.e.*, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65, respectively, or SEQ ID NO:69, SEQ ID NO:70, and SEQ ID NO:71, respectively, or SEQ ID NO:75, SEQ ID NO:76, and SEQ ID NO:77, respectively), and (b) a VL CDR1, a VL CDR2, and a VL CDR3 of 16C5 (*i.e.*, SEQ ID NO:66, SEQ ID NO:67, and SEQ ID NO:68, respectively, or SEQ ID NO:72, SEQ ID NO:73, and SEQ ID NO:74, respectively, or SEQ ID NO:78, SEQ ID NO:79, and SEQ ID NO:80, respectively). In specific embodiments, a polynucleotide described herein encodes (a) a VH CDR1, a VH CDR2, and a VH CDR3 of 18C6 (*i.e.*, SEQ ID NO:83, SEQ ID NO:84, and SEQ ID NO:85, respectively, or SEQ ID NO:89, SEQ ID NO:90, and SEQ ID NO:91, respectively, or SEQ ID NO:95, SEQ ID NO:96, and SEQ ID NO:97, respectively), and (b) a VL CDR1, a VL CDR2, and a VL CDR3 of 18C6 (*i.e.*, SEQ ID NO:86, SEQ ID NO:87, and SEQ ID NO:88, respectively, or SEQ ID NO:92, SEQ ID NO:93, and SEQ ID NO:94, respectively, or SEQ ID NO:98, SEQ ID NO:99, and SEQ ID NO:100, respectively).

[00403] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises an amino acid sequence described herein (*e.g.,* SEQ ID NO:1, SEQ ID NO:21, SEQ ID NO:41, SEQ ID NO:61, SEQ ID NO:81, or SEQ ID NO:101), wherein the antibody immunospecifically binds to MUC16.

[00404] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a light chain variable region that comprises an amino acid sequence described herein (*e.g.,* SEQ ID NO:2, SEQ ID NO:22, SEQ ID NO:42, SEQ ID NO:62, SEQ ID NO:82, or SEQ ID NO:102), wherein the antibody immunospecifically binds to MUC16.

[00405] In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:101, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:102. In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:101, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:2. In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody

described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:101, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:42. In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:1, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:2. In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:21, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:22. In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:41, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:42. In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:61, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:62. In certain embodiments, a polynucleotide described herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody described herein comprising a heavy chain variable region that comprises the amino acid sequence of SEQ ID NO:81, and a light chain variable region that comprises the amino acid sequence of SEQ ID NO:82.

[00406] In certain embodiments, a polynucleotide described herein encodes a VH comprising a nucleic acid sequence of SEQ ID NO:140, SEQ ID NO:142, SEQ ID NO:144, SEQ ID NO:146, or SEQ ID NO:148. In certain embodiments, a polynucleotide described herein encodes a VL comprising a nucleic acid sequence of SEQ ID NO:141, SEQ ID NO:143, SEQ ID NO:145, SEQ ID NO:147, or SEQ ID NO:149. In a specific embodiment, a polynucleotide described herein encodes a VH comprising a nucleic acid sequence of SEQ ID NO:140, and a VL comprising the nucleic acid sequence of SEQ ID NO:141 (*e.g.,* 10C6). In a specific embodiment, a polynucleotide described herein encodes a VH comprising a nucleic acid sequence of SEQ ID NO:142, and a VL comprising the nucleic acid sequence of SEQ ID

NO:143 (*e.g.*, 7B12). In a specific embodiment, a polynucleotide described herein encodes a VH comprising a nucleic acid sequence of SEQ ID NO:144, and a VL comprising the nucleic acid sequence of SEQ ID NO:145 (*e.g.*, 19C11). In a specific embodiment, a polynucleotide described herein encodes a VH comprising a nucleic acid sequence of SEQ ID NO:146, and a VL comprising the nucleic acid sequence of SEQ ID NO:147 (*e.g.*, 16C5). In a specific embodiment, a polynucleotide described herein encodes a VH comprising a nucleic acid sequence of SEQ ID NO:148, and a VL comprising the nucleic acid sequence of SEQ ID NO:149 (*e.g.*, 18C6).

[00407] In specific aspects, provided herein is a polynucleotide comprising a nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen binding fragment thereof comprising a light chain and a heavy chain, *e.g.*, a separate light chain and heavy chain. With respect to the heavy chain, in a specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a gamma (*e.g.*, gamma1, gamma2, gamma3, or gamma4) heavy chain. In a particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein wherein the antibody comprises a heavy chain, and wherein the amino acid sequence of the variable region of the heavy chain can comprise any amino acid sequence of SEQ ID NO:1, SEQ ID NO:21, SEQ ID NO:41, SEQ ID NO:61, SEQ ID NO:81, or SEQ ID NO:101, and wherein the constant region of the heavy chain is a human gamma heavy chain constant region.

[00408] With respect to the light chain, in a specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a kappa light chain. In another specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a lambda light chain. In yet another specific embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein comprising a human kappa light chain or a human lambda light chain. In a particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein wherein the antibody comprises a light chain, and wherein the amino acid sequence of the variable region of the light chain can comprise any amino acid sequence of SEQ ID NO:2, SEQ ID NO:22, SEQ ID NO:42, SEQ ID NO:62, SEQ ID NO:82, or SEQ ID NO:102,

and wherein the constant region of the light chain is a human kappa light chain constant region. In another particular embodiment, a polynucleotide provided herein comprises a nucleotide sequence encoding a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein comprise a light chain, wherein the amino acid sequence of the variable region of the light chain can comprise any amino acid sequence of SEQ ID NO:2, SEQ ID NO:22, SEQ ID NO:42, SEQ ID NO:62, SEQ ID NO:82, or SEQ ID NO:102, and wherein the constant region of the light chain is a human lambda light chain constant region.

[00409] For a detailed example for the generation of MUC16 Glycosylation Antibodies described herein, *see*, Section 6.2 and Section 6.3.

5.3.3 CELLS AND VECTORS

[00410] In certain embodiments, provided herein are cells (*e.g., ex vivo* cells) expressing (*e.g.,* recombinantly) one or more MUC16 Glycosylation Antibodies or antigen-binding fragments thereof (*see*, Section 5.1 and Section 5.2). Also provided herein are vectors (*e.g.,* expression vectors) comprising nucleotide sequences (see, for example, Section 5.3.2) encoding a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein for recombinant expression in host cells, preferably in mammalian cells. Also provided herein are cells (*e.g., ex vivo* cells) comprising such vectors or nucleotide sequences for recombinantly expressing a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described here. Also provided herein are methods for producing a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein, comprising expressing such MUC16 Glycosylation Antibody or antigen-binding fragment thereof from a cell (*e.g., ex vivo* cell). In a preferred embodiment, the cell is an *ex vivo* cell.

[00411] A vector (*e.g.,* expression vector) is a DNA molecule comprising a gene that is expressed in a cell (*e.g., ex vivo* cell). Typically, gene expression is placed under the control of certain regulatory elements, including constitutive or inducible promoters, tissue-specific regulatory elements and enhancers. Such a gene is said to be "operably linked to" the regulatory elements, *e.g.,* a promoter. A recombinant host may be any prokaryotic or eukaryotic cell that contains either a cloning vector or expression vector. This term also includes those prokaryotic or eukaryotic cells, as well as a transgenic animal, that have been genetically engineered to

contain the cloned gene(s) in the chromosome or genome of the host cell or cells of the host cells (*e.g., ex vivo* cells). In one embodiment, the promoter is the CMV promoter.

[00412] In certain embodiments, provided herein is a vector comprising one or more polynucleotide as described in Section 5.3.2. In certain embodiments, a polynucleotide as described in Section 5.3.2 can be cloned into a suitable vector and can be used to transform or transfect any suitable host. Vectors and methods to construct such vectors are known to one of ordinary skill in the art and are described in general technical references (see, in general, "Recombinant DNA Part D," Methods in Enzymology, Vol. 153, Wu and Grossman, eds., Academic Press (1987)). In certain embodiments, the vector comprises regulatory sequences, such as transcription and translation initiation and termination codons, which are specific to the type of host (*e.g.,* bacterium, fungus, plant, insect, or mammal) into which the vector is to be introduced, as appropriate and taking into consideration whether the vector is DNA or RNA. In certain embodiments, the vector comprises regulatory sequences that are specific to the genus of the host. In certain embodiments, the vector comprises regulatory sequences that are specific to the species of the host.

[00413] In certain embodiments, the vector comprises one or more marker genes, which allow for selection of transformed or transfected hosts. Non-limiting examples of marker genes include biocide resistance, *e.g.,* resistance to antibiotics, heavy metals, etc., complementation in an auxotrophic host to provide prototrophy, and the like. In a preferred embodiment, the vector comprises ampicillin and hygromycin selectable markers.

[00414] In certain embodiments, an expression vector can comprise a native or normative promoter operably linked to a polynucleotide as described in Section 5.3.2. The selection of promoters, for example, strong, weak, inducible, tissue-specific and developmental-specific, is within the skill in the art. Similarly, the combining of a nucleic acid molecule, or fragment thereof, as described above with a promoter is also within the skill in the art.

[00415] Non-limiting examples of suitable vectors include those designed for propagation and expansion or for expression or both. For example, a cloning vector can be selected from the group consisting of the pUC series, the pBluescript series (Stratagene, LaJolla, Calif.), the pET series (Novagen, Madison, Wis.), the pGEX series (Pharmacia Biotech, Uppsala, Sweden), and the pEX series (Clontech, Palo Alto, Calif.). Bacteriophage vectors, such as lamda-GT10, lamda-GT11, lamda-ZapII (Stratagene), lamda-EMBL4, and lamda-NM1149, can also be used.

Non-limiting examples of plant expression vectors include pBI110, pBI101.2, pBI101.3, pBI121 and pBIN19 (Clontech). Non-limiting examples of animal expression vectors include pEUK-C1, pMAM and pMAMneo (Clontech). The TOPO cloning system (Invitrogen, Carlsbad, Calif.) can also be used in accordance with the manufacturer's recommendations.

[00416] In certain embodiments, the vector is a mammalian vector. In certain embodiments, the mammalian vector contains at least one promoter element, which mediates the initiation of transcription of mRNA, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. In certain embodiments, the mammalian vector contains additional elements, such as, for example, enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. In certain embodiments, highly efficient transcription can be achieved with, for example, the early and late promoters from SV40, the long terminal repeats (LTRS) from retroviruses, for example, RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (*e.g.,* the human actin promoter). Non-limiting examples of mammalian expression vectors include, vectors such as pIRESlneo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clonetech Labs, Palo Alto, Calif.), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Non-limiting example of mammalian host cells that can be used in combination with such mammalian vectors include human Hela 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[00417] In certain embodiments, the vector is a viral vector, for example, retroviral vectors, parvovirus-based vectors, *e.g.,* adeno-associated virus (AAV)-based vectors, AAV-adenoviral chimeric vectors, and adenovirus-based vectors, and lentiviral vectors, such as Herpes simplex (HSV)-based vectors. In certain embodiments, the viral vector is manipulated to render the virus replication deficient. In certain embodiments, the viral vector is manipulated to eliminate toxicity to the host. These viral vectors can be prepared using standard recombinant DNA techniques described in, for example, Sambrook et al., Molecular Cloning, a Laboratory Manual, 2d edition, Cold Spring Harbor Press, Cold Spring Harbor, N.Y. (1989); and Ausubel et al.,

Current Protocols in Molecular Biology, Greene Publishing Associates and John Wiley & Sons, New York, N.Y. (1994).

[00418] In certain embodiments, a vector or polynucleotide described herein can be transferred to a cell (*e.g.,* an *ex vivo* cell) by conventional techniques and the resulting cell can be cultured by conventional techniques to produce a MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein. Accordingly, provided herein are cells comprising a polynucleotide encoding a MUC16 Glycosylation Antibody or antigen-binding fragment thereof, a heavy or light chain thereof, or a light chain fusion polypeptide thereof, operably linked to a promoter for expression of such sequences in the host cell. In certain embodiments, a vector encoding the heavy chain operably linked to a promoter and a vector encoding the light chain operably linked to a promoter can be co-expressed in the cell for expression of the entire MUC16 Glycosylation Antibody. In certain embodiments, a vector encoding a heavy chain operably linked to a promoter and a vector encoding a light chain fusion polypeptide operably linked to a promoter can be co-expressed in the cell for expression of an entire bispecific binding molecule. In certain embodiments, a cell comprises a vector comprising a polynucleotide encoding both the heavy chain and the light chain polypeptide of a MUC16 Glycosylation Antibody described herein operably linked to a promoter. In certain embodiments, a cell comprises a vector comprising a polynucleotide encoding both the heavy chain and the light chain fusion polypeptide of a bispecific binding molecule described herein operably linked to a promoter. In certain embodiments, a cell comprises two different vectors, a first vector comprising a polynucleotide encoding a heavy chain operably linked to a promoter, and a second vector comprising a polynucleotide encoding a light chain polypeptide operably linked to a promoter. In certain embodiments, a cell comprises two different vectors, a first vector comprising a polynucleotide encoding a heavy chain operably linked to a promoter, and a second vector comprising a polynucleotide encoding a light chain fusion polypeptide operably linked to a promoter. In certain embodiments, a first cell comprises a first vector comprising a polynucleotide encoding a heavy chain of a MUC16 Glycosylation Antibody described herein, and a second cell comprises a second vector comprising a polynucleotide encoding a light chain polypeptide of a MUC16 Glycosylation Antibody described herein. In certain embodiments, provided herein is a mixture of cells comprising such first cell and such second cell. In certain embodiments, a first cell comprises a first vector comprising a polynucleotide encoding a heavy

chain of a bispecific binding molecule described herein, and a second cell comprises a second vector comprising a polynucleotide encoding a light chain fusion polypeptide of a bispecific binding molecule described herein. In certain embodiments, provided herein is a mixture of cells comprising such first cell and such second cell. In a preferred embodiment, the cell expresses the vector or vectors such that the oligonucleotide is both transcribed and translated efficiently by the cell.

[00419] In embodiment, the cell expresses the vector, such that the oligonucleotide, or fragment thereof, is both transcribed and translated efficiently by the cell.

[00420] In certain embodiments, the cell is present in a host, which can be an animal, such as a mammal. Examples of cells include, but are not limited to, a human cell, a human cell line, E. coli (*e.g.,* E. coli TB-1, TG-2, DH5a, XL-Blue MRF' (Stratagene), SA2821 and Y1090), B. subtilis, P. aerugenosa, S. cerevisiae, N. crassa, insect cells (*e.g.,* Sf9, Ea4) and others set forth herein below. In a preferred embodiment, the cell is a CHO cell. In an especially preferred embodiment, the cell is a CHO-S cell.

[00421] In certain embodiments, a polynucleotide described herein can be expressed in a stable cell line that comprises the polynucleotide integrated into a chromosome by introducing the polynucleotide into the cell. In certain embodiments, the polynucleotide is introduced into the cell by, for example, electroporation. In certain embodiments, the polynucleotide is introduced into the cell by, for example, transfection of a vector comprising the polynucleotide into the cell. In certain embodiments, the vector is co-transfected with a selectable marker such as DHFR, GPT, neomycin, or hygromycin to allow for the identification and isolation of the transfected cells. In certain embodiments, the transfected polynucleotide can also be amplified to express large amounts of the encoded MUC16 Glycosylation Antibody or antigen-binding fragment thereof. For example, the DHFR (dihydrofolate reductase) marker can be utilized to develop cell lines that carry several hundred or even several thousand copies of the polynucleotide of interest. Another example of a selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277-279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of antibodies.

[00422] In one embodiment, the vector comprises (i) a first polynucleotide sequence encoding an immunoglobulin light chain that binds to MUC16, operably linked to a first promoter and (ii) a second polynucleotide encoding an immunoglobulin heavy chain that binds to MUC16, operably linked to a second promoter. In certain embodiments, the vector is a viral vector.

[00423] In one embodiment, the vector comprises (i) a first polynucleotide sequence encoding a light chain fusion polypeptide comprising an immunoglobulin light chain fused to a scFv, via a peptide linker, wherein the light chain binds to MUC16 and wherein the scFv binds to CD3, operably linked to a first promoter and (ii) a second polynucleotide encoding an immunoglobulin heavy chain that binds to MUC16 operably linked to a second promoter. In certain embodiments, the vector is a viral vector.

5.4 PHARMACEUTICAL COMPOSITIONS

[00424] In certain embodiments, provided herein are compositions (*e.g.,* pharmaceutical compositions) and kits comprising a pharmaceutically effective amount of one or more MUC16 Glycosylation Antibodies or antigen-binding fragments thereof (*see*, Section 5.1 and Section 5.2). In certain embodiments, the pharmaceutical compositions comprise immune cells, for example T cells, recombinantly expressing an antibody, antigen-binding fragment thereof, and/or CAR described herein. Compositions may be used in the preparation of individual, single unit dosage forms. Compositions provided herein can be formulated for parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intra-Ommaya, intraocular, intravitreous, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, intrathecal, intraventricular in the brain, intraparenchymal in the brain, or transdermal administration. In a preferred embodiment, the composition is formulated for parenteral administration. In an especially preferred embodiment, the composition is formulated for intravenous administration. In a preferred embodiment, the composition is formulated for intraperitoneal administration. In a specific embodiment, the composition is formulated for intraperitoneal administration to treat peritoneal metastases. In a preferred embodiment, the composition is formulated for intrathecal administration. In a specific embodiment, the

composition is formulated for intrathecal administration to treat brain metastases. See, for example, Kramer et al, 2010, 97: 409-418. In a preferred embodiment, the composition is formulated for intraventricular administration in the brain. In a specific embodiment, the composition is formulated for intraventricular administration to treat brain metastases. See, for example, Kramer et al, 2010, 97: 409-418. In a preferred embodiment, the composition is formulated for intraparenchymal administration in the brain. In a specific embodiment, the composition is formulated for intraparenchymal administration to treat a brain tumor or brain tumor metastases. See, for example, Luther et al., 2014, Neuro Oncol, 16: 800-806, and Clinical Trial ID NO NCT01502917.

[00425] In a specific embodiment, the composition is formulated for intraperitoneal administration for peritoneal metastases.

[00426] In certain embodiments, provided herein is a composition comprising one or more polynucleotide comprising nucleotide sequences encoding a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein. In certain embodiments, provided herein is a composition comprising a cell, wherein the cell comprises one or more polynucleotide comprising nucleotide sequences encoding a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein. In certain embodiments, provided herein is a composition comprising a vector, wherein the vector comprises one or more polynucleotide comprising nucleotide sequences encoding a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein. In certain embodiments, provided herein is a composition comprising a cell, wherein the cell comprises a vector, wherein the vector comprises one or more polynucleotide comprising nucleotide sequences encoding a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein.

[00427] In certain embodiments, a composition described herein is a stable or preserved formulation. In certain embodiments, the stable formulation comprises a phosphate buffer with saline or a chosen salt. In certain embodiments, a composition described is a multi-use preserved formulation, suitable for pharmaceutical or veterinary use. In certain embodiments, a composition described herein comprises a preservative. Preservatives are known to one of ordinary skill in the art. Non-limiting examples of preservatives include phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (*e.g.,* hexahydrate), alkylparaben (methyl,

ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, and sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (*e.g.,* 0.2, 0.3. 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (*e.g.,* 0.5, 0.9, 1.1, 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (*e.g.,* 0.005, 0.01), 0.001-2.0% phenol (*e.g.,* 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (*e.g.,* 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

[00428] It can be sometimes desirable to deliver the compositions provided herein to a subject over prolonged periods of time, for example, for periods of one week to one year or more from a single administration. Various slow release, depot or implant dosage forms can be utilized. For example, a dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from *e.g.,* N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) *e.g.,* a zinc tannate salt. Additionally, a composition provided herein, preferably, a relatively insoluble salt such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, *e.g.,* sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer, for example, as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above can also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow release, depot or implant compositions, *e.g.,* gas or liquid liposomes are known in the

literature (U.S. Pat. No. 5,770,222 and "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978).

[00429] The range of at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof composition provided herein (*see*, Section 5.1 and Section 5.2) includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 microgram/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, *e.g.,* solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

[00430] In certain embodiments, compositions provided herein comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. In certain embodiments, pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but not limited to, Gennaro, Ed., Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (Easton, Pa.) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein.

[00431] In certain embodiments, compositions provided herein contain one or more pharmaceutical excipient and/or additive. Non-limiting examples of pharmaceutical excipients and additives are proteins, peptides, amino acids, lipids, and carbohydrates (*e.g.,* sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Non-limiting examples of protein excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Non-limiting examples of amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. In certain embodiments, the amino acid is glycine. Non-limiting examples of carbohydrate excipients include monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like;

polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. In certain embodiments, the carbohydrate excipient is mannitol, trehalose, or raffinose.

[00432] In certain embodiments, a composition provided herein includes one or more buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Non-limiting examples of buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. In certain embodiments, the buffer is an organic acid salts such as citrate. Other excipients, *e.g.,* isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The compositions can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably, the compositions provided herein have pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

[00433] In certain embodiments, a composition provided herein includes one or more polymeric excipient/additive such as, for example, polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (*e.g.,* cyclodextrins, such as 2-hydroxypropyl-.beta.-cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (*e.g.,* polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (*e.g.,* phospholipids, fatty acids), steroids (*e.g.,* cholesterol), and/or chelating agents (*e.g.,* EDTA).

[00434] Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic.RTM. polyls, other block co-polymers, and chelators such as EDTA and EGTA can optionally be added to the compositions to reduce aggregation. These additives are particularly useful if a pump or plastic

container is used to administer the composition. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the protein to aggregate.

[00435] Additional pharmaceutical excipients and/or additives suitable for use in a composition provided herein are known to one of skill in the art and are referenced in, for example, "Remington: The Science & Practice of Pharmacy", 19.sup.th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, N.J. (1998), which are entirely incorporated herein by reference. In certain preferred embodiments, the carrier or excipient materials are carbohydrates (*e.g.,* saccharides and alditols) and buffers (*e.g.,* citrate) or polymeric agents.

[00436] Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the composition is a concentration sufficient to yield an anti-microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

[00437] The compositions provided herein can be prepared by a process which comprises mixing at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2) and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable composition, for example, a measured amount of at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein and preservative at the desired concentrations. The compositions provided herein can be prepared by a process that comprises mixing at least one MUC16 Glycosylation

Antibody or antigen-binding fragment thereof described herein and a selected buffer, preferably a phosphate buffer containing saline or a chosen salt. Mixing the at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable composition, for example, a measured amount of at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the protein and buffer at the desired concentrations. Variations of these processes would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the composition is prepared, are all factors that can be optimized for the concentration and means of administration used.

5.4.1 PARENTERAL FORMULATIONS

[00438] In certain embodiments, a composition provided herein is formulated for parenteral injectable administration. As used herein, the term "parenteral" includes intravenous, intravascular, intramuscular, intradermal, subcutaneous, and intraocular. For parenteral administration, the composition can be formulated as a solution, suspension, emulsion or lyophilized powder in association, or separately provided, with a pharmaceutically acceptable parenteral vehicle. Non-limiting examples of such vehicles are water, saline, Ringer's solution, dextrose solution, glycerol, ethanol, and 1-10% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (*e.g.,* sodium chloride, mannitol) and chemical stability (*e.g.,* buffers and preservatives). The formulation is sterilized by known or suitable techniques.

[00439] Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

[00440] Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent such as aqueous solution or a sterile injectable solution or suspension in a solvent. As the usable

vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent, or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 entirely incorporated herein by reference.

5.4.2 PULMONARY FORMULATIONS

[00441] In certain embodiments, a composition comprising a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2) is formulated for pulmonary administration. For pulmonary administration, the composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. Compositions for pulmonary administration can be delivered by any of a variety of inhalation or nasal devices known in the art for administration of a therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal administration of a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein are also known in the art. All such devices use formulations suitable for the administration for the dispensing of a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non aqueous) or solid particles. Metered dose inhalers like the Ventolin® metered dose inhaler, typically use a propellent gas and require actuation during inspiration (See, *e.g.*, WO 94/16970, WO 98/35888). Dry powder inhalers like Turbuhaler™ (Astra), Rotahaler®. (Glaxo), Diskus® (Glaxo), devices marketed by Inhale Therapeutics, to name a few, use breath-actuation of a mixed powder (U.S. Pat. No. 4,668,218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO 94/08552 Dura, U.S. Pat. No. 5,458,135 Inhale, WO 94/06498 Fisons, entirely incorporated herein by reference). Nebulizers like the Ultravent® nebulizer (Mallinckrodt), and the Acorn II® nebulizer (Marquest Medical Products) (U.S. Pat. No. 5,404,871 Aradigm, WO 97/22376), the above references entirely incorporated herein by reference, produce aerosols from solutions, while metered dose

inhalers, dry powder inhalers, etc. generate small particle aerosols. Such examples of commercially available inhalation devices are non-limiting examples are not intended to be limiting in scope.

[00442] In certain embodiments, a spray comprising a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2) can be produced by forcing a suspension or solution of at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein through a nozzle under pressure. The nozzle size and configuration, the applied pressure, and the liquid feed rate can be chosen to achieve the desired output and particle size. An electrospray can be produced, for example, by an electric field in connection with a capillary or nozzle feed. Advantageously, particles of a composition comprising at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein delivered by a sprayer have a particle size less than about 10 um, preferably in the range of about 1 um to about 5 um, and most preferably about 2 um to about 3 um.

[00443] Formulations of a composition comprising at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2)suitable for use with a sprayer typically include the at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein in an aqueous solution at a concentration of about 0.1 mg to about 100 mg per ml of solution or mg/gm, or any range or value therein, *e.g.,* but not limited to, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/ml or mg/gm. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the MUC16 Glycosylation Antibody or antigen-binding fragment thereof composition, such as a buffer, a reducing agent, a bulk protein, or a carbohydrate. Bulk proteins useful in formulating such a composition include albumin, protamine, or the like. Typical carbohydrates useful in formulating antibody composition proteins include sucrose, mannitol, lactose, trehalose, glucose, or the like. The composition can also include a surfactant, which can reduce or prevent surface-induced aggregation of the composition caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxy ethylene sorbitol fatty acid esters. Amounts will generally range between

0.001 and 14% by weight of the formulation. Preferred surfactants are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like.

[00444] In certain embodiments, the composition is administered via a nebulizer, such as jet nebulizer or an ultrasonic nebulizer. Typically, in a jet nebulizer, a compressed air source is used to create a high-velocity air jet through an orifice. As the gas expands beyond the nozzle, a low-pressure region is created, which draws a solution of antibody composition protein through a capillary tube connected to a liquid reservoir. The liquid stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types can be employed to achieve the desired performance characteristics from a given jet nebulizer. In an ultrasonic nebulizer, high-frequency electrical energy is used to create vibrational, mechanical energy, typically employing a piezoelectric transducer. This energy is transmitted to the formulation of antibody composition protein either directly or through a coupling fluid, creating an aerosol including the antibody composition protein. Advantageously, particles of antibody composition protein delivered by a nebulizer have a particle size less than about 10 um, preferably in the range of about 1 um to about 5 um, and most preferably about 2 um to about 3 um.

[00445] In certain embodiments, the composition is administered via a metered dose inhaler (MDI), wherein a propellant, at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2), and any excipients or other additives are contained in a canister as a mixture including a liquefied compressed gas. Actuation of the metering valve releases die mixture as an aerosol, preferably containing particles in the size range of less than about 10 um, preferably about 1 um to about 5 um, and most preferably about 2 um to about 3 um. The desired aerosol particle size can be obtained by employing a formulation of antibody composition protein produced by various methods known to those of skill in the art, including jet-milling, spray drying, critical point condensation, or the like. Preferred metered dose inhalers include those manufactured by 3M or Glaxo and employing a hydrofluorocarbon propellant.

[00446] Formulations of a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2) for use with a metered-dose inhaler device will generally include a finely divided powder containing at least one Anti-IL-6 antibody as a suspension in a non-aqueous medium, for example, suspended in a propellant with the aid of

a surfactant. The propellant can be any conventional material employed for this purpose, such as chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, HFA-134a (hydrofluoroalkane-134a), HFA-227 (hydrofluoroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein as a suspension in the propellant, to protect the active agent against chemical degradation, and the like. Suitable surfactants include sorbitan trioleate, soya lecithin, oleic acid, or the like. In some cases solution aerosols are preferred using solvents such as ethanol. Additional agents known in the art for formulation of a protein can also be included in the formulation.

5.4.3 ORAL FORMULATIONS

[00447] In certain embodiments, a composition provided herein is formulated for oral administration. In certain embodiments, for oral administration, compositions and methods of administering at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein rely on the co-administration of adjuvants such as, for example, resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether, to artificially increase the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors such as, for example, pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol, to inhibit enzymatic degradation. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, such as, for example, inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, alpha.-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.

[00448] In certain embodiments, tablets and pills for oral administration can be further processed into enteric-coated preparations. In certain embodiments, liquid preparations for oral administration include, for example, emulsion, syrup, elixir, suspension and solution

preparations allowable for medical use. These preparations can contain inactive diluting agents ordinarily used in said field, for example, water. Liposome preparations can be utilized for oral administration preparations, for example, as described for insulin and heparin (U.S. Pat. No. 4,239,754). Additionally, microspheres of artificial polymers of mixed amino acids (proteinoids) can be utilized to in oral administration of pharmaceuticals, for example, as described in U.S. Pat. No. 4,925,673. Furthermore, carrier compounds, such as those described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,871,753, are used in oral administration of biologically active agents.

5.4.4 MUCOSAL FORMULATIONS

[00449] In certain embodiments, a composition provided herein is formulated for absorption through mucosal surfaces. In certain embodiments, for absorption through mucosal surfaces, compositions and methods of administering at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2) include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. No. 5,514,670). Mucous surfaces suitable for application of the emulsions provided herein can include, for example, corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, for example, suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration excipients include, for example, sugars, calcium stearate, magnesium stearate, pregelinatined starch, and the like (U.S. Pat. No. 5,849,695).

5.4.5 TRANSDERMAL FORMULATIONS

[00450] In certain embodiments, a composition provided herein is formulated for transdermal administration. In certain embodiments, for transdermal administration, the composition comprises at least one MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see*, Section 5.1 and Section 5.2) encapsulated in a delivery device such as, for example, a liposome or polymeric nanoparticles, microparticle, microcapsule, or microspheres

(referred to collectively as microparticles unless otherwise stated). A number of suitable devices are known for transdermal administration, including microparticles made of synthetic polymers such as polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other proteins, alginate and other polysaccharides, and combinations thereof (U.S. Pat. No. 5,814,599).

5.4.6 KITS

[00451] Also provided herein are kits comprising one or more antibodies described herein, or antigen-binding fragments thereof, or conjugates thereof. In a specific embodiment, provided herein is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions described herein, such as one or more antibodies or an antigen-binding fragment thereof described herein. In some embodiments, the kits contain a pharmaceutical composition described herein and a prophylactic or therapeutic agent.

[00452] Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, a dosage form, and/or instructions for use thereof. In certain embodiments, the instructions included with the kit provide guidance with respect to the dosage amounts and/or dosing regimens for administration of the pharmaceutical composition(s).

[00453] Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, packets, sachets, tubes, inhalers, pumps, bags, vials, containers, syringes and any packaging material suitable for a selected pharmaceutical composition and intended mode of administration and treatment.

[00454] Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors, drip bags, patches and inhalers.

[00455] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer the ingredients. For example, if an ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the ingredient can be dissolved to form a particulate-free

sterile solution that is suitable for parenteral administration or can be reconstituted as a suspension for oral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

5.5 USES AND METHODS

5.5.1 THERAPEUTIC USES AND METHODS

[00456] In certain embodiments, provided herein are methods for treating a cancer in a subject, in particular, a MUC16-positive cancer in a subject, comprising administering to the subject in need thereof a therapeutically effective amount of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see*, Section 5.1 and Section 5.2). In a specific embodiment, the subject is a subject as described in Section 5.5.5. In a specific embodiment, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is administered at a dose as described in Section 5.5.3. In a specific embodiment, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is administered according to a method as described in Section 5.5. In a specific embodiment, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is administered in combination with one or more additional pharmaceutically active agents as described in Section 5.5.4.

[00457] For use of a MUC16 Glycosylation Antibody or fragment thereof in a subject of a particular species, a MUC16 Glycosylation Antibody or fragment thereof is used that binds to MUC16 of that particular species. For example, to treat a human, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof is used that binds to human MUC16. In a specific embodiment, the MUC16 Glycosylation Antibody or antigen-binding fragment thereof is an immunoglobulin.

[00458] In addition, for use of a MUC16 Glycosylation Antibody or fragment thereof in a subject of a particular species, the MUC16 Glycosylation Antibody, preferably, the constant region of a MUC16 Glycosylation Antibody or antigen binding fragment thereof, is derived from

that particular species. For example, to treat a human, the MUC16 Glycosylation Antibody or fragment thereof can comprise a MUC16 Glycosylation Antibody or antigen binding fragment thereof that is an immunoglobulin, wherein the immunoglobulin comprises a human constant region. In a specific embodiment, the subject is a human.

[00459] In a specific embodiment, the MUC16-positive cancer is ovarian cancer, lung cancer, pancreatic cancer, breast cancer, fallopian tube cancer, uterine (*e.g.,* endometrial) cancer, primary peritoneum cancer or cancer of any other tissue that expresses the MUC16 receptor.

[00460] In specific embodiments, treatment can be to achieve beneficial or desired clinical results including, but not limited to, alleviation of a symptom, diminishment of extent of a disease, stabilizing (*i.e.*, not worsening) of state of a disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. In a specific embodiment, "treatment" can also be to prolong survival as compared to expected survival if not receiving treatment. In specific embodiments, the administration of a MUC16 Glycosylation Antibody or antigen binding fragment thereof described herein, or a pharmaceutical composition described herein to a subject with cancer (*e.g.,* ovarian cancer, lung cancer, pancreatic cancer, breast cancer, fallopian tube cancer, uterine (*e.g.,* endometrial) cancer, or primary peritoneum cancer, or cancer of any other tissue that expresses the MUC16 receptor) achieves at least one, two, three, four or more of the following effects: (i) the reduction or amelioration of the severity of one or more symptoms of cancer; (ii) the reduction in the duration of one or more symptoms associated with cancer; (iii) the prevention in the recurrence of a symptom associated with cancer; (iv) the reduction in hospitalization of a subject; (v) a reduction in hospitalization length; (vi) the increase in the survival of a subject; (vii) the enhancement or improvement of the therapeutic effect of another therapy; (viii) the inhibition of the development or onset of one or more symptoms associated with cancer; (ix) the reduction in the number of symptoms associated with cancer; (x) improvement in quality of life as assessed by methods well known in the art; (x) inhibition of the recurrence of a tumor; (xi) the regression of tumors and/or one or more symptoms associated therewith; (xii) the inhibition of the progression of tumors and/or one or more symptoms associated therewith; (xiii) a reduction in the growth of a tumor; (xiv) a decrease in tumor size (*e.g.,* volume or diameter); (xv) a reduction in the formation of a newly formed tumor; (xvi) prevention, eradication, removal, or control of primary, regional and/or metastatic tumors; (xvii)

a decrease in the number or size of metastases; (xviii) a reduction in mortality; (xix) an increase in relapse free survival; (xx) the size of the tumor is maintained and does not increase or increases by less than the increase of a tumor after administration of a standard therapy as measured by conventional methods available to one of skill in the art, such as magnetic resonance imaging (MRI), dynamic contrast-enhanced MRI (DCE-MRI), X-ray, and computed tomography (CT) scan, or a positron emission tomography (PET) scan; and/or (xxi) an increase in the length of remission in patients. Treatment can be to achieve one or more of the foregoing.

5.5.2 DIAGNOSTIC USES

[00461] In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof (*see,* Section 5.1 and Section 5.2) described herein can be used for diagnostic purposes to detect, diagnose, or monitor a condition described herein (*e.g.,* a condition involving MUC16-positive cancer cells). In certain embodiments, MUC16 Glycosylation Antibodies or antigen-binding fragments thereof for use in diagnostic purposes are labeled as described in Section 5.2.

[00462] In certain embodiments, provided herein are methods for the detection of a condition described herein comprising (a) assaying the expression of MUC16 or a fragment thereof in cells or a tissue sample of a subject using one or more MUC16 Glycosylation Antibodies or antigen-binding fragments thereof described herein; and (b) comparing the level of MUC16 or the fragment thereof expression with a control level, for example, levels in normal tissue samples (*e.g.,* from a subject not having a condition described herein, or from the same patient before onset of the condition), whereby an increase or decrease in the assayed level of MUC16 or the fragment thereof expression compared to the control level of MUC16 or the fragment thereof expression is indicative of a condition described herein.

[00463] Antibodies described herein can be used to assay the levels of MUC16 or a fragment thereof in a biological sample using classical immunohistological methods as described herein or as known to those of skill in the art (*e.g.,* see Jalkanen *et al.*, 1985, J. Cell. Biol. 101:976-985; and Jalkanen *et al.*, 1987, J. Cell . Biol. 105:3087-3096). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{121}In), and technetium (^{99}Tc);

luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[00464] In certain embodiments, monitoring of a condition described herein (*e.g.,* a MUC16-positive cancer), is carried out by repeating the method for diagnosing for a period of time after initial diagnosis.

[00465] Presence of the labeled molecule can be detected in the subject using methods known in the art for in vivo scanning. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

5.5.3 DOSES AND REGIMENS

[00466] A MUC16 Glycosylation Antibody or antigen-binding fragment thereof (*see,* Section 5.1 and Section 5.2), or composition (*see*, Section 5.4), or cells expressing the antibodies, or antigen-binding fragments thereof, described herein may be delivered to a subject by a variety of routes. These include, but are not limited to, parenteral, intranasal, intratracheal, oral, intradermal, topical, intramuscular, intraperitoneal, transdermal, intravenous, intratumoral, conjunctival and subcutaneous routes. Pulmonary administration can also be employed, *e.g.,* by use of an inhaler or nebulizer, and formulation with an aerosolizing agent for use as a spray. In one embodiment, a MUC16 Glycosylation Antibody or antigen-binding fragment thereof, or a composition described herein is administered parenterally to a subject (*e.g.,* a subject as described in Section 5.5.5). In a specific embodiment, said parenteral administration is intravenous, intramuscular, or subcutaneous.

[00467] The amount of a MUC16 Glycosylation Antibody or antigen-binding fragment thereof, or composition which will be effective in the treatment and/or prevention of a condition will depend on the nature of the disease, and can be determined by standard clinical techniques.

[00468] The precise dose to be employed in a composition will also depend on the route of administration, and the type of cancer, and should be decided according to the judgment of the practitioner and each subject's circumstances. For example, effective doses may also vary depending upon means of administration, target site, physiological state of the patient (including age, body weight and health), whether the patient is human or animal, other medications

administered, or whether treatment is prophylactic or therapeutic. Treatment dosages are optimally titrated to optimize safety and efficacy.

[00469] In certain embodiments, an *in vitro* assay is employed to help identify optimal dosage ranges. Effective doses may be extrapolated from dose response curves derived from *in vitro* or animal model test systems.

[00470] For a MUC16 Glycosylation Antibody or antigen binding fragment thereof, the dosage may range from about 0.0001 to 100 mg/kg, and more usually 0.01 to 15 mg/kg, of the patient body weight. For example, dosages can be 1 mg/kg body weight, 10 mg/kg body weight, or within the range of 1-10 mg/kg or in other words, 70 mg or 700 mg or within the range of 70-700 mg, respectively, for a 70 kg patient. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible.

[00471] In certain embodiments, such as in the administration of engineered cells expressing the antibodies or antigen-binding fragments thereof, or CARs, a subject is administered to the subject at a range of about one million to about 100 billion cells, such as, e.g., 1 million to about 50 billion cells (e.g., about 5 million cells, about 25 million cells, about 500 million cells, about 1 billion cells, about 5 billion cells, about 20 billion cells, about 30 billion cells, about 40 billion cells, or a range defined by any two of the foregoing values), such as about 10 million to about 100 billion cells (e.g., about 20 million cells, about 30 million cells, about 40 million cells, about 60 million cells, about 70 million cells, about 80 million cells, about 90 million cells, about 10 billion cells, about 25 billion cells, about 50 billion cells, about 75 billion cells, about 90 billion cells, or a range defined by any two of the foregoing values), and in some cases about 100 million cells to about 50 billion cells (e.g., about 120 million cells, about 250 million cells, about 350 million cells, about 450 million cells, about 650 million cells, about 800 million cells, about 900 million cells, about 3 billion cells, about 30 billion cells, about 45 billion cells) or any value in between these ranges. In some embodiments, the dose of total cells and/or dose of individual sub- populations of cells is within a range of between at or about 104 and at or about 109 cells/kilograms (kg) body weight, such as between 105 and 106 cells / kg body weight, for example, at or about 1 x 10^5 cells/kg, 1.5 x 10^5 cells/kg, 2 x 10^5 cells/kg, or 1 x 10^6 cells/kg, 2 x 10^6 cells/kg, 5 x 10^6 cells/kg, or 10 x 10^6 cells/kg body weight. For example, in some

embodiments, the cells are administered at, or within a certain range of error of, between at or about 10^4 and at or about 10^9 T cells/kilograms (kg) body weight, such as between 10^5 and 10^7 T cells / kg body weight.

[00472] A MUC16 Glycosylation Antibody or antigen-binding fragment thereof can be administered on multiple occasions. Intervals between single dosages can be 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 6 months, 1 year, or 2 years.

5.5.4 COMBINATION THERAPIES

[00473] In a specific embodiment, the methods provided herein for treating cancer (*e.g.*, ovarian cancer, pancreatic cancer, lung cancer, breast cancer, fallopian tube cancer, uterine (*e.g.*, endometrial) cancer, or primary peritoneum cancer) in a subject, comprising administering to a subject in need thereof a pharmaceutical composition comprising a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein (*see,* Section 5.1 and Section 5.2), further comprise administering to the subject one or more additional therapeutic agents. In a specific embodiment, the additional therapeutic agent is for treating the cancer in the subject (*e.g.,* ovarian cancer, pancreatic cancer, lung cancer, breast cancer, fallopian tube cancer, uterine (*e.g.,* endometrial) cancer, and primary peritoneum cancer). In a specific embodiment, the additional therapeutic agent is for treating any side effects of treatment with a MUC16 Glycosylation Antibody or an antigen-binding fragment described herein described herein (*see,* Section 5.1 and Section 5.2).

[00474] In one embodiment, a first MUC16 Glycosylation Antibody or antigen-binding fragment thereof is administered that recognizes an epitope in MUC16 that comprises *N*-glycosylated Asn1806 but does not comprise *N*-glycosylated Asn1800 (*i.e.*, it requires *N*-glycosylated Asn1806, but not *N*-glycosylated Asn1800, for binding to MUC16) in combination with a second MUC16 Glycosylation Antibody or antigen-binding fragment thereof that recognizes an epitope in MUC16 that comprises *N*-glycosylated Asn1806 and also comprises *N*-glycosylated Asn1800 (*i.e.*, both *N*-glycosylated sites are part of the epitope recognized by the MUC16 Glycosylation Antibody or antigen-binding fragment thereof). Such a first MUC16 Glycosylation Antibody or antigen binding fragment thereof can be identified by (i) its ability to immunospecifically bind a cell recombinantly expressing a first form of MUC16, which first form of MUC16 is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO: 133; (ii) its lack of immunospecific binding to a cell recombinantly expressing a third

form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139; and (iii) its ability to immunospecifically bind a cell recombinantly expressing a fourth form of MUC16, which fourth form is glycosylated, and wherein the amino acid sequence of the fourth form is SEQ ID NO: 152, wherein the cell recombinantly expressing the first form of MUC16, the cell recombinantly expressing the third form of MUC16, and the cell recombinantly expressing the fourth form of MUC16 are of the same cell type. Such a second MUC16 Glycosylation Antibody or antigen-binding fragment thereof can be identified by (i) its ability to immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; and (ii) its lack of immunospecific binding to a cell recombinantly expressing a fifth form of MUC16, which fifth form is glycosylated, and wherein the amino acid sequence of the fifth form is SEQ ID NO:172, wherein the cell recombinantly expressing the first form of MUC16 is the same type of cell as the cell recombinantly expressing the fifth form of MUC16. The protein encoded by the amino acid sequence of SEQ ID NO: 172 is also referred to herein as $MUC16^{c114\text{-}N23}$. $MUC16^{c114\text{-}N23}$ consists of the C-terminal 114 amino acid residues of mature MUC16 (SEQ ID NO: 150 being the sequence of mature MUC16), except that the asparagines at amino acid positions 24 and 30 (corresponding to amino acid positions Asn1800 and Asn1806 of SEQ ID NO: 150) have been mutated to alanines. Thus, $MUC16^{c114\text{-}N23}$ is not capable of being *N*-glycosylated at amino acids positions 24 and 30 of SEQ ID NO: 172 (corresponding to amino acid positions Asn1800 and Asn1806 of SEQ ID NO: 150).

[00475] In one embodiment, a first MUC16 Glycosylation Antibody or antigen-binding fragment thereof is administered that recognizes an epitope in MUC16 that comprises *N*-glycosylated Asn1806 but does not comprise *N*-glycosylated Asn1800 (*i.e.*, it requires *N*-glycosylated Asn1806, but not *N*-glycosylated Asn1800, for binding to MUC16) in combination with a second antibody or antigen-binding fragment thereof that recognizes an epitope in MUC16 that comprises *N*-glycosylated Asn1800 but does not comprise *N*-glycosylated Asn1806 (*i.e.*, it requires *N*-glycosylated Asn1800, but not *N*-glycosylated Asn1806, for binding to MUC16). Such a first MUC16 Glycosylation Antibody or antigen binding fragment thereof can be identified by (i) its ability to immunospecifically bind a cell recombinantly expressing a first form of MUC16, which first form of MUC16 is glycosylated, and wherein the amino acid

sequence of the first form is SEQ ID NO: 133; (ii) its lack of immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139; and (iii) its ability to immunospecifically bind a cell recombinantly expressing a fourth form of MUC16, which fourth form is glycosylated, and wherein the amino acid sequence of the fourth form is SEQ ID NO: 152, wherein the cell recombinantly expressing the first form of MUC16, the cell recombinantly expressing the third form of MUC16, and the cell recombinantly expressing the fourth form of MUC16 are of the same cell type. Such a second antibody or antigen-binding fragment thereof can be identified by (i) its ability to immunospecifically bind to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133; (ii) its ability to immunospecifically bind to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139; and (iii) its lack of immunospecific binding to a cell recombinantly expressing a fourth form of MUC16, which fourth form is glycosylated, wherein the amino acid sequence of the fourth form is SEQ ID NO:152, wherein the cell recombinantly expressing the first form of MUC16, the cell recombinantly expressing the third form of MUC16, and the cell recombinantly expressing the fourth form of MUC16 are of the same type of cell.

[00476] In specific embodiments, the additional agent is an agent used to treat ovarian cancer. In specific embodiments, the additional agent is an agent used to treat pancreatic cancer. In specific embodiments, the additional agent is an agent used to treat lung cancer. In specific embodiments, the additional agent is an agent used to treat breast cancer. In specific embodiments, the additional agent is an agent used to treat fallopian tube cancer. In specific embodiments, the additional agent is an agent used to treat uterine (*e.g.,* endometrial) cancer. In specific embodiments, the additional agent is an agent used to treat primary peritoneum cancer.

[00477] A MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein (*see,* Section 5.1 and Section 5.2) described herein can be administered with an additional therapeutic agent concurrently or sequentially (before and/or after). The antibody or antigen binding fragment thereof and the additional therapeutic agent can be administered in the same or different compositions, and by the same or different routes of administration. A first therapy (which is a MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described

herein (*see,* Section 5.1 and Section 5.2), or the additional therapeutic agent) can be administered prior to (*e.g.,* 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.,* 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of the second therapy (the MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see,* Section 5.1 and Section 5.2) described herein, or the additional therapeutic agent) to a subject with cancer (*e.g.,* ovarian cancer, pancreatic cancer, lung cancer, breast cancer, fallopian tube cancer, uterine (*e.g.,* endometrial) cancer, and primary peritoneum cancer). In certain embodiments, an additional therapeutic agent administered to a subject in combination with MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see,* Section 5.1 and Section 5.2) is administered in the same composition (pharmaceutical composition). In other embodiments, an additional therapeutic agent administered in combination with MUC16 Glycosylation Antibody or an antigen-binding fragment thereof described herein (*see,* Section 5.1 and Section 5.2) is administered to a subject in a different composition than the MUC16 Glycosylation Antibody or antigen-binding fragment thereof described herein (*see,* Section 5.1 and Section 5.2) (*e.g.,* two or more pharmaceutical compositions are used).

5.5.5 PATIENT POPULATION

[00478] A subject treated in accordance with the methods provided herein can be any mammal, such as a rodent, a cat, a canine, a horse, a cow, a pig, a monkey, a primate, or a human, etc. In a preferred embodiment, the subject is a human. In another preferred embodiment, the subject is a canine. As used herein, the terms "subject" and "patient" are used interchangeably.

[00479] In certain embodiments, a subject treated in accordance with the methods provided herein has been diagnosed with a MUC16-positive cancer, including but not limited to, ovary, lung, pancreas, breast, uterine, fallopian tube, or primary peritoneum cancer, or cancer of any other tissue that expresses the MUC16.

[00480] The following examples are offered by way of illustration and not by way of limitation.

6. EXAMPLES

6.1 EXAMPLE 1: EXPRESSION OF THE CARBOXY-TERMINAL PORTION OF MUC16/CA125 INDUCES TRANSFORMATION AND TUMOR INVASION

6.1.1 INTRODUCTION

[00481] The serum CA125 antigen, an antigenic fragment of MUC16, has been a mainstay of ovarian cancer assessment and management since the early 1980s, but its biology and contribution to ovarian cancer manifestations have been poorly understood (*see*, References 1-3 as recited in Section 6.1.5, below). The cloning of CA125, achieved in 2001, first identified MUC16 as a tethered mucin with a small intracellular domain, a transmembrane domain, an ectodomain proximal to the putative cleavage site, and a large, heavily glycosylated region of 12-20 tandem repeats, each 156 amino acids long (FIG. 1A) (*see*, References 4-6 as recited in Section 6.1.5, below). Serous cancers of the ovary, fallopian tube, and uterus often express large amounts of MUC16, and aberrant MUC16 expression can be found in several other malignancies, including cancers of the lung, pancreas, and breast. Expression of other tethered mucins is a common feature of epithelial organs, and they are often over-expressed in malignancy. Two prominent examples are MUC1, which is over-expressed in many breast and ovarian cancers, and MUC4, which is characteristically abundant in pancreatic and gastrointestinal cancers (*see*, Reference 7 as recited in Section 6.1.5, below). Both of these mucins have been identified as having transforming properties (*see*, References 8 and 9 as recited in Section 6.1.5, below). The transforming mechanisms are different and incompletely understood. MUC1 has a beta-catenin homology region that has been shown to translocate to the nucleus and act as a transcription factor (*see*, References 10 and 11 as recited in Section 6.1.5, below). In contrast, MUC4 has HER-binding domains within its transmembrane region and acts, at least in part, through the HER family kinases (*see*, References 12 and 13 as recited in Section 6.1.5, below). MUC16 lacks homologous regions to either of these domains and appears to have evolved independently (*see*, Reference 12 as recited in Section 6.1.5, below). Compared to both MUC1 and MUC4, the expression of MUC16 is more restricted and is normally expressed, almost exclusively, to the Müllerian tract and the ocular epithelium (*see*, References 14-16 as recited in Section 6.1.5, below). The tandem repeat regions of the MUC16 molecule

appear to function as key interacting proteins with mesothelin and other stromal proteins (*see*, Reference 17 as recited in Section 6.1.5, below). These interactions are probably responsible for the classic patterns of serosal spread by ovarian cancers. In clinical settings, high levels of the circulating elements from MUC16, which encode the CA125 antigen, are associated with an adverse clinical outcome, independent of stage, grade and other traditional clinical factors (*see*, Reference 18 as recited in Section 6.1.5, below). Others have identified the C-terminal of MUC16 as important in invasion and growth, but the specific regions of the proximal MUC16 sequence responsible for transformation have not been delineated (*see, e.g.,* Therialt et al. Gynecol Oncol 2011, 121(3):434-443 and Giannakouros et al. Int. J. Oncol. 2015, 41(1):91-98). Amplification of genomic regions encoding MUC16 in ovarian cancer DNA and over-expression of MUC16 mRNA have been observed in The Cancer Genome Atlas (TCGA) ovarian cancer project and is associated with worse outcome (*see*, Reference 19 as recited in Section 6.1.5, below). Loss of MUC16 in the mouse is not associated with a distinct phenotype, but the effect of persistent or aberrant MUC16 expression is not known (*see*, Reference 20 as recited in Section 6.1.5, below). The data in this example show that the expression of the 114 C-terminal amino acid residues of MUC16 ($MUC16^{c114}$, SEQ ID NO:133), and in particular, glycosylation of residue Asn30 of $MUC16^{c114}$ (corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150)) is associated with specific alterations of signal transduction, gene expression, and aggressive biological behavior.

6.1.2 MATERIALS AND METHODS

6.1.2.1 Synthesis of MUC16 Carboxy-Terminus (MUC16c114) and MUC16-CA125 Domain (MUC16c344) DNA Constructs and Glycosylated Fusion Protein

[00482] DNA constructs encoding truncated forms of MUC16 (designated $MUC16^{c344}$, $MUC16^{c114}$, $MUC16^{c80}$, and $MUC16^{c86}$; FIG. 1B and FIG. 1C) were generated. EcoRV and NotI multiple cloning sites of the phrGFP II-C vector (phrGFP) (Stratagene, LaJolla, CA) were used to incorporate $MUC16^{c114}$, $MUC16^{c80}$, $MUC16^{c86}$ and $MUC16^{c344}$ DNAs to generate GFP fusion constructs were obtained with the GFP protein present on the carboxy-terminus of the truncated MUC16 fusion protein. PCR products for the MUC16 fragments ($MUC16^{c344}$, $MUC16^{c114}$, $MUC16^{c80}$, and $MUC16^{c86}$) were created using pBK-CMV-MUC16-B53 DNA as a template (Yin BWT, et al., International Journal of Cancer, 2002, 98(5):737-740), and PCR products

were purified in a 1% agarose gel, sequenced, and inserted into the EcoRV and NotI multiple cloning sites of the phrGFP II-C vector (phrGFP). The pFUSE-hIgG1-Fc2 vector was purchased from InvivoGen (San Diego, CA). Polymerase chain reaction (PCR) primers were designed for the ectodomain $MUC16^{c57\text{-}114}$ (from position 1777 to 1834 of SEQ ID NO:150) or the sugar-binding domain of $^{117\text{-}244}$LGALS3 DNA sequences were synthesized (Sigma-Genosys, The Woodlands, TX) with the restriction enzyme site EcoRV as the forward primer and the restriction enzyme site NcoI as the reverse primer. PCR products for the $MUC16^{c57\text{-}114}$ fragment were created using pBK-CMV-MUC16-B53 DNA as a template and LGALS3 cDNA clone (MGC:2058 IMAGE:3050135 GenBank: AAH01120.1; DBSource accession BC001120.2), which was obtained from ATCC (Manassas, VA) was used as a DNA template to synthesize the sugar-binding domain of the LGALS3 PCR product. PCR products were purified in a 1% agarose gel, sequenced, and inserted into the pFUSE-hIgG1-Fc2 vector.

6.1.2.2 Primers and PCR

[00483] Forward and Reverse primers for MUC16-cytoplasmic domain ($MUC16^{c114}$, carboxy-terminus 114 aa) (5'-CCATGCGATATCGCCACCATGGTGAACTTCTCGCCACTGGCT-3' and 5'-TACGGCGGCCGCTTGCAGATCCTCCAGGTCTAGG-3', SEQ ID NO:121 and SEQ ID NO:122, respectively). $MUC16^{c344}$ (one tandem repeat which has only one cysteine loop, 344 aa) (5'-CCATGCGATATCGCCACCATGGTGACAGGCCCTGGGCTGGACAGA-3' and 5'-TACGGCGGCCGCTTGCAGATCCTCCAGGTCTAGG-3', SEQ ID NO:123 and SEQ ID NO:124, respectively) with EcoRV and KOZAK in the forward primer and NotI in the reverse primer. $MUC16^{c114}$–GFP DNA construct was used to create $MUC16^{c80}$ and $MUC16^{c86}$ constructs by quick change primers. Forward and Reverse primers for $MUC16^{c57\text{-}114}$ pFUSE-hIgG1-Fc2 vector (5'-CCATGCGATATCAAACTTCTCGCCACTGGCT-3' and 5'-AGATCTAACCATGGGAAGGTCAGAATTCCCAGT-3', SEQ ID NO:125 and SEQ ID NO:126, respectively) and Forward and Reverse primers for the sugar binding domain of $^{117\text{-}244}$LGALS3 for pFUSE-hIgG1-Fc2 vector (5'-CATGCGATATCACCTTATAACCTGCCTTTG-3'and 5'-AGATCTAACCATGGTATATGAAGCACTGGT-3', SEQ ID NO:127 and SEQ ID NO:128, respectively) with EcoRV in the forward primer and NcoI in the reverse primer. All the above primers were synthesized by Sigma Genosys, The Woodlands, TX.

[00484] PCR conditions were achieved by the following processes: DNA was melted at 95°C for 5 minutes in order to achieve denaturation. Thirty repeat cycles of heating at 97°C for 30

seconds, annealing at 60°C for 1 minute, and extending at 72°C for 1 minute were conducted. This was followed by an extension of the generated PCR product strand at 72°C for 5 minute and then cooled at 4°C overnight.

[00485] phrGFP II-C vector DNA, $MUC16^{c114}$, $MUC16^{c80}$, $MUC16^{c86}$, $MUC16^{c344}$, and $MUC16^{c678}$ gel purified DNAs individually digested overnight at 37oC water bath with EcoRV and NotI (New England Biolabs, Beverly, MA) restriction enzymes. pFUSE-hIgG1-Fc2 vector DNA, $MUC16^{c57\text{-}114}$ and $^{117\text{-}244}$LGALS3 gel purified DNAs individually digested overnight at 37°C water bath with EcoRV and NcoI (New England Biolabs, Beverly, MA) restriction enzymes. $MUC16^{c114}$ and phrGFP; $MUC16^{c344}$ and phrGFP; or $MUC16^{c678}$ and phrGFP restriction digested DNA's were gel purified and ligated overnight using T4 Ligase (Roche Diagnostics Corporation, Indianapolis, IN). Similarly, $MUC16^{c57\text{-}114}$ and pFUSE-hIgG1-Fc2; $^{117\text{-}244}$LGALS3 and pFUSE-hIgG1-Fc2 restrict digested DNA's were gel purified and ligated overnight using T4 Ligase (Roche Diagnostics Corporation, Indianapolis, IN). Ligated DNA were transformed into XL-1 Blue super competent cells (Stratagene, La Jolla, CA) following manufacturer's protocol and plated them on agar plates with LB medium containing Kanamycin (50 µg/mL, Sigma Chemical Co., St. Louis, MO) for phrGFP vectors or on agar plates with LB medium containing 25 µg/ml of Zeocin (Invitrogen, CA). Clones were selected the following day and Miniprep DNA was extracted using Wizard Plus Miniprep DNA purification system (Promega Corporation, Madison, WI). Selected clones DNA was sequence at MSKCC DNA sequencing core facility using forward and reverse primers of MUC16 and phrGFP to confirm MUC16 and phrGFP presence in the sequences as a fused constructs or $MUC16^{c57\text{-}114}$ and pFUSE-hIgG1-Fc2 or $^{117\text{-}244}$LGALS3 and pFUSE-hIgG1-Fc2. Megaprep DNA from such clones were made by using Wizard Plus Megaprep DNA purification system (Promega Corporation, Madison, WI) which were also confirmed for the presence of MUC16 and phrGFP or $MUC16^{c57\text{-}114}$ and pFUSE-hIgG1-Fc2 or $^{117\text{-}244}$LGALS3 and pFUSE-hIgG1-Fc2 in their sequences as a fused constructs.

6.1.2.3 Fluorescent Activated Cell Sorting (FACS)

[00486] Transfected cells were trypsinized, washed and counted by haemocytometer. Cells were distributed into multiple eppendorf tubes with at least 0.5-1 X 10^6/tube. Cells were washed with PBS containing 1% FCS and 0.025% Sodium Azide (FACS buffer). For surface FACS staining, cells were incubated either without (for second antibody control) or with 1 µg/tube of

bioreactive supernatants of MUC16-carboxy-terminus monoclonals (4H11.2.5), Mouse anti-human OC125 (M3519) (DakoCytomation, Dako North America Inc., Carpinteria, CA) for 30 minutes on ice. Cells in eppendorf tubes were also for surface stained with 1 µg/tube of non-specific isotype matched control mouse antibodies (13C4 for IgG1 and 4E11 for IgG2b monoclonals obtained from MSKCC Monoclonal core facility)(data not shown) and incubated on ice for 30 minutes. All cells were washed 3 times with FACS buffer. Cells were incubated with 1 µg/tube of second antibody Goat anti-mouse IgG1-PE or IgG2b-PE for 30 minutes on ice and then washed 3 times with FACS buffer. The cells were analyzed by FACS Calibur.

6.1.2.4 Cell Cultures

[00487] NIH/3T3 (3T3) cells (fibroblasts) were obtained through the American Type Culture Collection (ATCC, Manassas, VA), and A2780 cells are a human ovarian carcinoma cell line (*see*, Reference 28 as recited in Section 6.1.5, below). Both cell lines were maintained according to published conditions. Stable MUC16-positive cell lines were created by transfection of MUC16 expression vectors (phrGFP-MUC16^{c344}, phrGFP-MUC16^{c114}, phrGFP-MUC16^{c80}, and phrGFP-MUC16^{c86}) and selected using geneticin (G418, Invitrogen, Grand Island, NY) in their respective culture medium and isolated based on expression of green fluorescence protein (GFP). The MUC16^{c114} transfectants have cell surface expression of MUC16 protein from the putative cleavage site to the carboxy-terminus (amino acids 1777 to 1890 of SEQ ID NO:150) (*see*, Reference 5 as recited in Section 6.1.5, below). Cell lines with longer MUC16 fragments were prepared in a similar manner, including lines with expression of MUC16^{c344}–GFP vector that have cell surface expression of MUC16 protein as a 344 amino acid fragment extending to the carboxy-terminus of MUC16 (amino acids 1547 to 1890) (*see*, Reference 5 as recited in Section 6.1.5, below).

6.1.2.5 Transfection

[00488] All of the constructs were introduced into NIH/3T3 (3T3) and A2780 cells using DOTAP (Roche Diagnostics, Indianapolis Corporation, IN) following the manufacturer's protocol. Stable transfectants were selected with 400 µg/mL of G418 for 3T3 and A2780 cells in their respective culture media. They were cell sorted twice for GFP expression at the MSKCC Flow Cytometry Core Facility (FCCF), and selected cells were grown as lines for up to 15 passages. Routine monitoring by FACS analysis was done to confirm the GFP-positivity of these lines. Protein extracts of these lines were analyzed by western blot using anti-hrGFP

(Stratagene, La Jolla, CA) and anti-MUC16-carboxy-terminus monoclonal antibodies (*see*, References 5 and 14 as recited in Section 6.1.5, below).

6.1.2.6 Growth Curves

[00489] One thousand stable transfected cells/well were seeded in 200 µL of culture media/well in multiple 96 well flat bottomed plates and incubated at 37ºC and 5% CO_2 for 5 days. Every day, triplicate cultured plates were developed with 25 µL/well of Alamar Blue (ABD Serotec Co. UK) and incubated at 37ºC and 5% CO_2 for 4 hours. Plates were read on PerSeptive Biosystems CytoFluor Multiwell Fluorescent Plate Reader Model # 4000 with excitation at 530 nM and emission at 620 nM. Growth curves over 4 days were recorded, and the mean values from triplicate plates were plotted accordingly.

6.1.2.7 Soft Agar Assay

[00490] Stable transfected cells were placed in an agarose suspension and plated over a thin agarose layer and analyzed for their ability to form anchorage independent colonies. One to five million cells in 10 mL of media-agarose suspension were plated per dish and incubated at 37ºC and 5% CO_2. The plates were monitored for colony formation. Additional culture media was overlaid every 4-5 days. After 11-14 days of culture, colonies were enumerated, and pictures of the colonies were taken.

6.1.2.8 Transfection into eukaryotic expression vectors

[00491] The MUC16$^{c57\text{-}114}$-pFUSE-hIgG1-Fc2 and $^{117\text{-}244}$LGALS3-pFUSE-hIgG1-Fc2 constructs were separately transfected into human embryonic kidney (HEK) FreeStyle 293F cells (Invitrogen, CA) that express and secrete fusion proteins into serum free media. Three 10% SDS-PAGE gels were run with 5 µg/lane of fusion protein supernatants from transient transfected HEK 293F cells with pFUSE- hIgG1-Fc2 control empty vector, MUC16$^{c57\text{-}114}$-pFUSE-hIgG1-Fc2 vector, and LGALS3-pFUSE-hIgG1-Fc2 vector. One gel was directly stained with Gelcode reagent, as per the manufacturer's protocol. Proteins from two gels were transferred onto two nitrocellulose membranes that were blocked with 5% non-fat milk-Phosphate Buffered Saline containing 0.1% Tween-20 (PBST) for 1 hour at room temperature on a shaker. The membranes were probed with anti-human IgG1-Fc-HRP (γ1 chain specific)(Southern Biotech Inc., CA) at 1:5,000 dilution in 5% non-fat milk PBST; 4H11- HRP mAb at 1:2000 dilution (*see*, Reference 14 as recited in Section 6.1.5, below) in 5% non-fat milk

PBST and anti-human GAL3 mAb (Santa Cruz Biotechnology, CA) at 1:200 dilution in 5% non-fat milk PBST overnight at 4°C on a shaker. The GAL3-membrane was washed thrice with PBST and labeled with anti-mouse IgG-HRP second antibody at 1:3,000 dilution in 5% non-fat milk PBST for 1 hour at room temperature on a shaker. Membranes were washed thrice with PBST, and then they were treated with ECL reagent (Perkin Elmer, NY) chemiluminiscence substrate for 5 minutes, and the illuminated signals were captured on X-ray films.

6.1.2.9 Invasion

[00492] Basement membrane invasion was determined in matrigel invasion chambers (BD Biosciences, Bedford, MA). Matrigel migration was measured at 48 hours in triplicate wells and compared with phrGFP vector controls and expressed as % phrGFP Control matrigel invasion. 0.1 µg/mL of Tunicamycin (Sigma-Aldrich, St. Louis MO cat # T7765) or 5 µg/mL of $MUC16^{c57\text{-}c114}$-pFUSE-hIgG1- Fc2 or 5 µg/mL of $^{117\text{-}244}$LGALS3 pFUSE-hIgG1-Fc2 fusion protein treated stable cell line matrigel migration after 48 hours was measured and expressed as % phrGFP Control matrigel invasion.

[00493] BD BioCoat™ Matrigel™ Invasion Inserts or Chambers (catalog # 354480 in 24 well plate) and Control Inserts (catalog # 354578 in 24 well plate) were purchased from BD Biosciences, MA. Matrigel Invasion assay was performed as per manufacturer's protocol. Briefly, the matrigel chambers in 24 well plates (stored at -20°C) and control inserts (stored at 4°C) were allowed to come to room temperature. Both inserts were rehydrated with 0.5 mL of serum free medium in the insert as well as in the outside well of the 24 well plate, for 2 hrs at 37°C 5% CO_2 humidified incubator. Cultured 3T3 or A2780 cells were trypsinized and washed with culture medium. A million cells were separated into another centrifuge tube and washed 3 times with serum free medium. These cells were later adjusted to give 10,000 cells in 0.5 mL serum free medium. The medium in the rehydrated inserts were removed and the insert was transferred into a new 24 well plate containing 0.75 mL of 10% Foetal Bovine Serum (FBS) containing culture medium in the well which serves as a chemo attractant. Immediately, 0.5 mL of the cells (10,000 cells) in serum free medium was added to the insert. Proper care was taken to see that there was no air bubble trapped in the insert and the outside well. The 24 well plate was incubated at 37°C 5% CO_2 humidified incubator for 48 hrs. After incubation, the non-invading cells were removed from the upper surface of the membrane by "scrubbing" by inserting a cotton tipped swab into matrigel or control insert and gently applied pressure while

moving the tip of the swab over the membrane surface. The scrubbing was repeated with a second swab moistened with medium. Then the inserts were stained in a new 24 well plate containing 0.5 mL of 0.5% crystal violet stain in distilled water for 30 minutes. Following staining, the inserts were rinsed in 3 beakers of distilled water to remove excess stain. The inserts were air dried in a new 24 well plate. The invaded cells were hand counted under an inverted microscope at 200X magnification. Several fields of triplicate membranes were counted and recorded in the figure.

6.1.2.10 Real-Time Polymerase Chain Reaction

[00494] RNA isolation was prepared by following the RiboPure Kit (Ambion, Austin, TX) protocol. RT PCR for a panel of metastasis and extracellular matrix protein genes was performed utilizing the RT2 Profiler PCR Array system (Super Array, Frederick, MD), as previously described (*see*, Reference 29 as recited in Section 6.1.5, below).

6.1.2.11 Tumor Growth in Athymic Nude Mice

[00495] Transfected cell lines and appropriate control cell lines were introduced into the flank or peritoneal cavity of athymic nude mice, and routine animal care was provided by the MSKCC Antitumor Assessment Core Facility. For tumor growth assessment experiments, 2 million cells from each tumor line were implanted into each of 5-15 athymic nude mice. Tumor measurements were taken twice a week, and tumor growth was recorded to a maximum size of 1500 mm^3 per MSKCC RARC guidelines.

6.1.2.12 Western Blot Analysis

[00496] Stable cell lines were cultured in 10 cm dishes in their respective culture media and incubated at 37°C and 5% CO_2 for 3 days. They were then washed twice with ice cold PBS and scraped with 1-2 mL of ice cold PBS and centrifuged. The pelleted cells were lysed with 0.2 mL of modified Ripa lysis buffer (20 mM Tris-HCL, pH 7.4; 150 mM NaCl; 1% NP-40; 1 mM Na3VO4; 1 mM PMSF; 1 mM DTT; with protease and phosphatase inhibitors cocktails (cat # 11836170001 from Roche Diagnostics, IN)) for 30 min on ice and centrifuged at 4°C for 10 min. Protein concentration of the supernatant was measured using Bio-Rad Protein Assay (BioRaD Laboratories, Hercules, CA). Equal amounts of protein were separated by SDS-Poly Acrylamide Gel Electrophoresis (SDS-PAGE) and transferred to PVDF membrane using BioRad transfer apparatus at 4oC. The membranes were blocked with 3% Bovine Serum Albumin (BSA) or 5%

non-fat milk in PBS with 0.1% Tween-20 (PBST) at 4°C overnight. Membranes were developed with a variety of primary antibodies (Cell Signaling, MA: Akt cat #9272; Phospho-Akt (Ser473)(193H12) cat # 4058; p44/43 MAPK (Erk1/2) cat # 9102; Phospho- p44/43 MAPK (Erk1/2)(Thr202/Tyr204) cat #9101); (Sigma-Aldrich, Inc., St. Louis, MO: β-Actin cat # A5441); (Southern BioTech, Birmingham, AL: Anti-human-Fc-IgG1-HRP cat # 9054-05 and Abgent, San Diego, CA: Polyclonal LGALS3 antibody cat # AP11938b) at 4°C overnight. The membranes were washed three times with PBST, and developed with HRP conjugated anti-mouse or anti-rabbit antibody (GE Healthcare, UK) (1:5000 dilution) for 1 hour at room temperature. Membranes were then washed three times with PBS-T and developed with a Western Lightning Chemiluminescence reagent (ECL, Perkin Elmer) for 1-5 minutes at room temperature, and the signals were developed on HyBlot CL film (Denville Scientific Inc. Metuchen, NJ).

6.1.2.13 TCGA expression analysis of MUC16

[00497] Comprehensive genomic data were available for 316 serous ovarian cancer samples as part of the TCGA project (tcga.cancer.gov). Gene-level DNA copy-number calls were derived from CBS- segmented Agilent 1M microarray data using GISTIC. MUC16 mRNA expression was measured using three different platforms (Agilent 244K Whole Genome Expression Array, Affymetrix HT-HG-U133A, and Affymetrix Exon 1.0 arrays), and gene expression values were derived as described previously (*see*, Reference 30 as recited in Section 6.1.5, below). Somatic mutations in MUC16 were identified whole exome capture followed by next-generation sequencing (SOLiD or Illumina). All TCGA data were downloaded from the cBio Cancer Genomics Portal (www.cbioportal.org). mRNA expression values were then correlated with the corresponding DNA copy-number categories (homozygous deletion, hemizygous deletion, diploid, gain, high-level amplification) and somatic mutations were overlaid across all samples and plotted as a boxplot using the statistical framework R (www.R-project.org) as previously described (*see*, Reference 31 as recited in Section 6.1.5, below). Clinical data were obtained from the TCGA data portal (tcga-data.nci.nih.gov/tcga/).

6.1.2.14 MUC16^{c354} transgenic mice

[00498] The conditional carboxy-terminus 354 amino acids (MUC16^{c354}) transgenic construct was made using vector phrGFP II-C (Stratagene, La Jolla, CA), and CMV promoter was replaced with CAG promoter from vector pCAG-CreERT2 (Addgene, Cambridge, MA).

$MUC16^{c354}$ fragment was amplified by PCR from the construct B53 that was made by Yin BW et al (*see*, References 5 and 6 as recited in Section 6.1.5, below). The $MUC16^{c354}$ conditional construct contains the following units: pCAG, 5' loxP, hrGFP, BGHpA, 3' loxP, $MUC16^{c354}$, HA, and SV40pA.

[00499] Using the above $MUC16^{c354}$ conditional transgenic construct, the MSKCC Mouse Genetics Core Facility performed the microinjection procedure on B6CBAF1/J mice. Twelve $MUC16^{c354}$ conditional transgenic mice were identified from 99 mice by Southern Blot. All 12 pro-founders were mated with B6.FVB-Tg(EIIa-cre)C5379Lmgd/J mice (The Jackson Laboratory, Bar Harbor, MI) to remove hrGFP, which was located between two loxPs. $MUC16^{c354}$ PCR positive female mice for each pro- founder were dissected. The organs (brain, colon, heart, kidney, liver, lung, ovary, and spleen) from these dissected mice were minced and homogenized. The protein samples were analyzed by western blot to identify the founders which highly express $MUC16^{c354}$. The resulting transgenic mice were maintained on a mixed background.

[00500] Two founders of transgenic $MUC16^{c354}$ mice were crossed with p53 heterozygous mice (B6.129S2- Trp53tm1Tyj/J) (The Jackson Laboratory, Bar Harbor, MI) to create double transgenic MUC16c354:p53+/-. The resulting transgenic mice were maintained on a mixed background. All mice were genotyped by PCR using extracted toe or tail DNA. All experimental animals were maintained in accordance with the guidelines approved by the MSKCC Institutional Animal Care and Use Committee and Research Animal Resource Center and the NIH Guide for the Care and Use of Laboratory Animals.

6.1.2.15 Histological analysis

[00501] Mice at 12 months of age were sacrificed and necropsied. Following macroscopic examination, dissected tissue samples were fixed for 24 hours in 10% neutral buffered formalin, then processed in alcohol and xylene, embedded in paraffin, sectioned at 5 μm thickness, and stained with hematoxylin and eosin (H&E). Tissues were examined by a veterinary pathologist (SM), and neoplastic and non- neoplastic lesions were diagnosed according to published guidelines on rodent pathology nomenclature.

6.1.2.16 Statistical Analysis

[00502] Student's two sided paired t test was used to compare groups for studies of in vitro growth, invasion, and soft agar growth potential. The chi square test was used to analyze RT-

PCR data for significance, according to provided software (SuperArray). The comparisons of the tumor volumes were made using area under the curve assessments for total tumor volume over time in each animal. The assessment of tumor volume was made based on the last day that all animals were alive in both groups. A non-parametric test for ranks (Wilcoxon two sample test) was used to test for a difference in distributions among the groups. In the animal survival studies, a time to event analysis was performed, with the event defined as time to tumor volume exceeding 1,500 mm^3 or ulceration. Animals with tumor volume less than 1,500 mm^3 were followed for up to 60 days and then censored. The Kaplan-Meier method was used to estimate survival distribution (*see*, Reference 32 as recited in Section 6.1.5, below).

6.1.3 RESULTS

[00503] Following apparent cleavage and release of the tandem repeat region of the MUC16 protein, approximately 114 amino acids of the carboxy-terminus (c114) of the protein are thought to remain on the cell surface, and the potential functions of this part of the molecule are not known. The role of this most proximal part of the MUC16 protein in malignant transformation and behavior in 3T3 fibroblasts and ovarian cancer cell lines was analyzed. To test the effect of the residual c114 amino acid element proximal to the cleavage site, two vectors were designed: (1) $MUC16^{c114}$-GFP vector, and (2) the truncated $MUC16^{c344}$-GFP vector (FIG. 1) and these vectors and the phrGFP control vector, were independently transfected into 3T3 fibroblast cells. $MUC16^{c114}$- and $MUC16^{c344}$-expressing cell lines were selected and maintained with G418, and $MUC16^{c114}$ and $MUC16^{c344}$ stable expression was confirmed by FACS analysis using monoclonal antibodies that recognize unique amino acid sequences of the MUC16 carboxy-terminus (*see*, Reference 14 as recited in Section 6.1.5, below). The cell lines that express 344 amino acids from the MUC16 (SEQ ID NO:132) protein ($MUC16^{c344}$-GFP lines) bear the classic CA125 epitope, which is recognized by the OC125 antibody on the cell surface by FACS analysis, and the CA125 is released into the cell culture supernatant. OC125 does not recognize $MUC16^{c114}$-GFP cells. However, all of the transfected lines were cell surface positive for the $MUC16^{c114}$ extracellular sequences (SEQ ID NO:133), proximal to the putative cleavage site and recognized by the MUC16 ectodomain-specific 4H11 antibody (*see*, Reference 14 as recited in Section 6.1.5, below; FIG. 1).

6.1.3.1 3T3 cells

[00504] To investigate the transforming properties conferred by the residual, post-cleavage elements of MUC16, the characteristics of the 3T3 MUC16^{c114}-GFP and 3T3 MUC16^{c344}-GFP cell lines were analyzed and the effects of these two minimal MUC16 elements were compared to the vector controls. Expression of either the most proximal 114 amino acids (MUC16^{c114}) or the proximal 344 amino acids (MUC16^{c344}) of the MUC16 sequence had no significant effect on the in vitro growth rates for any of the transfected cell lines when compared with that of the parental line FIG. 2A. However, expression of the same elements of the MUC16 protein substantially altered 3T3 anchorage dependent growth in soft agar cloning. Both the minimal c114 fragment and the c344 fragment significantly increased the number of soft agar colonies compared to the vector only controls (FIG. 3A). The proximal portions of MUC16 protein expression also enhanced the migration ($p<0.0001$) of MUC16 + 3T3 cells in classic matrigel invasion assays compared to the 3T3 cells transfected with phrGFP vector controls (FIG. 3B). When the 3T3 cells expressing various MUC16 protein fragments were examined for expression of selected metastasis and invasion gene transcripts, there were multiple invasion genes upregulated, including chemokine ligand 12 (CXCL12), Cadherin 11 (CDH11), and the matrix metalloproteinases MMP2 and MMP9 (FIG. 3C). Other transcripts including Fibronectin (FN1) and Neurofibromin (NF2) are consistently decreased. MUC16 might act through canonical signaling pathways in ways similar to the effects of MUC1 and MUC4, since MUC16 alters in vivo tumor growth and increases invasive properties of cells bearing the MUC16 protein. The interacting ERK and AKT pathways have previously been identified as important signaling mechanisms in ovarian cancer and regulators of tumor cell invasion (*see*, References 21 and 22 as recited in Section 6.1.5, below). As shown in FIG. 3D, there was activation of both pathways as evidenced by increases in pAKT(S473) and pERK (T202/Y204).

[00505] The most unambiguous hallmark of oncogenic transformation is the ability to promote growth in immunodeficient mice. In order to measure the effects of MUC16 on tumor growth rate, a flank tumor model was utilized to facilitate regular tumor measurements. As shown in FIG. 3E, when the MUC16 expressing 3T3 cell lines (vector phrGFP, MUC16^{c114}-GFP and MUC16^{c344}-GFP) were implanted into the flanks of athymic nude mice, both the MUC16^{c114}-GFP and MUC16^{c344}-GFP formed larger tumors compared to the vector only controls at 4 weeks. There was not a statistical difference between the cell line expressing the MUC16^{c114}-GFP and MUC16^{c344}-GFP proteins (FIG. 3E), suggesting the oncogenic effects of

MUC16 expression are linked to the most proximal parts of the molecule. This increase in tumor growth rate was seen throughout the period of tumor growth and is consistent with the clinical linkage between high levels of MUC16 expression (as serum CA125) and poor survival (*see*, Reference 18 as recited in Section 6.1.5, below).

6.1.3.2 A2780 Human Ovarian Cancer Cells

[00506] While the expression of MUC16 protein in 3T3 cells was clearly linked to hallmarks of transformation, some fully transformed ovarian cancer cell lines lack MUC16 expression when cultured. In order to explore the contribution of MUC16 to the behavior of human ovarian cancer cells, A2780 cells (a human ovarian carcinoma cell line that does not express MUC16) were transfected with $MUC16^{c114}$-GFP or $MUC16^{c344}$-GFP. The MUC16-expressing cells were selected by G418 and subjected to FACS for MUC16 and GFP expression. Since these cells grow well in soft agar in the absence of MUC16 expression, the effect of $MUC16^{c344}$ and $MUC16^{c114}$ on matrigel invasion was analyzed. As shown in FIG. 4A, $MUC16^{c114}$ and $MUC16^{c344}$ expression clearly promoted matrigel invasion in A2780 cells. Likewise, the effect of $MUC16^{c114}$ and $MUC16^{c344}$ on the activation of the ERK and AKT pathways is similar to that seen in the 3T3 cells, increasing the basal levels of both pAKT(S473) and pERK (T202/Y204) (FIG. 4B). Thus, even in the malignant ovarian cell lines, increased expression of MUC16 carboxy-terminus elements is linked to increased invasion and oncogene activation. In addition, the in vivo tumor growth of $MUC16^{c114}$- and $MUC16^{c344}$-transfected A2780 lines was analyzed (FIG. 4C). In both settings, the $MUC16^{c114}$ cell line and the $MUC16^{c344}$ cell line grew more rapidly than the vector only controls. In this human cancer model, the vector controls did grow at a sufficient rate to eventually kill the animals.

6.1.3.3 Glycosylation studies

[00507] To determine the specific part of $MUC16^{c114}$ responsible for transformation, two additional MUC16 fragments were constructed: (1) $MUC16^{c80}$, wherein a 34 amino acid sequence from the ectodomain of $MUC16^{c114}$ (from position1798 to 1831, as numbered in the original publication) was deleted (FIG. 1D; SEQ ID NO:135) (*see*, Reference 5 as recited in Section 6.1.5, below); and (2) $MUC16^{c86}$, wherein the $MUC16^{c114}$ construct retained the entire ectodomain of MUC16 but removed a 28 amino acid sequence from the cytoplasmic domain's putative Ezrin domain, the potential tyrosine phosphorylation sites and SH2 domain (from position1857 to 1884) (FIG. 1D; SEQ ID NO:134). These constructs were introduced into 3T3

cells and selected by FACS for cell surface expression of the remaining MUC16^{c80} and MUC^{c86} sequences. These two additional cell populations were then examined for MUC16^{c80}- and MUC^{c86}-dependent changes. The MUC16^{c86} construct (construct with the intact ectodomain) retained a much greater capacity for soft agar colony formation than the MUC16^{c80} construct (construct with the intact cytoplasmic) domain (FIG. 5A). This was also true of the capacity for matrigel invasion (FIG. 5B). The MUC16^{c80} expressing 3T3 cells had a rate of invasion that was not statistically different than that of the phrGFP vector control. In contrast, the MUC16^{c86} expressing 3T3 cells retained a more invasive phenotype, similar to the intact MUC16^{c114} and MUC16^{c344} cells. When the activation of AKT and ERK pathways was examined, the results were consistent with the soft agar colony and matrigel invasion studies (FIG. 5C). Expression of the MUC16^{c80} fragment (without the complete intact ectodomain) did not activate ERK and AKT and was similar to the phrGFP vector control, in contrast, the MUC16^{c86} (with the intact ectodomain) expressing 3T3 cells were similar to the full MUC16^{c114} expressing 3T3 cells in the activation of ERK and AKT. Finally, the importance of the intact ectodomain was confirmed in the xenograft tumor models.

[00508] Loss of the intact MUC16 ectodomain (3T3 MUC16^{c80}) resulted in a loss of MUC16^{c114}-dependent 3T3 growth enhancement compared to the MUC16^{c114} control, while the MUC16^{c86}-expressing 3T3 cells had a modest growth delay but had a similar overall effect to the MUC16^{c114} expressing 3T3 cells (FIG. 5D). Thus, the extracellular part of the MUC16^{c114} fragment was responsible for the transformative effects of MUC16 in 3T3 cells. To further investigate the role of the extracellular fragment of MUC16^{c114}, co- precipitation studies were performed with the MUC16^{c114}-expressing 3T3 cell, using a panel of MUC16- targeting antibodies (*see*, Reference 14 as recited in Section 6.1.5, below). No co-precipitating single bands were identified by silver staining, and specific western blots for EGFR, integrins and HER3 were negative. However, analysis of the MUC16^{c114} sequence suggested that the three potential *N*-glycosylation sites (Asn1777, Asn1800, and Asn1806 (FIG. 6, SEQ ID NO:132 and SEQ ID NO:133)) in the ectodomain might play a role. The role of these *N*-glycosylation sites was analyzed. Using site-specific point mutation, all three of the asparagines were changed to alanines. This modified MUC16^{c114} construct, designated MUC16$^{c114\text{-}N123}$, was introduced into 3T3 cells, and MUC16$^{c114\text{-}N123}$-expressing cells were isolated by FACS and 4H11 ectodomain antibodies. As shown in FIG. 7A, these asparagine to alanine mutations completely abrogated

the MUC16^{c114}-induced enhancement of matrigel invasion seen with the parent MUC16^{c114} expression vector in 3T3 cells. To confirm the role of *N*-glycosylation, the 3T3 cells were treated with the glycosylation inhibitor Tunicamycin (0.1 μg/mL), and a significant decreasement in matrigel invasion was noted. Two synthetic protein inhibitors were also tested to further explore the role of the MUC16^{c114} extracellular sequence. The MUC16 external sequence (from position 1777 to1834 as numbered in Reference 5 as recited in Section 6.1.5, below) was attached to a human Fc backbone pFUSE (MUC16$^{c57\text{-}c114}$ pFUSE) to provide a "dummy" receptor. This construct was compared to both the MUC16^{c114} invasion and a pFUSE vector control. As shown in FIG. 7B, the "dummy" receptor construct diminished the overall effect of the MUC16^{c114} expression vector on matrigel invasion (FIG. 7). Presuming that lectins were linked to the effect of the glycosylated MUC16^{c114} protein, a second inhibitor was constructed from the sugar-binding domain of LGALS3 (amino acids 117 to 244; FIG. 7 and FIG. 8) (*see*, Reference 23 as recited in Section 6.1.5, below) attached to the same pFUSE backbone ($^{117\text{-}244}$LGALS3pFUSE). Like Tunicamycin, both of these protein inhibitors interfered with the interaction of MUC16^{c114} with other cell surface proteins while the pFUSE vector alone had no effect (FIG. 7B). As with other interventions, the effect on pAKT expression and pERK was diminished in parallel with the loss of matrigel invasion when the *N*-glycosylation sites were removed, as shown in FIG. 7C. However, the MUC16$^{c114\text{-}N123}$ construct had high levels of expression of the MUC16$^{c114\text{-}N123}$ protein, as demonstrated by 4H11 (MUC16 ectodomain-specific) binding. The impact of *N*-glycosylation loss was likewise confirmed in the reduction of growth in the transfected 3T3 cells in nu/nu mice, as shown in FIG. 7D.

6.1.3.4 Transgenic Mouse

[00509] The effect of expression of the carboxy-terminal MUC16 elements in transgenic mice and the rate of spontaneous tumor formation was examined. Conditional transgenic mice expressing MUC16^{c354} (the full c114 sequence and the most proximal CA125 bearing tandem repeat) were generated. The CMV early enhancer plus chicken β actin promoter (CAG) was utilized to force substantial MUC16^{c354} expression in all murine tissues. This strategy was chosen because the physiology of the human ovary is very different from the murine reproductive system, and tissue-specific ovarian promoters have been weak and relatively difficult to use in transgenic systems. The strategy for these mice is shown in FIG. 9A.

[00510] Conditional transgenic animals were selected by southern blot, as shown in FIG. 9B, and crossed with EIIa-Cre mice to produce MUC16^{c354} transgenic founders. As shown in FIG. 9C, two founders were chosen and a colony of MUC16^{c354} transgenic mice was created. The two founders highly express MUC16^{c354} in many organs, *e.g.*, brain, colon, heart, kidney, liver, lung, ovary, and spleen. These mice have no effect from the widespread ectopic expression of MUC16^{c354}, with normal ratios of male:female progeny, normal rates of fertility, and apparently normal life span, exceeding 2 years. Necropsy of two apparently healthy animals (one male and one female) from the control population and the MUC16^{c354} transgenic mice at 3-month intervals up to 1 year was only remarkable for mild/moderate uterine endometrial hyperplasia in older female mice, but the incidence and severity was not significantly different than the wild type controls. Selected tissues are shown in FIG. 10. Only one spontaneous soft tissue tumor (sarcoma) was observed in the colony of more than 100 animals observed for 2 years or more.

[00511] Based on this result, it was hypothesized that a "second hit" would potentially be required. It is noteworthy than murine models of BRCA1 mutation also require a second hit, and loss of p53 significantly increased the frequency of tumors. MUC16^{c354} mice were crossed with p53+/- mice from The Jackson Laboratory. There was limited early effect. However, after approximately 6 months, MUC16^{c354} mice with p53+/- began to develop spontaneous sarcomatous tumors of the soft tissue and lymphoma at a rate higher than that of normal control animals. Selected tumors are shown in the panel insets of FIG. 9D. The Kaplan-Meier survival for these mice is shown in FIG. 9E. The MUC16^{c354}:p53+/- mice showed a significantly worse overall survival due to spontaneous tumor development ($p < 0.014$). The total number of tumors seen in each group were: p53 +/- mice, 20/107 mice; MUC16^{c354} and p53 +/- mice, 34/91 mice; MUC16^{c354} mice, 1/72 mice; wildtype mice, 0/91 mice. When 8 collected tumors were examined for p53 genomic sequencing, all of the spontaneous tumors had loss of the normal allele of p53, indicating that MUC16 dependent tumor development also requires loss of normal p53 function.

6.1.3.5 Ovarian TCGA

[00512] Based on the of the MUC16 fragments on transformation and tumor aggressiveness in the experimental models, the link between genetic alterations in MUC16 and the outcomes in ovarian cancer was examined. The TCGA ovarian cancer project is a well-studied collection containing 316 serous ovarian cancers with complete data, including clinical outcome data.

Since expression of MUC16 protein is an important driver of cancer behavior, the impact of MUC16 copy number on MUC16 mRNA expression was analyzed. The MUC16 transcript expression was generally related to the MUC16 gene copy number, although there was a broad variation in MUC16 transcript expression in all of the groups examined (except, of course, the rare homozygous deletion of MUC16). In most cases, the MUC16 mRNA expression was clustered at higher transcript numbers than the normal fallopian tube samples included as controls. Gene copy number is one of several variables that will potentially alter the expression of MUC16 protein, but it is clear that MUC16 mRNA expression (and MUC16 protein, of course) is often increased in serous ovarian cancer. The combined impact of MUC16 over-expression or mutation on clinical outcomes in the TCGA data set was also examined. When the TCGA data set is divided into MUC16 expression quintiles, the 20% of patients with the highest MUC16 expression had a significantly worse survival than the patients with lower MUC16 expression ($p=0.02969$). This relationship was further strengthened when the 18 patients with MUC16 mutations were included in the high MUC16 expression group ($p=0.02117$), as shown in FIG. 11A. Taken together, this analysis demonstrates that MUC16 expression has an adverse impact on the survival of patients with ovarian cancer and confirms the negative biologic effects of MUC16 expression identified in our preclinical models.

[00513] Ovarian cancers often demonstrate activation of the PI3K pathway. These activations occur primarily through amplification and overexpression rather than point mutation events as ovarian cancer is generally characterized by alterations in copy number. Based on the activation of the PI3K/AKT pathway in our cell line models, the relationship between MUC16 and other activating genetic alterations in the PI3K pathway was examined. As shown in FIG. 11B, overexpression and mutation events associated with MUC16 are generally complementary with other pathway events like PTEN loss, amplification of AKT1, AKT2, or PI3KCA. The mechanism of this MUC16-driven AKT activation remains unknown. Further, the role of ERK activation was examined but no link between MUC16 expession and ERK pathway mutations was identified.

6.1.4 DISCUSSION

[00514] MUC16, encoding the CA125 antigen, circulates in the plasma of many patients with ovarian cancer (*see*, Reference 1 as recited in Section 6.1.5, below). MUC16 is unique among the tethered mucins for its limited expression outside mullerian tissues (*see*, References 2 and 14

as recited in Section 6.1.5, below). While increasingly viewed as an adverse prognostic factor independent of tumor bulk, the biological mechanism for its negative impact has not been well understood (*see*, Reference 18 as recited in Section 6.1.5, below). The NH_2-portion of the molecule contains multiple tandem repeats that encode the CA125 antigen and appear to serve as important adhesion partners to mesothelin and some galectins (FIG. 1A) (*see*, References 5, 17, and 24-26 as recited in Section 6.1.5, below). While these adhesion functions have been suggested to be critical in MUC16-related adverse outcome, these studies do not explain all of the observed changes in ovarian cancer cell behavior. The cloning of the MUC16 glycoprotein has provided basic structural information about the MUC16 gene product (*see*, References 4 and 5 as recited in Section 6.1.5, below). The data presented in this example are the first data to indicate that MUC16 may mediate signaling from the environment into the cancer cell, in particular, the data presented in this example identify the glycosylated MUC16 ectodomain as critical to MUC16 alterations in cancer cell behavior.

[00515] This example demonstrates that 114 amino acids from the carboxy-terminus of MUC16 are sufficient to transform NIH/3T3 (3T3) cells, supporting both increased soft agar growth and increased matrigel invasiveness. While others have identified the most membrane proximal C-terminal portion of MUC16 as the critical elements in MUC16-induced behaviors, we link these behaviors to the *N*-glycosylation sites in the retained MUC16 ectodomain. These changes are associated with an altered gene-expression profile and increased expression of critical invasion genes such as MMP2, MMP9, CXCL12, and CDH11. While longer elements can induce a more virulent behavior, even the residual 114 amino acids proximal to the putative cleavage site are sufficient in 3T3 cells to induce the same changes in invasion gene expression. Moreover, glycosylation of Asn30 of $MUC16^{c114}$ (corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150) was essential for $MUC16^{c114}$ oncogenic properties. Without being bound by any particular theory, these findings are most consistent with an "outside in" signal transduction by the most proximal portions of the protein, including a residual extracellular domain along with the transmembrane domain and cytoplasmic tail. In contrast to the results of Theriault (Therialt et al. Gynecol Oncol 2011, 121(3):434-443) and Giannakouros (Giannakouros et al. Int. J. Oncol. 2015, 41(1):91-98), loss of the intracellular cytoplasmic domain had less impact than loss of the glycosylated ectodomain. These differences may reflect the specific mutations chosen and the methodology to reduce expression. The "inside-out" signal appears to activate a

transcription of a gene program that facilitates the implantation and growth of MUC16 expressing cells in soft agar and nude mice. When the transfected cells are examined for activation of common oncogenic pathways, both AKT and ERK pathways appear to be activated by constitutive expression of MUC16. The mechanism by which MUC16 increases AKT/ERK phosphorylation is unclear and will require further studies. The absence of co-precipitating receptors suggests that other mechanisms may also be involved. Although MUC16 sequences are very different, other tethered mucins, including both MUC1 and MUC4, have been shown to act as signal-generating oncogenes in 3T3 cells and rat fibroblasts (*see*, References 8 and 9 as recited in Section 6.1.5, below). It is likely that the role of mucins on the cancer cell surface play important roles through mechanisms that are still being defined.

[00516] Based on the findings in 3T3 cells, the results of the MUC16 transgenic mouse experiment is highly supportive. By itself, the same MUC16 proximal 354 sequence could be readily expressed in nearly all murine tissues with no adverse effect in the transgenic mouse. The rate of spontaneous tumor formation was very low in those mice, and reproductive function seemed unaffected. However, like other murine ovarian cancer models, loss of p53 function appears to play a strong permissive role in MUC16-dependent tumor formation (*see*, Reference 27 as recited in Section 6.1.5, below). These results certainly are consistent with uniform p53 inactivation, which characterizes ovarian cancer in the TCGA data set.

[00517] These findings describe MUC16-linked changes in cellular behavior and gene transcription. The in vitro and in vivo models are consistent with the adverse effects of MUC16 expression levels in serous ovarian cancer and promote the understanding of MUC16 as a pathogenic contributor to the behaviors of ovarian cancer. The adverse impact of increasing CA125 expression is consistent with increased in vivo tumor growth and lethality of MUC16 (+) 3T3 transfectants (*see*, Reference 18 as recited in Section 6.1.5, below).

6.1.5 REFERENCES CITED IN EXAMPLE 1

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6.2 EXAMPLE 2: MUC16 GLYCOSYLATION ANTIBODIES

6.2.1 INTRODUCTION

[00550] The CA125 antigen, recognized by the OC125 antibody (*see*, Reference 1 as recited in Section 6.2.5, below) is a heavily glycosylated antigen expressed in the tandem repeat domains from the extracellular portion of the MUC16 glycoprotein (*see*, References 2 and 3 as recited in Section 6.2.5, below). This circulating antigen is predominantly derived from benign or malignant Mullerian tissues and is FDA approved as a tumor marker for human ovarian cancer but its function and role in carcinogenesis is not known (*see*, References 4-6 as recited in Section 6.2.5, below). MUC16 belongs to a family of complex tethered mucins and it consists of a large, heavily glycosylated extracellular domain, a small ectodomain between the membrane and the putative cleavage site, a hydrophobic transmembrane region, and a short intracellular tail (FIG. 1) (*see*, References 7 and 8 as recited in Section 6.2.5, below). Most MUC16 protein is released into the surrounding space following cleavage and the ectodomain remains on the cell surface. OC125 and most of other MUC16-reactive monoclonal antibodies (mAb) react with antigens in the tandem repeat region present exclusively in the cleaved portion of the molecule. Since these epitopes are likely to be found in circulation, the existing mAbs cannot be used to track the fate of the remaining MUC16 protein fragment, and may not accurately reflect the true distribution of MUC16 expression (*see*, Reference 9 as recited in Section 6.2.5, below). -Others have shown that glycosylation surface proteins can regulate cell proliferation and differentiation through galectin 3 based interactions with the *N*-glycosylation sites of tyrosine kinase receptors like EGFR, PDGFR and others (KS Lau Cell 129:123, 2007). As demonstrated in Example 1

(*see*, Section 6.1), proximal parts of MUC16 (as little as 114 amino acids) can transform immortalized 3T3 cells and this effect appears to be abrogated by Tunicamycin.

[00551] This example demonstrates the precise glycosylation sites which mediate these effects and the mandatory role of Galectin 3 in MUC16 dependent transformation. Thus, antibodies able to bind to the proximal peptide sequence (*e.g.*, $MUC16^{c114}$) in a glycosylation-specific manner were developed to inhibit key MUC16-mediated cancer functions such as adhesion and invasion. Monoclonal antibodies directed at the crucial *N*-glycosylation site within MUC16 ectodomain were generated by using defined synthetic N-glycopeptide antigens as key epitope mimics. These antibodies inhibited the oncogenic biology of MUC16 by decreasing MUC16-driven matrigel invasion, oncogene activation and tumor growth in contrast to other non-glycosylated protein directed mAbs which had no effect. These antibodies demonstrated a mechanism for mucin transformation and provide a useful tool for diagnostic and therapeutic use in MUC16 positive tumors.

6.2.2 MATERIALS AND METHODS

6.2.2.1 SYNTHESIS OF GLYCOPEPTIDES

[00552] Antibodies specific for the third glycosylation site (Asn30, analogous to Asn1806 of MUC16) of a 55-amino acid sequence of MUC16 ($MUC16^{c55}$: NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNS (SEQ ID NO:129) were generated using synthetic glycopeptides as key epitope mimics incorporating a well-defined chitobiose ($GlcNAc_2$) on Asn30 of $MUC16^{c55}$ (SEQ ID NO:129, FIG. 13). The synthesis of the homogeneous N-glycopeptide was highly convergent and involved a coupling between the partially protected full-length peptide ($MUC16^{c55}$; SEQ ID NO:129) and the chitobiose amine under Lansbury aspartylation conditions (*see*, Reference 11 as recited in Section 6.2.5, below). $MUC16^{c55}$ (SEQ ID NO:129) was obtained by microwave-assisted, Fmoc solid-phase peptide synthesis (SPPS), followed by on-resin N-acetylation (Ac2O, DIEA), deallyation of Asp^{30} ($Pd(PPh_3)_4$, $PhSiH_3$) and subsequent cleavage off resin (1-2% TFA/CH2Cl2). Using a one-flask aspartylation/deprotection procedure (as described in Reference 12 as recited in Section 6.2.5, below), the free carboxylic acid side chain at position Asn30 was coupled with chitobiose amine (*see*, Reference 13 as recited in Section 6.2.5, below), followed by TFA-treatment (Cocktail R: 90% TFA, 5% thioanisol, 3% ethanedithiol, 2% anisol)

to provide glycopeptide $GlcNAc_2$-55-mer. The presence of pseudoproline motifs served to mitigate undesired aspartimide formation during the aspartylation.

[00553] In addition, the $Man_3GlcNAc_2$-containing peptide was prepared in a similar one-flask sequence.

[00554] Shorter glycopeptides encompassing Asn30 and Asn24 (analogous to Asn1800 and Asn1806, respectively, of MUC16) of $MUC16^{c55}$ (SEQ ID NO:129) were prepared (1) 18-mer: CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), and (2) 15-mer: CGTQLQNFTLDRSSV (SEQ ID NO:131). The 18-mer and 15-mer glycopeptides were conjugated to heyhole limpet Hemocyanin (KLH). The 15-mer (SEQ ID NO:131) incorporated chitobiose at Asn7 (analogous to Asn1806 of MUC16). The 15-mer glycopeptides was synthesized in a manner analogous to the synthesis of the 55mer glycopeptides.

[00555] The 18-mer (SEQ ID NO:130) incorporated chitobiose at Asn4 and Asn10 (analogous to Asn1800 and Asn1806, respectively, of MUC16). Allyl-protection of Asn4 and Asn10 of the 18-mer (analogous to Asn1800 and Asn1806, respectively, of MUC16) resulted in significant aspartimide formation. Thus, the more hindered O-2-phenylisopropyl ester (O-2-PhiPr, OPp) was used in the SPPS to provide after N-acetylation, and simultaneous resin cleavage/OPp removal (1-2% TFA/CH2Cl2) the partially protected peptide with free Asn4 and Asn10 side chains of the 18-mer (analogous to Asn1800 and Asn1806, respectively, of MUC16). Highly convergent installation of two chitobiose units through a double Lansbury aspartylation followed by global acid deprotection was performed to generate the bis-glycosylated 18-mer peptide (27% after HPLC purification).

[00556] Final coupling of the N-terminal cysteine residues of the 18-mer and 15-mer glycopeptides with the maleimide-derivatized carrier protein provided the KLH-conjugated constructs for mouse vaccination.

6.2.2.2 Mouse immunization protocol.

[00557] Five BALB/c and five Swiss Webster mice were immunized with the 55-mer glycopeptide (*see*, Section 6.2.2.1) three times every three weeks in the presence of 25 μL of Titermax adjuvant to immunize mice. Three weeks later, the mice were immunized with a mixture of mono-glycosylated 15-mer (SEQ ID NO:131) and bis-glycosylated 18-mer (SEQ ID NO:130) KLH-conjugated constructs. Sera were analyzed for reactivity against the 55-mer $GlcNAc_2$-glycosylated and the shorter glycopeptides unconjugated to KLH. Unglycosylated 55-

mer, 15-mer and 18-mer peptides, together with two MUC16-unrelated chitobiose-containing peptides were used as negative controls for screening. Mice were further immunized with the 15-mer and 18-mer KLH-conjugates two more times every three weeks and the responses were analyzed by ELISA after each immunization.

6.2.2.3 Invasion

[00558] *See*, Section 6.1.2.9. For shRNA experiments, BD BioCoat™ Matrigel™ Invasion Inserts or Chambers (catalog # 354480 in 24 well plate) and Control Inserts (catalog # 354578 in 24 well plate) were purchased from BD Biosciences, MA. Matrigel Invasion assay was performed as per manufacturer's protocol. Briefly, the matrigel chambers in 24 well plates (stored at -20°C) and control inserts (stored at 4°C) were allowed to come to room temperature. Both inserts were rehydrated with 0.5 mL of serum free medium in the insert as well as in the outside well of the 24 well plate, for 2 hrs at 37°C 5% CO_2 humidified incubator. Cultured SKOV3 cells were trypsinized and washed with culture medium. A million cells were separated into another centrifuge tube and washed 3 times with serum free medium. These cells were later adjusted to give 5,000 cells in 0.5 mL serum free medium. The medium in the rehydrated inserts were removed and the insert was transferred into a new 24 well plate containing 0.75 mL of 10% Foetal Bovine Serum (FBS) containing culture medium in the well which serves as a chemo attractant. Immediately, 0.5 mL of the cells (5,000 cells) in serum free medium was added to the insert. Proper care was taken to see that there was no air bubble trapped in the insert and the outside well. The 24 well plate was incubated at 37°C 5% CO_2 humidified incubator for 48 hrs. After incubation, the non-invading cells are removed from the upper surface of the membrane by "scrubbing" by inserting a cotton tipped swab into matrigel or control insert and gently applied pressure while moving the tip of the swab over the membrane surface. Scrubbing was repeated with a second swab moistened with medium. Then the inserts were stained in a new 24 well plate containing 0.5 mL of 0.5% crystal violet stain in distilled water for 30 minutes. Following staining the inserts were rinsed in 3 beakers of distilled water to remove excess stain. The inserts were air dried in a new 24 well plate. The invaded cells were hand counted under an inverted microscope at 200X magnification. Several fields of triplicate membranes were counted and recorded in the figure.

6.2.2.4 Tumor Growth in Athymic Nude Mice

[00559] *See*, Section 6.1.2.11.

6.2.2.5 Binding Assay of Biotinylated Glycopeptides

[00560] Binding affinity was determined using ForeBio Octet QK. 5 µg/mL of biotinylated chitobiose-conjugated 18-mer glycopeptide was loaded onto a streptavidin biosensor. After washing off excess antigen, mouse antibodies were tested at 10 µg/mL for association and dissociation steps, respectively. Binding parameters were calculated using 1:1 binding site model, partial fit.

6.2.2.6 Immunohistochemistry of Tissue Microarray

[00561] Core-needle biopsies of pre-existing paraffin-embedded tissue were obtained from the so-called donor blocks and then relocated into a recipient paraffin-arrayed "master" block by using the techniques by Kononen et al. (*see*, Kononen J, et al. Nat Med 1998;4(7):8447) and subsequently modified by Hedvat et al (*see*, Hedvat CV et al. Hum Pathol 2002;33(10):968-74). A manually operated Tissue Arrayer MTA-1 from Beecher Instruments Inc. (Sun Prairie, WI) was used to produce sample circular spots (cores) that measured 0.6 to 1.0 mm in diameter. The cores were arrayed 0.3 to 0.4 mm apart from each other. A layer of control tissues was strategically laid around the actual tissue microarrays in order to avoid edging effects. The specific composition of each tissue microarray is delineated below. Slides of tissue microarrays for ovarian cancer or control tissue were prepared by cutting 4 um sections from formalin-fixed paraffin-embedded tissue.

[00562] Immunohistochemistry was performed on the tissue microarrays standard OC125 (Ventana, Tuscon, AZ), 4H11 (*see*, Rao et al. Appl. Immunohistochem Mol Morphol, 2010, 18(5):462-72) and the 19C11 monoclonal antibody. Sections of the tissue microarrays were cut at 4 microns, placed on Superfrost/Plus microscope slides (Fisher brand) and baked in a 60° oven for at least 60 minutes. The slides were then deparaffinized and hydrated to distilled water, soaked in citrate buffer at pH 6.00 for 30 minutes at 97° C, washed in running water for 2-5 minutes, incubated for 5 minutes in 3% hydrogen peroxide diluted in distilled water. Slides were washed in distilled water for 1 minute, transferred to a bath of phosphate buffered saline (PBS), pH 7.2, for two changes of 5 minutes each and placed in 0.05% BSA diluted in PBS for a minimum of 1 minute. After drying around tissue sections, normal serum was applied at a 1:20 dilution in 2% BSA/PBS and incubated for a minimum of 10 minutes at room temperature in a humidity chamber. The serum was then suctioned off without allowing the sections to dry, and approximately 150 lambda of new antibody at a dilution of 1:1000 was placed on the tissue. The

slide was incubated overnight (approximately 15-18 hours) at 4° C in a humidity chamber. Primary antibody was washed off using three changes of PBS for 10 minutes each. Secondary antibody, biotinylated α-mouse from Vector laboratories (Burlingame, Ca), was applied at 1:500 dilution in 1% BSA/PBS and incubated for 45-60 minutes at room temperature in humidity chamber. The antibody was washed off again using three changes of PBS as above. Slides were then transferred to a bath of diaminobenzidine (DAB), diluted in PBS for 5-15 minutes. The slides were then washed in tap water for 1 minute, counterstained using Harris modified hematoxylin (Fisher), decolorized with 1% acid alcohol and blue in ammonia water, dehydrated with 3 changes each of 95% ethanol, 100% ethanol and xylene for 2 minutes each and coverslipped with permanent mounting medium.

6.2.2.7 Internalization Assay

[00563] Internalization of ^{89}Zr-19C11 was investigated on SKOV3 cells expressing MUC16^{c114}. Approximately 1×10^5 cells were seeded in a 12-well plate and incubated overnight at 37°C 5% CO_2 incubator. A volume of radiolabeled protein was added to each well and the plates were incubated at 37°C and 4°C for 1, 5, 12, and 24 hours. Following each incubation period, the medium was collected and the cells were rinsed with 1 mL of phosphate buffered saline (PBS). Surface-bound activity was collected by washing the cells in 1 mL of 100 mM acetic acid with 100 mM glycine (1:1, pH 3.5) at 4°C. The adherent cells were then lysed with 1 mL of 1 M NaOH. Each wash was collected and counted for activity. The ratio of activity of the final wash to the total activity of all the washes was used to determine the % internalized.

6.2.3 RESULTS

6.2.3.1 MUC16 patho-biology is dependent on *N*-glycosylation of C-terminal MUC16 ectodomain.

[00564] Example 1 (*see*, Section 6.1) demonstrated that expression of MUC16^{c114} resulted in a more aggressive *in vitro* / *in vivo* behavior of 3T3 mouse fibroblasts, resulting in significant increase in MUC16^{c114}-driven matrigel invasion and a more rapid tumor growth in vivo. Thus, the SKOV-3 cell line (a human ovarian cell line lacking expression of MUC16), was examined for the effect of MUC16^{c114} dependent properties. MUC16^{c114} expression led to cell surface expression and a nearly 3 fold increase in matrigel invasion (compare lanes 1 and 2 of FIG. 12A). This increase in invasion was dependent upon the *N*-glycosylation of asparagine at amino acid position 1 (Asn1), 24 (Asn24), and 30 (Asn 30) of MUC16^{c114} (corresponding to Asn1777,

Asn1800, and Asn1806 of mature MUC16 (SEQ ID NO:150), respectively; $MUC16^{c114\text{-}N123}$), as mutation of Asn30 to alanine ($MUC16^{c114\text{-}N3}$, FIG. 12A, lane 3), mutation of Asn1 and Asn24 to alanine ($MUC16^{c114\text{-}N12}$, FIG. 12A, lane 4), and mutation of Asn1, Asn24, and Asn30 to alanine ($MUC16^{c114\text{-}N123}$, FIG. 12A, lane 4), abrogated matrigel invasion. *See*, also, FIG. 12B. Moreover, $MUC16^{c114}$-induced increased matrigel invasion was dependent upon MGAT5 (the first enzyme involved in the *N*-glycosylation reaction) and/or LGALS3 (an enzyme amplified in many high grade serous cancers), as knockdown shRNA experiments which reduced MGAT5 or LGALS3 expression had a similar effect as $MUC16^{c114}$ mutation at the *N*-glycosylation sites and reduced invasion to near basal levels (FIG. 12A, lanes 6-10).

[00565] The most unambiguous hallmark of oncogenic transformation is the ability to promote growth in immunodeficient mice. In order to measure the effects of MUC16 *N*-glycosylation, MGAT5, and LGALS2 on tumor growth rate, a flank tumor model was utilized to facilitate regular tumor measurements. As shown in FIG. 12C, when 3T3 cell lines expressing vector (phrGFP), $MUC16^{c114}$, $MUC16^{c114\text{-}N123}$, $MUC16^{c114}$ and an anti-MGAT5 shRNA ($MUC16^{c114}$-shMGAT5), or $MUC16^{c114}$ and an anti-LGALS3 shRNA ($MUC16^{c114}$-shLGALS3) were implanted into the flanks of athymic nude mice, only the $MUC16^{c114}$ 3T3 cells formed larger tumors compared to the vector only controls at 24 days. These data corroborate the *in vitro* analyses indicating that MUC16 *N*-glycosylation, MGAT5, and LGALS3 are required for tumor growth.

6.2.3.2 Synthesis of homogeneous *N*-glycopeptides as key epitope mimics for mAb development

[00566] Since *N*-glycosylation at the Asn30 site of $MUC16^{c114}$ (corresponding to Asn 1806 of mature MUC16 (SEQ ID NO:150); $MUC16^{c114\text{-}N3}$) was determined to be a central requirement for MUC16 oncogenic action, glycan profiling of $MUC16^{c114\text{-}N12}$ expressed in SKOV3 cells was performed, as $MUC16^{c114\text{-}N12}$ retains the capacity to be N-glycosylated at Asn30 (corresponding to Asn 1806 of mature MUC16 (SEQ ID NO:150)). The glycome analysis showed a highly diverse *N*-glycosylation pattern for this C-terminal MUC16 fragment, with the critical chitobiose ($GlcNAc_2$) stem as the minimal repeating unit to which various mannose moieties are attached (FIG. 13A).

[00567] Thus, glycosylation-directed mAbs were generated in an effort to inhibit the glycosylation-dependent effects of MUC16 on metastasis and invasion. These antibodies were

designed to target N-glycopeptide epitopes containing the crucial third glycosylation site (Asn30 of $MUC16^{c114}$) on a shorter 55-amino acid sequence within the MUC16 ectodomain ($MUC16^{C55}$; SEQ ID NO:129). *See*, Section 6.2.2.1 and FIG. 13B, FIG. 13C, and FIG. 13D for a description of the synthesis of the glycopeptides utilized as immunogens. *See*, Section 6.2.2.2 for a description of the immunization process.

[00568] Antibodies were generated via immunization with short (55-mer, 18-mer, and 15-mer) MUC16 glycopeptides comprising chitobiose at the amino acid residues corresponding to Asn24 and/or Asn30 of $MUC16^{c114}$ (corresponding to Asn1800 and Asn1806, respectively, of mature MUC16 (SEQ ID NO:150)). In addition to being the smallest motif common to larger N glycans, chitobiose would also enable a better exposure of the underlying MUC16-derived peptide for inducing antibodies that not only show dependence on the glycan but also peptide specificity. This hypoglycosylation is a frequent, distinctive feature in mucin glycoproteins on the surface of tumor cells in comparison with normal cells.

6.2.3.3 Mouse vaccination with synthetic glycopeptides/glycoconjugates and serologic assays

[00569] Mouse vaccination and sera collection was performed according to the protocol described in the Section 6.2.2.2. After three immunizations with $GlcNAc_2$-55-mer (FIG. 13B), mice were further immunized with a mixture of KLH-conjugated constructs (mono-glycosylated 15-mer (SEQ ID NO:131; FIG. 13C) and bis-glycosylated 18-mer (SEQ ID NO:130; FIG. 13D)), two out of ten mice showed positive ELISA signals for both 55-mers (with and without GlcNAc2) but the response was generally weak, suggesting that mice did not fully sensitize with the 55-mer immunizations. Two more immunizations with KLH conjugates ($GlcNAc_2$-15-mer (FIG. 13C) and $(GlcNAc_2)_2$-18-mer (FIG. 13D)), resulted in enhanced IgG immune responses against the shorter 15-mer and 18-mer glycopeptides, particularly in two mice (Mouse 7 and Mouse 8). However, these antibodies did not show any detectable reactivity by ELISA with the 55-mer-glyco-peptides, which suggests that, in this particular assay, the epitope in this large fragment is either inaccessible or conformationally different. Mouse 5, which responded to both of the 55-mers (chitobiose-containing and/or non-glycosylated peptide) was negative to $Man_3GlcNAc_2$-derivatized 55-mer. Not surprisingly, the 4H11 mAb (Rao et al. Appl. Immunohistochem Mol Morphol, 2010, 18(5):462-72), which is directed to the non-glycosylated

peptide backbone, showed no binding to the unconjugated 15/18-mer glycopeptides, indicating that there may be some differences in available epitopes. *See*, FIG. 14.

6.2.3.4 Glycosylation-dependent monoclonal antibody development and *in vitro* biological assays – MUC16-driven matrigel invasion

[00570] One of ten mice (Mouse 7) were selected whose serum showed the highest reactivity ratio to the short glycopeptides versus the non-glycosylated ones, and therefore showed some preference for the presence of the sugar. The spleen of mouse 7 was harvested and standard hybridoma culture technology provided IgG-producing hybridoma cell lines. The splenocytes were fused with hybridoma fusion partner giving an extraordinarily high fusion efficiency (>5.5 colonies/well on average, with > 30,000 hybridomas). Supernatants were selected and screened for reactivity by ELISA against the individual glycopeptides. Preliminary ELISA analysis for the fusion test plate against 15mer-chitobiose peptide and 18mer-chitobiose peptide (combined in the same well) showed some positive signals, which points to the presence of anti-peptide antibodies, albeit their glycosylation dependence could not be fully assessed at this point. *See*, FIG. 14. Nonetheless, a higher ratio of antibodies with favored positivity, and therefore more specific, to the chitobiose-glycosylated antigens was observed in comparison to the non-glycosylated ones. Upon culture dilution, a single clone growing in each well (1:1 ratio above) was obtained and primary screening revealed that antibodies produced by these hybridomas do not recognize the 4H11 epitope, which lies close to the non-glycosylated 15-/18-mer. *See*, FIG. 14. After completing the monoclonal antibody screening at higher dilution, antibodies showing preference for the glycopeptide epitope were obtained. Thus, this process afforded 36 chitobiose-dependent primary mAbs that were tested for reactivity against MUC16. Out of those, 15 mAbs were evaluated (in parallel to 4H11) for their effect on invasion by matrigel assay with SKOV3-MUC16^{c114} transfectant (FIG. 15A). MUC16 Glycosylation Antibodies 1B5, 10C6, 13A7, 18C6, 19C11, 16C5, 6H10, 21F8, 7B12 showed inhibition of matrigel invasion, whereas 4H11 had no effect on this property, indicating that antibodies directed to Asn30 of MUC16^{c114} (corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150)) inhibit the biology of MUC16. MUC16 Glycosylation Antibodies were subsequently subcloned and purified. Binding parameters for certain MUC16 Glycosylated Antibodies were determined (*see*, Table 9).

[00571] **Table 9.** Binding parameters of MUC16 Glycosylated Antibodies

Antibody	k_d (1/s)	Error in k_d (1/s)	k_a (1/s)	K_D (nM)

Antibody	k_d (1/s)	Error in k_d (1/s)	k_a (1/s)	K_D (nM)
10C6.E4	*	--	**	>1000
19C11.H6	2.42×10^{-3}	2.35×10^{-4}	3.80×10^{4}	63.7
13A7.C8	*	--	**	>1000
16C5.C1	1.72×10^{-3}	1.20×10^{-4}	6.68×10^{4}	25.7
7B12.B3	1.04×10^{-3}	1.09×10^{-4}	7.50×10^{4}	13.8
18C6.D12	6.78×10^{-4}	1.83×10^{-4}	6.14×10^{4}	11.1
1B5.A7	1.49×10^{-3}	1.12×10^{-4}	7.35×10^{4}	20.2
4H11	--	--	--	--

*= Low calculation confidence; no fit for off-rate
**= k_a is too low for association rate determination

[00572] Finally, immunohistochemistry of human ovarian tissue samples performed with the MUC16 Glycosylation Antibody 10C6 displayed improved detection of MUC16 as compared to immunohistochemistry performed 4H11 or OC125 (FIG. 16E).

6.2.3.5 MUC16 Glycosylation Antibodies are Specific for MUC16 Glycosylation.

[00573] To investigate the specificity of the MUC16 Glycosylation Antibodies, FACs analyses were performed on (i) cells expressing native (mature) MUC16 (OVCA-433 cells), (ii) SKOV3 cells, which lack MUC16 expression, expressing a control vector (SKOV3 phrGFP cells), (iii) SKOV3 cells expressing $MUC16^{c114}$ (SKOV3 $MUC16^{c114}$), (iv) SKOV3 cells expressing $MUC16^{c114\text{-}N1}$ (SKOV3 $MUC16^{c114\text{-}N1}$), (v) SKOV3 cells expressing $MUC16^{c114\text{-}N3}$ SKOV3 $MUC16^{c114\text{-}N3}$), or (vi) SKOV3 cells expressing SKOV3 $MUC16^{c114\text{-}N123}$ (SKOV3 $MUC16^{c114\text{-}N123}$), in the presence or absence of MUC16 Glycosylated Antibody (18C6, 19C11, 10C6, 1B5, or 13A7) or the monoclonal anti-MUC16 antibody, 4H11 (Table 10). Antibodies 4H11, 18C6, 19C11, 10C6, 1B5, and 13A7 demonstrated binding to OVCA-433 cells (Table 10; compare ID NOs: 3-8 to negative controls, ID NOs: 1 and 2). In contrast, as expected based upon the design of the studies and generation of the antibodies, none of antibodies 4H11, 18C6, 19C11, 10C6, 1B5, and 13A7 bound SKOV3 phrGFP cells (Table 10, ID NOs: 11-16 as compared to the negative controls, ID NOs: 9 and 10). Antibodies 4H11, 18C6, 19C11, 10C6, 1B5, and 13A7 bound SKOV3 $MUC16^{c114}$ (Table 10, ID NOs: 19-24 as compared to the negative controls, ID NOs: 17 and 18). Mutation of Asn1 of $MUC16^{c114}$ (corresponding to Asn1777 of mature MUC16 (SEQ ID NO:150)) did not inhibit antibody binding to SKOV3 $MUC16^{c114\text{-}N1}$ cells (Table 10, ID NOs: 27-32 as compared to negative controls, ID NOs: 25 and 26). However, mutation of Asn30 of $MUC16^{c114}$ (corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150)) abrogated binding of MUC16 Glycosylated Antibodies 18C6, 19C11, 10C6,

1B5, and 13A7 (Table 10, ID NOs: 36-40, as compared to negative controls, ID NOs: 33 and 34). Moreover, mutation of Asn30 of $MUC16^{c114}$ (corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150)) did not abrogate binding of antibody 4H11, which is not a MUC16 Glycosylated Antibody (Table 10, ID NO: 35, as compared to negative controls, ID NOs: 33 and 34). In addition, asparagine to alanine mutations at Asn1, Asn24, and Asn30 (corresponding to Asn1777, Asn1800, and Asn1806, respectively, of mature MUC16 (SEQ ID NO:150)), abrogated binding of MUC16 Glycosylated Antibodies 18C6, 19C11, 10C6, and 1B5 (Table 10, ID NOs: 44-47, as compared to negative controls, ID NOs: 41 and 42), while binding of 4H11 was not abrogated. It is noted that 13A7 maintained binding to the SKOV3 $MUC16^{c114\text{-}N123}$ cells. These data demonstrate that MUC16 Glycosylation Antibodies bind to $MUC16^{c114}$ in a glycosylation-dependent fashion.

[00574] Table 10. FACs analysis of MUC16 Glycosylation Antibodies with OVCA-433 or SKOV3-transfectant cells.

ID NO	Muc16 Glycosylation Antibodies	Mean % PE
1	OVCA-433 cells	0.12*
2	OVCA-433 + G anti M IgG PE	5.01*
3	OVCA-433 + 4H11 + G anti M IgG PE	82.4
4	OVCA-433 + 18C6 + G anti M IgG PE	91.4
5	OVCA-433 + 19C11 + G anti M IgG PE	93.7
6	OVCA-433 + 10C6 + G anti M IgG PE	84.5
7	OVCA-433 + 1B5 + G anti M IgG PE	94.6
8	OVCA-433 + 13A7 + G anti M IgG PE	92.8
9	SKOV3 phrGFP cells	1.01*
10	SKOV3 phrGFP + G anti M IgG PE	1.2*
11	SKOV3 phrGFP + 4H11 + G anti M IgG PE	3.39*
12	SKOV3 phrGFP + 18C6 + G anti M IgG PE	2.09*
13	SKOV3 phrGFP + 19C11 + G anti M IgG PE	1.69*
14	SKOV3 phrGFP + 10C6 + G anti M IgG PE	1.84*
15	SKOV3 phrGFP + 1B5 + G anti M IgG PE	1.5*
16	SKOV3 phrGFP + 13A7 + G anti M IgG PE	2.66*
17	SKOV3 $MUC16^{c114}$ cells	0.218*
18	SKOV3 $MUC16^{c114}$ + G anti M IgG PE	2.42*
19	SKOV3 $MUC16^{c114}$ + 4H11 + G anti M IgG PE	85.7
20	SKOV3 $MUC16^{c114}$ + 18C6 + G anti M IgG PE	73.1
21	SKOV3 $MUC16^{c114}$ + 19C11 + G anti M IgG PE	69.3
22	SKOV3 $MUC16^{c114}$ + 10C6 + G anti M IgG PE	72.9
23	SKOV3 $MUC16^{c114}$ + 1B5 + G anti M IgG PE	73.2
24	SKOV3 $MUC16^{c114}$ + 13A7 + G anti M IgG PE	68.4
25	SKOV3 $MUC16^{c114\text{-}N1}$ cells	0.139*

ID NO	Muc16 Glycosylation Antibodies	Mean % PE
26	SKOV3 MUC16$^{c114\text{-}N1}$ + G anti M IgG PE	2.84*
27	SKOV3 MUC16$^{c114\text{-}N1}$ + 4H11 + G anti M IgG PE	91.5
28	SKOV3 MUC16$^{c114\text{-}N1}$ + 18C6 + G anti M IgG PE	83
29	SKOV3 MUC16$^{c114\text{-}N1}$ + 19C11 + G anti M IgG PE	81.7
30	SKOV3 MUC16$^{c114\text{-}N1}$ + 10C6 + G anti M IgG PE	83
31	SKOV3 MUC16$^{c114\text{-}N1}$ + 1B5 + G anti M IgG PE	85.4
32	SKOV3 MUC16$^{c114\text{-}N1}$ + 13A7 + G anti M IgG PE	84.5
33	SKOV3 MUC16$^{c114\text{-}N3}$ cells	0.0202*
34	SKOV3 MUC16$^{c114\text{-}N3}$ + G anti M IgG PE	0.856*
35	SKOV3 MUC16$^{c114\text{-}N3}$ + 4H11 + G anti M IgG PE	15.6
36	SKOV3 MUC16$^{c114\text{-}N3}$ + 18C6 + G anti M IgG PE	1.48*
37	SKOV3 MUC16$^{c114\text{-}N3}$ + 19C11 + G anti M IgG PE	1.25*
38	SKOV3 MUC16$^{c114\text{-}N3}$ + 10C6 + G anti M IgG PE	1.4*
39	SKOV3 MUC16$^{c114\text{-}N3}$ + 1B5 + G anti M IgG PE	1.06*
40	SKOV3 MUC16$^{c114\text{-}N3}$ + 13A7 + G anti M IgG PE	2.39*
41	SKOV3 MUC16$^{c114\text{-}N123}$ cells	0.274*
42	SKOV3 MUC16$^{c114\text{-}N123}$ + G anti M IgG PE	7.02*
43	SKOV3 MUC16$^{c114\text{-}N123}$ + 4H11 + G anti M IgG PE	32.3
44	SKOV3 MUC16$^{c114\text{-}N123}$ + 18C6 + G anti M IgG PE	11.6*
45	SKOV3 MUC16$^{c114\text{-}N123}$ + 19C11 + G anti M IgG PE	5.25*
46	SKOV3 MUC16$^{c114\text{-}N123}$ + 10C6 + G anti M IgG PE	5.84*
47	SKOV3 MUC16$^{c114\text{-}N123}$ + 1B5 + G anti M IgG PE	7.39*
48	SKOV3 MUC16$^{c114\text{-}N123}$ + 13A7 + G anti M IgG PE	28.7

* Indicates no binding is considered to be observed.

6.2.3.6 MUC16 Glycosylation Antibodies Inhibit Matrigel Invasion.

[00575] Given the glycosylation specificity of MUC16 Glycosylation Antibodies (Table 9), the ability of the MUC16 Glycosylation Antibody bioreactive supernatants to inhibit matrigel invasion in a glycosylation-specific manner was evaluated. Thus, matrigel invasion assays were performed with SKOV3 ovarian cancer stable cell lines expressing phrGFP (FIG. 15A, lane 1) or phr-GFP-MUC16^{c114} (MUC16^{c114}; FIG. 15A, lanes 2-18) in the presence (FIG. 15A, lanes 3-18) or absence (FIG. 15A, lanes 1 and 2) of MUC16 Glycosylation Antibody bioreactive supernatants. The MUC16 monoclonal antibody 4H11 (FIG. 15A, lane 3) was used as a control for the MUC16 Glycosylation Antibody bioreactive supernatants (FIG. 15A, lanes 4-18) to evaluate glycosylation dependency in matrigel invasion. Expression of MUC16^{c114}, either alone in the presence of 4H11 (FIG. 15A, lanes 2 and 3, respectively), resulted in an increase in

matrigel invasion activity. In contrast, incubation with MUC16 Glycosylation Antibodies (FIG. 15A, lanes 4-18) decreased matrigel invasion of the $MUC16^{c114}$-expressing ovarian cancer cells.

[00576] Next, the ability of purified MUC16 Glycosylated Antibodies to inhibit matrigel invasion was evaluated. To this end, SKOV3 cells expressing $MUC16^{c114}$ were incubated in the presence and absence the MUC16 antibody 4H11 or purified MUC16 Glycosylated Antibodies (FIG. 15B). MUC16 Glycosylated Antibodies 7B12, 19C11, 18C6, and 10C6 inhibited $MUC16^{c114}$-induced matrigel invasion (FIG. 15B, compare lanes 3-6 to the negative control, lane 2). In contrast, the monoclonal anti-MUC16 antibody 4H11 did not inhibit $MUC16^{c114}$-induced matrigel invasion (FIG. 15B, compare lanes 2 to the negative control, lane 1). These data demonstrate that, in contrast to the monoclonal antibody 4H11, MUC16 Glycosylation Antibodies (*e.g.,* 7B12, 19C11, 18C6, and 10C6) block matrigel invasion.

[00577] The ability of the MUC16 Glycosylation Antibodies to inhibit matrigel invasion was assayed in the context of $MUC16^{c114}$ *N*-glycosylation mutants (FIG. 16A). To this end, matrigel invasion assays were performed on SKOV3 phrGFP cells, SKOV3 $MUC16^{c114}$ cells, SKOV3 $MUC16^{c114\text{-}N1}$ cells, SKOV3 $MUC16^{c114\text{-}N2}$ cells, or SKOV3 $MUC16^{c114\text{-}N3}$ cells (FIG. 16A, lanes 1-5, respectively), in the presence of (i) a control antibody; (ii) 4H11 antibody; or (iii) the MUC16 Glycosylation Antibody 10C6. $MUC16^{c114}$-induced matrigel invasion was inhibited in SKOV3 $MUC16^{c114\text{-}N3}$ cells, as Asn30 of $MUC16^{c114}$ is necessary for $MUC16^{c114}$ matrigel invasion. Moreover, matrigel invasion was induced in SKOV3 $MUC16^{c114}$ cells, SKOV3 $MUC16^{c114\text{-}N1}$ cells, and SKOV3 $MUC16^{c114\text{-}N2}$ cells in the presence and absence of the MUC16 monoclonal antibody 4H11. In contrast, incubation of these cells with the MUC16 Glycosylation Antibody 10C6 abrogated matrigel invasion (FIG. 16A). These data were also corroborated in FIG. 16B and in 3T3 cells expressing $MUC16^{c344}$ mutants (FIG. 16C).

[00578] Taken together, these data indicate that MUC16 Glycosylation Antibodies, in contrast to the monoclonal anti-MUC16 antibody 4H11, are able to inhibit matrigel invasion in a glycosylation-dependent manner.

6.2.3.7 The MUC16 Glycosylation Antibody 19C11 is internalized.

[00579] Finally, the ability of a MUC16 Glycosylation Antibody targeting Asn30 of $MUC16^{c114}$ to be internalized was assessed. SKOV3 cells expressing $MUC16^{c114}$ were incubated with ^{89}Zr-DFO-labeled 19C11 antibody and internalization was determined via Radiotracer (FIG. 17). These data demonstrate that the labeled 19C11 antibody was internalized

when incubated with $MUC16^{c114}$-expressing SKOV3 cells incubated at 37°C as early as 1 hour post-treatment with the antibody. Cellular uptake of the labeled antibody was decreased at 4°C.

6.2.4 DISCUSSION

[00580] The MUC16/CA125 antigen, a member of the mucin family with substantial homology to MUC1, has long been associated with gynecological malignancies (*see*, Reference 4 as recited in Section 6.2.5, below). Despite not being sufficiently sensitive or specific as a general screening tool, CA125 measurement is regularly used to monitor patients with ovarian cancer through antibody-based detection methods. The vast majority of MUC16-reactive antibodies, such as OC125, are directed against glycosylation-dependent epitopes found in the cleaved fraction of the molecule, and are not useful as screening tools to detect the proximal portion of MUC16 after cleavage. As a consequence, biological studies of the remaining MUC16 protein fragment are lacking. The data in Example 1 (Section 6.1) demonstrated that a 114 amino acid sequence of the proximal MUC16 region ($MUC16^{C114}$) is sufficient to increase invasion and tumor growth on several ovarian cancer cell lines. The striking discovery herein that *N*-glycosylation of this C-terminal ectodomain, in particular at the third Asn site (Asn30, corresponding to Asn1806 of mature MUC16 (SEQ ID NO:150)), is crucial for MUC16 oncogenic effects suggests new roles for MUC16, which could then be considered not only a passive marker of disease but also a pathogenic molecule. Based on this premise, the development of monoclonal antibodies against these retained portions of MUC16 appears as a powerful tool to explore the patho-biology of this mucin and create MUC16 targeted therapeutics.

[00581] Previous studies identified mAbs against the non-cleaved C-terminal region of MUC16, although in contrast to prior antibodies, they were directed at the non-glycosylated peptide backbone instead of at complex glycoprotein epitopes. In particular, 4H11 showed high-affinity binding to the MUC16 ectodomain, and internalized by ovarian cancer cells more efficiently than OC125 because of the proximate location of the epitope. This finding suggested that the proximal region of the glycoprotein has an independent biology from the shed portion of MUC16 distal to the putative cleavage site. However, since 4H11 does not recognize the crucial glycosylation sites within the ectodomain that are required for MUC16 pathogenic action, its potential for future studies in targeted therapy is limited.

[00582] A panel of glycosylation-dependent monoclonal antibodies directed to the key glycopeptide epitopes in the MUC16 ectodomain were developed by using KLH-conjugated, synthetic glycopeptide mimics in combination with hybridoma technology. This methodology is preferred over polyclonal antibody generation, as at the polyclonal stage, the glycopeptide specificity was not complete and some binding was also detected to non-glycosylated MUC16 peptide fragments. To obtain the MUC16 Glycosylation Antibodies, a primary selection for monoclonal antibody generation was based on a higher ratio of glycosylation dependence in the multiclonal culture associated to some degree of preference for the presence of the sugar. The power of the new monoclonal antibodies and their higher specificity for the glycopeptide epitope has been demonstrated by studying their effect on MUC16-driven matrigel invasion. These MUC16 Glycosylation Antibodies were able to inhibit invasion in a matrigel assay whereas the non-glycosylation directed 4H11 was not. Based on the finding that *N*-glycosylation at Asn30 is essential for MUC16 action, these results confirm that the newly generated antibodies specifically target the key glycopeptide epitope of MUC16 ectodomain, which results in inhibition of the MUC16 patho-biology. Importantly, the MUC16 Glycosylation Antibody 10C6 significantly delayed MUC16-positive tumor growth in an athymic nude mouse model implanted with $MUC16^{c114}$-expressing ovarian cancer cells, demonstrating the potential of these monoclonal antibodies to emerge as a promising tool for their therapeutic use in optimized clinical applications.

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6.3 EXAMPLE 3: TUMOR PROMOTING EFFECTS OF MUC16 REQUIRE INTERACTION WITH GALECTIN-3 AND CELL SURFACE RECEPTORS

[00601] This example provides (a) a more detailed description of certain of the experiments described in Example 2 (Section 6.2); and (b) additional experiments as compared to Example 2 (Section 6.2).

6.3.1 INTRODUCTION

[00602] Overexpression of MUC16 / CA125 is common in serous ovarian cancer and elevated serum CA125 levels are associated with decreased survival. The CA125 antigen, recognized by the OC125 antibody, is a heavily glycosylated antigen expressed within the tandem repeat domains from the extracellular portion of the MUC16 glycoprotein (*see* References 3 and 22 in Section 6.3.13, below). This antigen is predominantly expressed by benign or malignant Mullerian tissues, but its function and role in carcinogenesis are not currently fully understood (*see* Reference 4 in Section 6.3.13, below). MUC16 is a highly complex tethered mucin consisting of a large, heterogeneously glycosylated extracellular domain, a 58 amino acid ectodomain between the cell membrane and the putative cleavage site, a hydrophobic transmembrane region, and a short intracellular tail (*see* Reference 21 in Section 6.3.13, below). OC125 and most other MUC16-reactive monoclonal antibodies (mAbs) recognize the immunogenic 156 amino acid tandem repeat region present in the cleaved portion of the molecule. Newer ectodomain-specific antibodies (*e.g.,* 4H11 and 4A5) recognize a peptide epitope in the post-cleavage, retained portion of MUC16 (*see* Reference 6 in Section 6.3.13, below). The C-terminal part of MUC16 ($MUC16^{c114}$) has been demonstrated to transform immortalized 3T3 cells, as measured by increased anchorage independent growth, activation of the AKT and ERK pathways, increased matrigel invasion, and enhanced growth in nude mouse xenografts (*see* Section 6.1 and Reference 19 in Section 6.3.13, below). These effects were dependent on the ectodomain of MUC16, while the loss of the 31 amino acid cytoplasmic tail had little effect on those properties. The mechanisms by which the ectodomain promotes oncogenic behaviors are not fully understood (*see* Reference 19 in Section 6.3.13, below). While there are no consensus protein-binding domains present, the 58 amino acid sequence of the

MUC16 ectodomain includes three *N*-glycosylation sites that represent potential interaction/regulatory sites for MUC16 with other cell surface molecules.

[00603] The *N*-glycosylation sites of tyrosine kinase receptors such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and others appear to interact with cellular lectins such as Galectin-3 to regulate surface residency, intensity of signaling, and cellular behavior (*see* Reference 12 in Section 6.3.13, below). The effects of *N*-glycosylation depend on the number of *N*-glycosylation sites on growth-enhancing receptors and on the affinity of Galectin-3 for complex N-glycosylated species. There are fewer *N*-glycosylation sites on the countervailing inhibitory signals from cell surface molecules such as transforming growth factor-beta (TGF-β) receptors. These receptors are sensitive to growth factor-related high nutrient fluxes and provide a dampening function in normal circumstances. However, mechanisms of cancer-associated glycoprotein interactions with classic receptor tyrosine kinases are not known. MUC1, MUC4, and MUC16 are all heavily glycosylated tethered glycoproteins characterized by the presence of transmembrane domains and overexpressed in epithelial cancers (*see* Reference 10 in Section 6.3.13, below).

[00604] This Example (Section 6.3) demonstrates that glycosylation of MUC16 plays a key role in mucin-related transformation by mediating complex cell surface interactions.

[00605] The C-terminal portion of MUC16 promoted oncogene activation, matrigel invasion and tumor growth. These effects were dependent on MGAT5 dependent glycosylation of two proximal N glycosylation sites in the 58 amino acid retained MUC16 ectodomain. Neither *N*- nor *O*-glycosylation sites in the more distal MUC16 tandem repeat region could functionally substitute for those two sites. Patterns of MUC16 glycosylation were diverse, but a chitobiose stem characterized the base of all *N*-glycosylation species. Antibodies against proximal, chitobiose containing MUC16 glycopeptides blocked Galectin 3-mediated binding to cell surface signaling receptors and inhibited the tumor promoting effects of MUC16.

[00606] Systematic alterations in MUC16 glycopeptides were employed to directly interrogate the relationship between glycan structure and the tumor-promoting effects exerted by MUC16 expression. These effects, including colocalization, oncogene activation, matrigel invasion, and tumor xenograph growth, were exerted by Galectin-3-mediated binding between a N-glycosylated sequence on the retained, noncirculating portion of MUC16 and cell surface molecules such as epidermal growth factor receptor (EGFR) and Integrin β1. Extracellular,

mucin-driven tumor promotion is a mechanism supported by findings and data presented herein that can be successfully targeted by N-glycosylation site directed antibodies.

[00607] As shown in this Example: (1) the extracellular glycosylation state of MUC16 drove ovarian serous cancer behavior; (2) invasion and MUC16+ xenograft growth depended on specific MUC16 *N*-glycosylation sites; (3) MUC16 formed heterotrimeric complexes with Galectin-3 and either EGFR or Integrin β1; and (4) anti-glycosylation site antibodies blocked extracellular MUC16 tumor promotion.

6.3.2 MATERIALS AND METHODS

6.3.2.1 Synthesis of MUC16 Carboxy-Terminus ($MUC16^{c114}$), MUC16-CA125 Domain ($MUC16^{c344}$), and Glycosylated Fusion Protein DNA Constructs

[00608] See Sections 6.1.2 and 6.2.2, and Reference 19 in Section 6.3.13, below, for a description of MUC16 C-terminal constructs. The pFUSE-human IgG1-Fc2 vector (pFUSE) was purchased from InvivoGen (San Diego, CA), and the construction of the chimeric proteins $MUC16^{c57\text{-}114}$-pFUSE and $^{117\text{-}244}$LGALS3-pFUSE are also described in Sections 6.1.2 and 6.2.2, and Reference 19 in Section 6.3.13 below.

6.3.2.2 Cell culture, Transfection, and Cell Line Characterization

[00609] The SKOV3, CAOV3, and OVCAR3 cell lines were obtained and maintained as described in Sections 6.1.2 and 6.2.2, and Reference 19 in Section 6.3.13 below. See Section 6.3.6 for details.

6.3.2.3 Synthesis of Glycopeptides

[00610] *See* Section 6.4 for a description of the detailed synthesis of the MUC16 glycopeptides.

6.3.2.4 Matrigel invasion

[00611] Basement membrane invasion was determined in matrigel invasion chambers (BD Biosciences, Bedford, MA). Stable cell lines were treated with 5 μg/mL of tunicamycin (Sigma-Aldrich, St. Louis MO cat # T7765), or 5 μg/mL of $MUC16^{c57\text{-}c114}$-pFUSE, or with 5 μg/mL of $^{117\text{-}244}$LGALS3-pFUSE fusion protein; matrigel migration was then measured after 48 hours in triplicate wells and compared with phrGFP vector control and $MUC16^{c114}$ transfectants. *See*, also, Sections 6.1.2 and 6.2.2, and Reference 19 in Section 6.3.13 below.

6.3.2.5 Tumor growth in athymic nude mice

[00612] Transfected cell lines and appropriate control cell lines were introduced into the flank of athymic female nude mice, and routine animal care was provided by the Memorial Sloan Kettering Cancer Center Antitumor Assessment Core Facility. Tumor measurements were taken twice per week, and tumor growth was recorded to a maximum size of 1,500 mm^3 per Memorial Sloan Kettering Cancer Center Research Animal Resource Center guidelines. *See*, also, Sections 6.1.2 and 6.2.2, and Reference 19 in Section 6.3.13 below.

6.3.2.6 Monoclonal Antibody Preparation; Mouse immunization protocol

[00613] The immunization protocol started with chitobiose-containing 55-mer MUC16 glycopeptide ($GlcNAc_2$-55-mer; SEQ ID NO: 129), which was administered to five BALB/c and five Swiss Webster mice three times every 3 weeks in the presence of an adjuvant. The fourth immunization was carried out with a mixture of KLH-conjugated, mono-glycosylated 15-mer ($GlcNAc_2$-15-mer-KLH; SEQ ID NO: 131) and bis-glycosylated 18-mer ($[GlcNAc_2]_2$-18-mer-KLH; SEQ ID NO: 130) MUC16 constructs. Sera were analyzed for reactivity against the $GlcNAc_2$-55-mer (SEQ ID NO: 129) and the unconjugated, chitobiose-bearing 15/18-mer glycopeptides (SEQ ID NO: 131 and SEQ ID NO: 130, respectively). In addition, non-glycosylated 55-mer (SEQ ID NO: 129), 15-mer (SEQ ID NO: 131) and 18-mer peptides (SEQ ID NO: 130), together with two MUC16-unrelated, chitobiose-containing peptides were used as negative controls for screening (SEQ ID NOs: 168 and 169). Mice were further immunized with the shorter KLH-conjugates (SEQ ID NO: 130 and SEQ ID NO: 131) two more times every 3 weeks and the responses were analyzed by ELISA after each immunization. *See* also Section 6.2.2.

6.3.2.7 ELISA

[00614] Sandwich ELISA was performed to assess the positivity of the antibodies to individual (glycol)peptides following routine core facility protocol for ELISA assay. *See* also Section 6.2.2.

6.3.2.8 Western blot analysis

[00615] Equal amounts of protein were separated by SDS-Poly Acrylamide Gel Electrophoresis (SDS-PAGE) and transferred to polyvinylidene difluoride (PVDF) or nitrocellulose membranes using BioRad transfer apparatus at 4°C. The membranes were blocked with 3% Bovine Serum Albumin (BSA) or 5% non-fat milk in PBS with 0.1% Tween-20 (PBST)

for 1 hour at room temperature. Membranes were developed with a variety of primary antibodies [Cell Signaling, MA: Akt cat #9272; Phospho-Akt (Ser473)(193H12) cat # 4058; p44/43 MAPK (Erk1/2) cat # 9102; Phospho-p44/43 MAPK (Erk1/2)(Thr202/Tyr204) cat #9101; Src cat # 2109S; Phospho-Src cat # 2101L; EGFR cat # 2237L; Phospho-EGFR (Y1068)(D7A5) XP(R) cat #3777S]; (Sigma-Aldrich, Inc., St. Louis, MO: beta-actin cat # A5441); (Southern BioTech, Birmingham, AL: anti-human-Fc-IgG1-HRP cat # 9054-05); (Abgent, San Diego, CA: polyclonal LGALS3 antibody cat # AP11938b); and (Origene, Rockville, MD: mouse monoclonal anti-EGFR v3 clone OTI3H2 cat # TA506224; mouse monoclonal anti-DDK clone 4C5 cat # TA50011-100) at 4˚C overnight. The membranes were washed three times with PBS-T and developed with HRP-conjugated anti-mouse or anti-rabbit antibody (GE Healthcare, UK) (1:5000 dilution) for 1 hour at room temperature. Membranes were then washed three times with PBS-T and developed with a Western Lightning Chemiluminescence reagent (ECL, Perkin Elmer) for 1-5 minutes at room temperature, and the signals were developed on HyBlot CL film (Denville Scientific Inc. Metuchen, NJ).

[00616] *See* also Sections 6.1.2 and 6.2.2, and Reference 6 in Section 6.3.13 below, for descriptions of western blot analysis protocols.

6.3.3 IMMUNOHISTOCHEMISTRY OF TISSUE MICROARRAY (TMA)

[00617] Immunohistochemistry of human TMA screening was performed as previously described (*see* Reference 6 in Section 6.3.13, below).

6.3.4 IMMUNOFLUORESCENCE STAINING OF OVCAR3, SKOV3-MUC16^{C344}, AND SKOV3-MUC16^{C114}

[00618] 50,000 cells were seeded in Delta TPG 0.17 mm dishes separately and cultured in their respective media at 37°C in 5% CO_2 overnight. The adhered cells were washed twice with PBS containing 1% fetal calf serum (FCS) and 0.025% Sodium Azide (FACS buffer). Cells were stained at 1:50 dilution with either EGFR(R-1)-Alexa Fluor 647 nm (Santa Cruz Biotechnology, CA, cat # sc-101 AF647) and 4H11 or Integrin β1(4B7R)-Alexa Fluor 647 nm (Santa Cruz Biotechnology, CA, cat # sc-9970 AF647) and 4H11 for 30 minutes at 4°C. Cells were washed with FACS buffer three times and then labeled with goat anti-mouse IgG2b-PE (Santa Cruz Biotechnology, CA, cat # sc-3766-PE) for 30 minutes at 4°C. Cells were washed with FACS buffer three times, and images were taken on a Zeiss Axio Observer Z1 with 20x/0.8NA air and 63x/1.4NA oil objectives using the ZEN2 acquisition software.

6.3.5 STATISTICAL ANALYSIS

[00619] To compare groups evaluated in the in vitro and in vivo studies of growth and invasion, data were analyzed for statistical significance using two-tailed Student's t-test with the GraphPad Prism software (San Diego, CA).

6.3.6 CELL CULTURE, TRANSFECTION, AND CELL LINE CHARACTERIZATION

[00620] *See* Reference 3 in Section 6.3.13 regarding the OVCA-433 cell line. The pLenti tetracycline-inducible system was purchased from Invitrogen, CA (cat # K4925-00) and was used to create pLenti-SKOV3^{c114}. shRNA hairpin knockout for EGFR-expressing viral plasmids were obtained by the Memorial Sloan Kettering Cancer Center High Throughput Screening (HTS) Core Facility; transfected HEK293 cells and viral supernatants were collected from HEK293 cells to infect pLenti-SKOV3^{c114}-shEGFR cell lines. The MUC16^{c114} transfectants had cell surface expression of MUC16 protein from the putative cleavage site to the carboxy-terminus (amino acids 1777 to 1890 of SEQ ID NO: 150) (*see* Reference 21 in Section 6.3.13, below). Cell lines with longer MUC16 fragments were prepared in a similar manner, including lines with expression of MUC16^{c344}–GFP vector that have cell surface expression of MUC16 protein as a 344 amino acid fragment extending to the carboxy-terminus of MUC16 (amino acids 1547 to 1890 of SEQ ID NO: 150) (*see* References 19 and 22 in Section 6.3.13, below).

6.3.7 TRANSFECTION

[00621] DNA constructs were introduced into SKOV3 cells using DOTAP (Roche Diagnostics, Indianapolis Corporation, IN) following the manufacturer's protocol. Stable transfectants were selected with 800 µg/mL of G418 for SKOV3 cells in their culture media. They were cell sorted twice for GFP expression, and selected cells were grown as lines of up to 15 passages. Routine monitoring of FACS analysis was done to confirm the GFP positivity of these lines. Protein extracts of these lines were analyzed by Western blot using anti-hrGFP (Stratagene, La Jolla, CA) and anti-MUC16-carboxy-terminus monoclonal antibodies (*see* Reference 19 in Section 6.3.13, below). As described in Section 6.1, the MUC16$^{c57\text{-}114}$-pFUSE-hIgG1-Fc2 and $^{117\text{-}244}$LGALS3-pFUSE-hIgG1-Fc2 constructs were separately transfected into human embryonic kidney (HEK) FreeStyle 293F cells (Invitrogen, CA) that express and secrete fusion proteins into serum free media, as per the manufacturer's protocol (*see* Section 6.1 and Reference 19 in Section 6.3.13, below). Secreted fusion proteins were purified and characterized

by Western blot analysis using anti-human IgG1-Fc-HRP (γ1 chain specific) (Southern Biotech Inc., Birmingham, AL) or 4H11-HRP or polyclonal anti-human LGALS3 antibody (Abgent, San Diego, CA). EGFRDDK-HIS (cat # TP700043), LGALS3Myc-DDK (cat # TP308785), and Integrin-β1Myc-DDK (cat # TP303818) purified proteins expressed in HEK293 cells were purchased from Origene, Rockville, MD.

6.3.8 IMMUNOFLUORESCENCE STAINING BY FACS ANALYSIS

[00622] MUC16 expression FACS analysis was performed as described in Section 6.1 and Reference 6 in Section 6.3.13 below.

6.3.9 GROWTH CURVES

[00623] Growth Curves were performed as described in Sections 6.1 and 6.2 and References 18 and 19 in Section 6.3.13 below.

6.3.10 NOMENCLATURE

[00624] As used in Example 3 (Section 6.3), "N1" refers to the asparagine at position 1777 of SEQ ID NO: 150, also referred to as "Asn1777". As used in Example 3 (Section 6.3), "N24" refers to the asparagine at position 1800 of SEQ ID NO: 150, also referred to as "Asn1800". As used in Example 3 (Section 6.3), "N30" refers to the asparagine at position 1806 of SEQ ID NO: 150, also referred to as "Asn1806".

6.3.11 RESULTS

6.3.11.1 MUC16 pathobiology is dependent on *N*-glycosylation of C-terminal MUC16 ectodomain

[00625] Expression of the most proximal 114 amino acids of the C-terminal MUC16 ectodomain (MUC16c114) led to more aggressive *in vitro*/*in vivo* behavior of 3T3 mouse fibroblasts, including a significant increase in MUC16-driven matrigel invasion and more rapid tumor growth *in vivo* (*see* Section 6.1 and Reference 19 in Section 6.3.13 below). To examine the role of MUC16 and its glycosylation effects in human ovarian cells, the MUC16-negative SKOV3 human ovarian cell line was examined for the impact of MUC16 expression (FIG.s 18A-18C). The transfection of SKOV3 cells with a $MUC16^{c114}$ stable expression vector led to high levels of cell surface MUC16 expression and greater than a two-fold increase in matrigel invasion, as shown in FIG. 19A. Twenty-four hour exposure of the cells to the *N*-glycosylation inhibitor tunicamycin profoundly decreased the invasive properties of SKOV3-$MUC16^{c114}$ cells

but had little effect on the matrigel invasion of SKOV3-phrGFP vector-only transfected cells (FIG. 19A).

[00626] Lectins have previously been implicated in the mediation of glycosylation effects (*see* Reference 17 in Section 6.3.13, below), and because Galectin-3 is often overexpressed in human ovarian cancers, a lectin-blocking construct was created by combining the sugar-binding domain of Galectin-3 ($^{117\text{-}244}$LGALS3) with a truncated pFUSE-human IgG1-Fc2 sequence (pFUSE) lacking a variable binding domain ("$^{117\text{-}244}$LGALS3-pFUSE") (*see* Reference 1 in Section 6.3.13, below). This chimeric molecule binds Galectin-3 ligands but lacks the ability to form Galectin-3 pentamers. As shown in FIG. 19A, when this galectin-blocking construct was introduced into cells, it had little effect on matrigel invasion by control SKOV3-phrGFP cells but significantly reduced SKOV3-MUC16^{c114} invasion. The control pFUSE vector lacking the Galectin-3 sugar-binding domain had no effect. A soluble MUC16 ectodomain, constructed by linking the same pFUSE vector to the 58 amino acids from the MUC16 ectodomain was also generated ("MUC16$^{c57\text{-}114}$-pFUSE"). As with the Galectin-3-pFUSE ($^{117\text{-}244}$LGALS3-pFUSE)-blocking construct, the MUC16$^{c57\text{-}114}$-pFUSE construct also significantly decreased invasion for the SKOV3-MUC16^{c114} cells, but not for the SKOV3-phrGFP cells. MGAT5 is the glycosylation enzyme that catalyzes the formation of the tetra-antennary N-glycans with the highest affinity for Galectin-3 binding (*see* Reference 9 in Section 6.3.13, below). MGAT5 knockout mice are resistant to tumor growth (*see* Reference 8 in Section 6.3.13, below). Without being bound by any particular theory, it was hypothesized that MUC16 effects would be dependent on both Galectin-3 and MGAT5 expression. As shown in FIG. 19B, shRNAs that reduce either MGAT5 or Galectin-3 (LGALS3) markedly decreased SKOV3-MUC16^{c114} invasion, while a negative control shRNA knocking down Lamelli had no effect.

[00627] Introduction of mutations to MUC16 ectodomain *N*-glycosylation sites (asparagine residues at positions N1, N24, and N30 of the MUC16^{c114} ectodomain) reduced observed MUC16-glycosylation dependent alterations. As shown in FIG. 19C, the asparagine to alanine mutation of the most distal asparagine (N1), adjacent to the cleavage site, had no negative effect on invasion. In contrast, the asparagine to alanine mutations of either of the more proximal asparagines (N24 or N30) negatively affected the invasion. In particular, preservation of the asparagine closest to the membrane surface (N30) was the most critical for enhancement of invasion, and that effect was not materially increased by additional asparagine to alanine

mutations of the other asparagine residues. A larger MUC16 construct with 344 amino acids from the MUC16 C-terminus ($MUC16^{c344}$) was also examined. When expression vectors bearing MUC16 mutations at N30 of $MUC16^{c344}$ or N24 and N30 of $MUC16^{c344}$ were transfected into the SKOV3 cell line, matrigel invasion was significantly reduced (FIG. 19D). Although this larger construct has seven additional *N*-glycosylation sites distal to the cleavage site, mutating the crucial proximal N24 and N30 sites still decreased the matrigel invasion, as shown in FIG. 19D, just as those mutations altered invasion with SKOV3-$MUC16^{c114}$.

[00628] Downstream activation of both the ERK and PI3K/AKT pathways in MUC16c114 transformation of 3T3 cells has been demonstrated (*see* Section 6.1 and Reference 19 in Section 6.3.13 below). In FIG. 19E, it can be seen that transfection of SKOV3 cells with $MUC16^{c114}$ activated a variety of oncogenes, including pERK1/2, pSRC, and phosphorylation of EGFR. FIG. 19E demonstrates that each of the following conditions impairs $MUC16^{c114}$-induced oncogene activation: knockdown of MGAT5 (shMGAT5), knockdown of Galectin-3 (shLGALS3), and the asparagine to alanine mutation of N30. These data are consistent with the decreases observed in matrigel invasion related to $MUC16^{c114}$ expression.

[00629] The effects of knocking down MGAT5 or LGALS3 or mutation of the $MUC16^{c114}$ ectodomain *N*-glycosylation sites were examined in xenograft tumor growth in nude mice. As shown in FIG. 19F, there was a complete abrogation of the $MUC16^{c114}$-induced tumor growth with any of these *N*-glycosylation directed interventions. The effect of $MUC16^{c114}$ on receptor stability was also examined. The presence of both *N*-glycosylation and linkage to the galectin lattice has been associated with stabilization of EGFR on the cell surface (*see* Reference 11 in Section 6.3.13 below). Without being bound by any particular theory, it was reasoned that increased presence of MUC16 stabilizes a cell surface galectin lattice, thereby stabilizing EGFR on the cell surface. As shown in FIG. 20A, the presence of EGFR on the cell surface of SKOV3 cells was increased when stable SKOV3-$MUC16^{c114}$ transfectants were compared to the vector-only controls using FACS analysis. Moreover, $MUC16^{c114}$ expression nearly doubled EGFR on the cell surface following cycloheximide (CHX) treatment to inhibit new EGFR synthesis, compared to phrGFP vector controls. The stability of the $MUC16^{c114}$ ectodomain (4H11 positive) was unchanged by CHX. Total EGFR over time was compared in stable SKOV3-$MUC16^{c114}$ and SKOV3-phrGFP cells treated with CHX for 24 hours by Western blotting, and EGFR was compared to β-Actin. Densitometry curves (FIG. 20B) indicated that the presence of

MUC16^{c114} on the cell surface stabilized EGFR in comparison to phrGFP-vector control. To exclude the possibility that this effect was related to selection of SKOV3-stable MUC16^{c114} clones, a tetracycline-inducible MUC16^{c114} system was utilized. As shown in FIG. 20C, tetracycline exposure for 24 hours had no effect on matrigel invasion for either control SKOV3 cells transfected with the empty phrGFP vector or the stable CMV-driven MUC16^{c114} expression vector. In the MUC16^{c114} tetracycline-inducible system, tetracycline exposure induced MUC16^{c114} dependent matrigel invasion similar to the stable transfectants, both control and MUC16^{c114}. The requirement for EGFR was examined via stable expression of an shRNA construct (shEGFR) introduced into SKOV3 cells that reduced EGFR expression. Both of the single cell clones for the shEGFR-transfected cells showed markedly decreased matrigel invasion. Tetracycline-induced expression of MUC16^{c114} in these two shEGFR cell lines had minimal effect on matrigel invasion compared to SKOV3-MUC16^{c114} cell lines, confirming that SKOV3-MUC16^{c114}-induced matrigel invasion was codependent on expression of EGFR. The stability of EGFR in tetracycline-induced SKOV3-MUC16^{c114} treated with CHX was studied by western blotting, and compared to β-actin. As shown in FIG. 20D, CHX exposure over 24 hours resulted in the steady decline of total EGFR protein in the un-induced MUC16(-) SKOV3 cells. When the same experiment was performed following tetracycline induction of SKOV3-MUC16$^{c114(tet)}$ cells, the CHX-induced rate of EGFR loss was reduced. Not only did MUC16 stabilize the EGFR content of the cells, it also stabilized the pEGFR expression levels in the tetracycline-induced SKOV3-MUC16$^{c114(tet)}$ cells compared to the uninduced SKOV3-MUC16$^{c114(tet)}$ cells (FIG. 21).

6.3.11.2 Synthesis of homogeneous N-glycopeptides as epitope mimics for monoclonal antibody (mAb) development

[00630] Having identified *N*-glycosylation at the N24 and N30 sites of MUC16^{c114} as a central requirement for MUC16 action, the glycan profile of a MUC16^{c114} mutated glycopeptide containing alanine to asparagine mutations at N1 and N24, purified from the SKOV3-MUC16^{c114} cell line, was analyzed (FIG. 22). This purified glycopeptide thus contained a single asparagine residue (N30) for *N*-glycosylation. The glycome analysis of the purified glycopeptide is shown in FIG. 22A. It was characterized by a diverse *N*-glycosylation pattern consisting largely of truncated glycosylated species that shared the common, proximal chitobiose ($GlcNAc_2$)

disaccharide as the minimal repeating unit to which fucose and various mannose residues are attached (FIG. 22A).

[00631] It was hypothesized that antibodies targeted against a MUC-16-ectodomain epitope encompassing the crucial N30 glycosylation site might inhibit MUC16 interaction with the galectin lattice, decreasing the adverse effects of MUC16 expression, including tumor growth and invasion. Thus, synthetic peptide antigens of various lengths (*i.e.*, 55, 18 and 15 amino acids in length; SEQ ID NOs: 129, 131, and 130, respectively) within the MUC16 ectodomain, glycosylated with chitobiose at this N30 site, were designed. Besides being the minimal motif common to larger, more complex *N*-glycans, the chitobiose disaccharide should also enable a better exposure of the underlying peptide to elicit glycan-directed antibodies that retain peptide specificity.

[00632] The synthesis of the 55-mer MUC16-ectodomain N-glycopeptide ($GlcNAc_2$-55-mer; SEQ ID NO: 129) was highly convergent and involved a coupling between conveniently protected full-length peptide (55-mer) and chitobiose amine , followed by acidic global deprotection using our one-flask aspartylation/deprotection procedure (*see* Sections 6.2 and 6.4 and references 7 and 20 in Section 6.3.13 below). Following a similar approach, the more elaborate $Man_3GlcNAc_2$-55-mer glycopeptide bearing a terminal trimannose glycan was also prepared by convergent aspartylation.

[00633] In order to focus the immune response against a smaller-sized epitope around the relevant glycosylation site, the shorter 15- and 18-mer glycopeptides bearing one (N30) and two chitobiose glycans (N24 and N30) respectively, were also synthesized (FIG. 22C; SEQ ID NOs: 131 and 130, respectively), the latter by analogy to the cluster presentation of the Tn antigen (GalNAc-α-O-Ser/Thr), which has been shown to be required for binding to some mAbs (*see* Sections 6.2 and 6.4 and references 14-16 in Section 6.3.13 below). These glycopeptides were then conjugated to the KLH carrier protein via an N-terminal cysteine to generate the corresponding immunogens for mouse vaccination.

6.3.11.3 Mouse vaccination with synthetic glycopeptides/glycoconjugates and serologic assays

[00634] Mouse vaccination and sera collection were performed according to the protocol described in Sections 6.2 and 6.4. After 3 immunizations with the $GlcNAc_2$-55-mer glycopeptide (SEQ ID NO: 129, FIG. 22B) followed by an immunization with an equal mixture

of the chitobiose-bearing, KLH-conjugated constructs (mono-glycosylated 15-mer (SEQ ID NO: 131) and bis-glycosylated 18-mer(SEQ ID NO: 130)), only 2 of 10 mice showed weakly positive ELISA signals for both 55-mers (with and without $GlcNAc_2$ (SEQ ID NO: 129)), suggesting that the mice had limited immune response to the 55-mer immunizations. Two more booster immunizations with both KLH conjugates ($GlcNAc_2$-15-mer (SEQ ID NO: 131) and $(GlcNAc_2)_2$-18-mer (SEQ ID NO: 130)) resulted in enhanced immune responses (IgG type) against the shorter glycopeptides, particularly in two mice (mouse 7 & mouse 8). The 4H11 mAb, directed at a different, non-glycosylated portion of the MUC16 peptide backbone, showed no binding to the 15-mer/18-mer glycopeptides, indicating a distinct recognized epitope separate from the mouse sera positivity.

[00635] The polyclonal serum from mouse 7 was further characterized by ELISA and screened by FACS on several cell lines with and without $MUC16^{c114}$ expression. These cell-sorting studies confirmed positive signals to both SKOV3-$MUC16^{c114}$ cells and OVCAR3 cells, similar to the anti-MUC16 4H11 antibody control (*see* Reference 6 in Section 6.3.13, below). SKOV3-phrGFP control cells lacking MUC16 were negative for binding with mouse 7 serum.

6.3.11.4 Glycosylation-directed mAb selection

[00636] The spleen of mouse 7 was harvested and the splenocytes were fused with hybridoma fusion partner with high fusion efficiency. Supernatants were selected and screened for reactivity by ELISA against the individual glycopeptides (FIG. 22C). Although multiple supernatants were reactive with the $GlcNAc_2$-15-mer and $(GlcNAc_2)_2$-18-mer glycopeptides, none of the hybridoma supernatants screened demonstrated a high degree of selectivity for the glycosylated over the non-glycosylated peptides in ELISA screening. MUC16 specificity was maintained and none of the positive supernatants were reactive with irrelevant peptides glycosylated with chitobiose. No overlap was seen with the peptide sequence recognized by the 4H11 mAb.

[00637] After serial subcloning, the process afforded multiple chitobiose-directed primary mAbs that were reactive with MUC16-glycosylated epitopes and the homologous non-glycosylated sequences but not with chitobiose-bearing irrelevant peptides serving as negative control. Of this pool, four high-affinity antibodies were selected and further purified for characterization.

6.3.11.5 Characterization of anti-MUC16 N30 glycosylation-targeted/directed mAbs

[00638] The results of the confirmatory characterization studies for four representative antibodies are shown by ELISA in FIG. 23A. The binding of the candidate antibodies to the various synthetic peptides was evaluated and compared to the binding of the 4H11 antibody, which recognizes the MUC16-ectodomain peptide backbone. The unrelated chitobiose-linked peptides exhibited no significant binding by any of the anti-glycan-MUC16 antibodies selected. All of the candidate antibodies showed similar binding affinities for both MUC16-derived 15-mers (*i.e.*, the non-glycosylated peptide and the corresponding chitobiose glycopeptide). Additional synthetic glycopeptides bearing alternative sugar moieties, including a single GlcNAc, a terminal trimannose-chitobiose ($Man_3GlcNAc_2$), and a fucosylated chitobiose ($GlcNAc_2Fuc$), did not substantially alter the antibody reactivity to the chitobiose-linked MUC16 peptides used for immunization.

[00639] Each antibody was also tested for glycan-$MUC16^{c114}$ and glycan-$MUC16^{c344}$ specificities on an extended panel of cell lines expressing differentially glycosylated MUC16 peptides (Table 11). In these studies, SKOV3-phrGFP transfectants were compared with the SKOV3-$MUC16^{c114}$ (full *N*-glycosylation), SKOV3-$MUC16^{N24c114}$ mutants (no N24 glycosylation site), SKOV3-$MUC16^{N30c114}$ (no N30 glycosylation site), and SKOV3-$MUC16^{N1\text{-}N24\text{-}N30c114}$ (no N1, N24, or N30 glycosylation sites). SKOV3-$MUC16^{c114}$ refers to SKOV3 cells expressing a truncated form of MUC16 which is capable of being *N*-glycosylated at N1, N24, and N30. SKOV3-$MUC16^{N24c114}$ refers to SKOV3 cells expressing a truncated mutant form of MUC16, wherein the amino acid position corresponding to Asn1800 of SEQ ID NO: 150 comprises an asparagine to alanine mutation, and, thus, is not capable of being *N*-glycosylated at this position. SKOV3-$MUC16^{N30c114}$ refers to SKOV3 cells expressing a truncated mutant form of MUC16, wherein the amino acid position corresponding to Asn1806 of SEQ ID NO: 150 comprises an asparagine to alanine mutation, and, thus, is not capable of being *N*-glycosylated at this position. SKOV3-$MUC16^{N1\text{-}N24\text{-}N30c114}$ refers to SKOV3 cells expressing a truncated mutant form of MUC16, wherein the amino acid positions corresponding to Asn1777, Asn1800, and Asn1806 of SEQ ID NO: 150 comprise asparagine to alanine mutations, and, thus, are not capable of being *N*-glycosylated at thse positions. As with the ELISA data, the results indicated that MUC16-specific targeting was present.

[00640] However, in contrast to the ELISA data, the loss of both N24 and N30 glycosylation sites in the MUC16 ectodomain reduced the glycosylation-targeted antibody reactivity, whereas reactivity to the 4H11 antibody was retained, thereby confirming the presence of cell-surface SKOV3-MUC16^{c114}. Cells bearing a MUC16 C-terminal chain extended to 344 amino acids (*e.g.* SKOV3-MUC16^{c344}) had also a similar requirement for N24 or N30 glycosylation (Table 11). Further, the reactivity with the antibodies against the glycan-MUC16 ectodomain was not diminished by downregulation of MGAT5 (Table 11), confirming that a chitobiose at the N24/N30 sites contributes to antibody binding with whole cells, regardless of more complex branching.

[00641] **Table 11.** Table 11 provides the geometric mean phycoerythrin (PE) fluorescence of 4H11 and four $GlcNAc_2$-MUC16 ectodomain monoclonal antibodies on SKOV3-MUC16 transfections with *N*-glycosylation site modifications. 4H11 retains binding to all of the cell lines (except the SKOV3-phrGFP line, which does not express MUC16) regardless of glycosylation modification, thus confirming MUC16 protein on the cell surface. When both the N24 and N30 sites of glycosylation were lost, there was a reduction of glycan-MUC16 antibody binding for both the MUC16^{c114} and the MUC16^{c344} transfectants. Limited loss of reactivity for the MGAT5 knockdown cell line confirmed that chitobiose is essential for each $GlcNAc_2$-MUC16 ectodomain antibody, while more extensive branching had limited effect.

					Anti-glycosylated-MUC16 ectodomain antibodies			
	Cells alone	**G anti M IgG2a-PE**	**G anti M IgG2b-PE**	**4H11 + G anti M IgG2b-PE**	**18C6 + G anti M IgG2b-PE**	**10C6 + G anti M IgG2a-PE**	**19C11 + G anti M IgG2a-PE**	**7B12 + G anti M IgG2a-PE**
SKOV3-phrGFP	46	50	57	77	56	70	77	80
SKOV3-c114	56	74	104	1124	2054	571	617	492
SKOV3-N24 mutc114	43	62	78	2654	1830	435	486	471
SKOV3-N30 mutc114	49	65	90	696	1696	645	536	444
SKOV3-N24N30 mutc114	125	142	155	655	461	264	236	185
SKOV3-N1-N24-N30mutc114	37	50	71	514	34	74	61	82
SKOV3-shMGAT5-c114	108	133	145	2384	855	645	525	289
SKOV3-c344	53	66	68	559	1652	792	578	422
SKOV3-N24mutc344	89	102	64	574	1569	991	661	512
SKOV3-N30mutc344	93	104	47	661	1064	687	454	440
SKOV3-N24-N30mutc344	80	161	140	765	277	231	195	220

"G anti M" refers to goat anti-mouse. "PE" refers to phycoerythrin.

[00642] The four representative MUC16 Glycosylation Antibodies (18C6, 10C6, 19C11, 7B12) characterized were evaluated together with 4H11 for binding affinity (Table 12) and their effect on invasion by matrigel assay with the SKOV3-MUC16^{c114} transfectants. As shown in FIGS. 23B-23D, the newly developed antibodies showed broad inhibition of matrigel invasion, whereas 4H11 was distinguished by its inability to block SKOV3-MUC16^{c114} mediated invasion, indicating that these antibodies targeting glycosylated peptide epitopes in the MUC16 ectodomain inhibited some of the crucial biological properties of MUC16 better than antibodies targeting closely adjacent epitopes. All of the MUC16 Glycosylation Antibodies were inhibitory in ovarian cancer cells expressing native, full length MUC16, such as CAOV3 and OVCA-433

cells. This suggests that the N24/N30 glycosylation sites were critical for the enhanced invasive properties of MUC16, while the presence of other MUC16 *N*- and *O*-glycosylation sites were insufficient to overcome MUC16 Glycosylation Antibody blocking of this critical epitope. Without being bound by any particular theory, antibody inhibition of the N24/30 binding of Galectin-3 to MUC16 would be predicted to impair EGFR cell surface stabilization as well. FIGS. 23B-23D demonstrate that when one of these antibodies (10C6) was introduced into the cell culture, the EGFR stabilizing effect of tetracycline-induced SKOV3-MUC16$^{c114(tet)}$ was overcome, and the rate of EGFR loss in CHX-exposed cells was similar to that of the un-induced SKOV3-MUC16$^{c114(tet)}$ cell lines without MUC16^{c114} expression. Immunohistochemistry staining with the antibodies was also examined in ovarian cancer tissue microarrays. As shown in FIG. 23E, each of the glycan directed-MUC16 ectodomain antibodies bound to serous ovarian cancer cells in paraffin-fixed tissue with limited interaction with other stromal tissue, similar to the 4H11 behavior. Finally, the effect of 10C6 antibody on the growth of SKOV3-MUC16^{344} in immunocompromised mice was tested. The SKOV3-MUC16^{c344} cells were utilized instead of the SKOV3-MUC16^{c114} cells as a more stringent test of antibody effect in MUC16-positive tumor cells with multiple *N*- and *O*-glycosylation sites. The 10C6 antibody decreased matrigel invasion by MUC16^{c344} cells (FIG. 23F), and significantly reduced the growth of SKOV3-MUC16^{c344} tumor cells in the mouse flank when administered to tumor-bearing mice twice per week (FIG. 23G).

[00643] Table 12.

Antibody	kd [1/s]	Error in kd [1/s]	ka [1/s]	kD [nM]
10C6.E4	*	--	**	>1000
19C11.H6	$2.42x10^{-3}$	$2.35x10^{-3}$	$3.80x10^{-4}$	63.7
7B12.B3	$1.04x10^{-3}$	$1.09x10^{-4}$	$7.50x10^{-4}$	13.8
18C6.D12	$6.78x10^{-4}$	$1.83x10^{-4}$	$6.14x10^{-4}$	11.1
4H11	--	--	--	--

* low calculation confidence, no fit for off-rate
** ka is too low for association rate determination

6.3.11.6 Galectin-dependent co-localization of MUC16 and other cell surface proteins

[00644] MUC16-stabilized EGFR appears to be an important driver of ovarian cancer cell invasion, and this interaction depends on EGFR, appropriately *N*-glycosylated MUC16 protein ectodomain, and the presence of Galectin-3. This interaction was evaluated with purified proteins

to establish the necessary/sufficient three-way interaction among these three proteins. For this purpose, purified MUC16$^{c57\text{-}114}$-pFUSE (produced in human embryonic kidney [HEK] FreeStyle 293F cells) (as the MUC16 part of the interaction), purified EGFR (produced by HEK293 cells), and purified Galectin-3 (LGALS3; produced by HEK293 cells) proteins were utilized. Because these proteins were produced in human cells, they were expected to bear typical, native glycosylated species. Without being bound by any particular theory, it was hypothesized that the three proteins would form heteromers that could be identified by immuno-coprecipitation. FIG. 24A illustrates the results of this immuno-coprecipitation, wherein each of the three proteins detected are shown in the direct immunoblot in the left three lanes. Using Agarose Protein A/G PLUS beads, one can see that the MUC16$^{c57\text{-}114}$-pFUSE protein bound to the Protein A/G PLUS-conjugated beads and was present in the eluate when separated on the SDS-PAGE gel. EGFR was only present in the combined eluate with MUC16$^{c57\text{-}114}$-pFUSE when Galectin-3 (LGALS3) was also present. Antibody 18C6 eliminated the EGFR–MUC16 interaction by blocking the *N*-glycosylation binding site of Galectin-3 (see FIG. 24A). Direct molecular dual immunofluorescence imaging also was used to confirm colocalization of the EGFR and MUC16 in living cells. As shown in FIG. 24B and FIG. 25A, EGFR and MUC16 were tightly co-localized in OVCAR3, SKOV3-MUC16c344, and SKOV3-MUC16c114 cells (*see* arrows in FIGs. 24B and 25A). These studies strongly confirmed that MUC16 combined with Galectin-3 to associate with EGFR on the surface of MUC16-positive ovarian cancer cells. Without being bound by any particular theory, since many growth-enhancing receptors are glycosylated, it was reasoned that lectin-dependent MUC16 cell-surface effects might include other N-glycosylated proteins and not be restricted to EGFR. The integrin proteins are often altered in cancer and participate in the "outside-in" signaling initiated by stromal–epithelial interactions triggering SRC phosphorylation and other downstream effects. FIG. 24C depicts the MUC16 interactions with Integrin β1, an integrin component frequently associated with cancer development and progression. As in the case of EGFR, purified MUC16$^{c57\text{-}114}$-pFUSE bound to Integrin β1 in a Galectin-3-dependent manner, and this heterotrimeric interaction required all 3 proteins. As with EGFR, the interaction was completely blocked by an anti-MUC16c114 glycosylation site-blocking antibody, 18C6. Colocalization of MUC16 and Integrin β1 was also confirmed by dual immunofluorescence in several ovarian cancer cell lines (FIG. 24D and FIG. 25B). Thus, *N*-glycosylation at key sites on MUC16-ectodomain peptide epitopes mediated the interaction with

cell-surface protein receptors in a lectin-specific manner to generate the characteristics of malignant behavior, including matrigel invasion, activation of the PI3K/ERK and SRC pathways, as well as enhanced MUC16-positive tumor growth in immunocompromised mice.

[00645] Without being bound by any particular mechanism, the mechanistic model for the cancer-related mucin, MUC16, and its effect on ovarian cancer cell behavior is shown in FIG. 26. In FIG. 26A, MUC16 binds to EGFR and Integrin β1 through Galectin-3 to enhance the stability and "inside-out" signals that promote growth and invasion. When the MUC16 ectodomain *N*-glycosylation sites are mutated or MGAT5 activity is suppressed (FIG. 26B), the binding is prevented and EGFR/Integrin signals are reduced. Similarly, if Galectin-3 protein expression is suppressed (FIG. 26C), the molecular association is lost, and the signals and invasion are reduced. Finally, when MUC16-ectodomain chimeric antibodies or chimeric "TRAP" LGALS3 molecules prevent molecular interaction, the cancer cell lacks any of the observed MUC16 tumor-promoting properties (FIG. 26D).

6.3.12 DISCUSSION

[00646] MUC16 and other tethered mucins, such as MUC1 and MUC4 can transform 3T3 cells and are associated with adverse outcomes. The mechanisms of aberrantly expressed mucins in cancer are complex and diverse. It is well described that *N*-glycosylation patterns play important roles in cellular growth in response to the local environment. The diversity of glycoprotein patterns is influenced by environmentally dependent hexosamine flux through Golgi-based glycosylation. Common growth factor receptors such as EGFR, insulin-like growth factor receptor (IGF1R), and PDGFR are preferentially glycosylated first in a nutrient-dependent manner, and those heavily glycosylated receptors are preferentially delivered to the cell surface. In contrast, inhibitory receptors such as TGF-β have fewer *N*-glycosylation sites and are presented on the cell surface later, with consequent inhibition of the growth program (*see* Reference 12 in Section 6.3.13 below). In ovarian cancer, EGFR expression has been linked to invasive behaviors and EGFR signaling is dependent on the glycosylation state of the receptors and the affinity of the N-glycosylated species for lectins (*see* Reference 2 in Section 6.3.13 below). The enzyme MGAT5 appears to be crucial for the synthesis of tetraantenary, branched N-glycans that have the highest affinity for Galectin-3, an important lectin overexpressed in cancer cells (*see* Reference 17 in Section 6.3.13 below).

[00647] This Example provided evidence that the behaviors associated with MUC16 expression are mediated through these processes on specific *N*-glycosylation sites on the most proximal ectodomain region of MUC16 relative to the cell surface. MGAT5-dependent patterns of *N*-glycosylation were required for high affinity interaction with Galectin-3 and cell-surface proteins to promote invasion, oncogene activation, and increased tumor growth in immunocompromised mice. In particular, *N*-glycosylation at the most proximal sites on the retained ectodomain of MUC16 after cleavage was critically important for this interaction. Interventions that removed these *N*-glycosylation sites, blocked the sites with dummy receptors, or interfered with their full *N*-glycosylation all impaired the transforming effects of MUC16. These transforming effects appeared to depend, not only on MUC16 alone, but also on the interaction of *N*-glycosylated MUC16 with Galectin-3 and other cell surface proteins at the proximal *N*-glycosylation sites. MUC16 ectodomain expression was shown to stabilize EGFR, a mediator of growth and invasion, and prolonged its residence on the SKOV3-MUC16^{c114} cell surface, compared to the parent SKOV3phrGFP cells. Even in a simplified MUC16 glycopeptide model retaining only one *N*-glycosylation site, the stochastic nature of glycosylation resulted in the presence of a variety of N-glycans that were all linked to the MUC16 protein backbone through a shared chitobiose stem. Thus, antibodies were prepared against the chitobiose-linked (at the N24/N30 sites) MUC16^{c114} glycan-peptide epitope of the MUC16 ectodomain. These new antibodies (MUC16 Glycosylation Antibodies) blocked MUC16 enhanced invasion, oncogene activation and *in vivo* tumor growth. Importantly, these MUC16 Glycosylation Antibodies inhibited the MUC16-related properties in cells with full-length MUC16 expression as well as test, truncated constructs with shorter MUC16 C-terminal expression. The MUC16 Glycosylation Antibodies interfered with EGFR stabilization of the ovarian cancer cell surface in the presence of CHX and impaired transplanted growth in nude mice. In addition, the effect of the MUC16 Glycosylation Antibodies also prevented the interaction of purified MUC16 with either purified EGFR or Integrin β1 in the presence of recombinant Galectin-3.

[00648] This Example reveals insights into the role of mucin overexpression in cancer. Through the formation of lectin-mediated, low affinity multi-molecular complexes, MUC16 was able to enhance the "outside-in" signal transduction in a glycosylation-dependent manner. The specific *N*-glycosylation sites responsible for maximal effect were unique and close to the cell

surface, while other, more distal *N*-glycosylation sites may have been less important. There are Galectin-3 inhibitors in clinical development but a dummy receptor "Galectin-3-TRAP" construct or truncated "MUC16-TRAP" molecules had a similar effect in the *in vitro* models of this Example. The MUC16 Glycosylation Antibodies identified in this Example inhibited the transforming effects of MUC16.

6.3.13 REFERENCES

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6.4 EXAMPLE 4: SUPPLEMENTAL CHEMISTRY INFORMATION

[00671] This example provides (a) a more detailed description of certain of the methods used and experiments described in Examples 2 and 3 (Sections 6.2 and 6.3); and (b) additional information as compared to Examples 2 and 3 (Sections 6.2 and 6.3).

6.4.1 GENERAL MATERIALS AND METHODS

[00672] All commercially available materials (Aldrich, Fluka, Novabiochem) were used without further purification. N-α-Fmoc protected amino acids, pseudoproline dipeptides, Oxyma Pure and NovaSyn TG Sieber resin were purchased from Novabiochem. 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) was purchased from Genscript. (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP) was purchased from Oakwood Products, Inc. Chitobiose octaacetate was purchased from Carbosynth Limited. TCEP solution (0.5 M, neutral pH) and heterobifunctional linker sulfo-GMBS was purchased from Pierce, ThermoScientific. All other reagents, including Keyhole Limpet Hemocyanin (KLH) were purchased from Aldrich. All solvents were reagent grade or HPLC grade (Fisher Scientific). Anhydrous tetrahydrofuran, diethyl ether, dichloromethane, toluene, and benzene were obtained from a dry solvent system (passed through column of neutral alumina under an argon atmosphere) and used without further drying.

[00673] Reactions were performed under an atmosphere of pre-purified dry argon. Air- and moisture-sensitive liquids and solutions were transferred via syringe. The appropriate carbohydrate reagents were dried via azeotropic removal of water with toluene. Molecular sieves were activated at 350 °C and were crushed immediately prior to use, then flame-dried

under vacuum. Organic solutions were concentrated under reduced pressure by rotary evaporation below 30 °C. NMR spectra (^{1}H and ^{13}C) were recorded on a Bruker Advance DRX-600 MHz spectrometer, and referenced to TMS or residual solvent. Low-resolution mass spectral analyses were performed with a JOEL JMS-DX-303-HF mass spectrometer or Waters Micromass ZQ mass spectrometer. Analytical TLC was performed on E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with cerium ammonium molybdenate (CAM) or 5% sulfuric acid in methanol. Silica flash column chromatography was performed on E. Merck 230-400 mesh silica gel 60.

6.4.1.1 UPLC/LC-MS analyses and RP-HPLC purification.

[00674] All reverse-phase chromatographic separations involved a mobile phase consisting of 0.05% trifluoroacetic acid (TFA) (v/v) in water and 0.04% TFA in acetonitrile. Reaction progress was monitored by UPLC-MS analysis on a Waters AcquityTM Ultra Preformance Liquid Chromatography system with a photodiode detector and single quadrupole mass detector, equipped with Acquity UPLC BEH C18/C8/C4 columns (1.7 µm, 2.1 × 100 mm), at a flow rate of 0.3 mL/min. Analytical LC-MS analyses were performed on a Waters 2695 Separations Module equipped with a Waters 2996 Photodiode Array Detector, using a Varian Microsorb C18 column (150 × 2.0 mm), a Varian Microsorb C8/C4 column (250 × 2.0 mm) or a Waters X-Bridge C18 column (150 × 2.1 mm), at a flow rate of 0.2 mL/min. Preparative scale HPLC purification was carried out on a Ranin HPLC solvent delivery system equipped with a Rainin UV-1 detector, using an Agilent Dynamax reverse phase HPLC Microsorb C18/C8/C4 column (250 × 21.4 mm), or a Waters X-Bridge C18 column (150 × 19.0 mm), at a flow rate of 16.0 mL/min.

6.4.2 EXPERIMENTAL PROCEDURES

6.4.2.1 Fmoc-based Solid Phase Peptide Synthesis (SPPS)

[00675] Automated peptide synthesis was performed on a CEM Liberty Microwave Peptide Synthesizer. Peptides were synthesized under standard Fmoc protocols on NovaSyn TG Sieber resin. The deblock mixture consisted of a solution of Oxyma Pure (0.1 M) in 20% piperidine/DMF. The following Fmoc amino acids from Novabiochem were used: Fmoc-Ala-OH, Fmoc-Arg(Pbf)-OH, Fmoc-Asn(Dmcp)-OH, Fmoc-Asp(OMpe)-OH, Fmoc-Asp(OPp)-OH, Fmoc-Asp(OAllyl)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Gln(Dmcp)-OH, Fmoc-Glu(OtBu)-OH,

Fmoc-Gly-OH, Fmoc-Ile-OH, Fmoc-Leu-OH, Fmoc-Met-OH, Fmoc-Phe-OH, Fmoc-Pro-OH, Fmoc-Ser(O*t*Bu)-OH, Fmoc-Thr(O*t*Bu)-OH, Fmoc-Tyr(O*t*Bu)-OH, Fmoc-Val-OH. The following Dmb (2,4-dimethoxybenzyl) and pseudoproline dipeptides (Novabiochem) were used: Fmoc-Asp(O*t*Bu)-(Dmb)Gly-OH, Fmoc-Gly-Thr($\psi^{Me,Me}$Pro)-OH, Fmoc-Phe-Thr($\psi^{Me,Me}$Pro)-OH, Fmoc-Ser(*t*Bu)-Ser($\psi^{Me,Me}$Pro)-OH.

6.4.2.2 N-terminal Acetylation of the Peptide-resin

[00676] Upon completion of automated synthesis on a 0.1 mmol scale, the peptide-resin was washed with DMF (2 mL) into a peptide synthesis vessel, and treated with acetic anhydride (188 µL, 2 mmol) and DIEA (384 µL, 2.2 mmol) in DMF (2 mL). The mixture was shaken by mild nitrogen bubbling for 1 hour, and then washed with DMF and CH_2Cl_2, before being subjected to deallylation.

6.4.2.3 On-resin Deallylation of Aspartic Acid Side Chain, Asp(OAllyl)

[00677] The *N*-acetylated resin-bound peptide (0.1 mol) was treated with $Pd(PPh_3)_4$ (7.5 mg, 6.5 µmol) and phenylsilane (75 µL, 0.6 mmol) in DMF/CH_2Cl_2 (4 mL, 1:1). After 20 minutes of mild nitrogen bubbling, the $Pd(PPh_3)_4$/phenylsilane treatment was repeated twice. The peptide-resin was then washed with DMF, CH_2Cl_2 and methanol, and dried under vacuum.

6.4.2.4 Cleavage from Resin [and Simultaneous Asp(*O*-2-Ph^{i}Pr) Side-chain Deprotection, where applicable]

[00678] After drying, the peptide-resin was subjected to a cleavage cocktail (1% TFA/CH_2Cl2, 4 mL) 5 cycles × 5 min, and this process was repeated four times. Additional cleavage sequences included treatment with 1.5% TFA/CH_2Cl2 (4 mL 5 cycles × 5 min), and 2% TFA/CH_2Cl_2 (4 mL 5 cycles × 5 min). The respective portions of cleavage solution were individually pooled into ice-cold Et_2O and concentrated. The corresponding oily residues were resuspended in a minimum amount of trifluoroethanol and precipitated with water. The resulting mixtures were immediately lyophilized to give the crude protected peptides bearing a C-terminal amide.

6.4.2.5 Coupling of Partially Protected Full-length Peptide (55-mer) with Glycan Amine via Lansbury Aspartylation Followed by Removal of Acid-Labile Protecting Groups with Cocktail R

[00679] Partially protected full-length peptide (1.0 equiv) and glycan amine (chitobiose: 4.0 equiv; $Man_3GlcNAc2$ 1.6 equiv) were combined and dissolved in anhydrous DMSO. To this

mixture, a freshly prepared solution of PyAOP (4.0 equiv) in DMSO was added, followed by DIEA (6.0 equiv). The reaction mixture was stirred for 3 hours, and quenched by addition of 1 mL of ice-cold water (0.05% TFA). The precipitate formed was isolated by centrifugation, resuspended in water/CH_3CN (1:1, 0.05% TFA) and immediately lyophilized.

[00680] The protected glycopeptide was then subjected to global acid deprotection by treatment with cocktail R (90% TFA, 5% thioanisol, 3% ethanedithiol, 2% anisol) (1 mL) for 2 hours. The residue was precipitated with ice-cold Et_2O (12 mL), and the resulting suspension was centrifuged to give a white pellet. The supernant was decanted and the pellet was triturated with ice-cold diethyl ether (12 mL). This process was repeated three times in total, and the resulting precipitate was solubilized in water/CH_3CN (1:1, 0.05% TFA) and lyophilized. The corresponding crude glycopeptide was purified by RP-HPLC.

6.4.2.6 Coupling of Partially Protected Small-sized Peptides (15- and 18-mers) with Chitobiose Amine via Lansbury/Double Lansbury Aspartylation Followed by Removal of Acid-Labile Protecting Groups

[00681] Partially protected peptide (1.0 equiv) and chitobiose amine (3.0 equiv / 7.0 equiv for the double Lansbury aspartylation) were combined and dissolved in anhydrous DMSO. To this mixture, a freshly prepared solution of PyAOP (4 equiv / 6 equiv in the latter case) in DMSO was added, followed by DIEA (6 equiv / 8 equiv, respectively). The reaction mixture was stirred for 2.5 hours, and quenched by addition of 1 mL of ice-cold water (0.05% TFA). The precipitate formed was isolated by centrifugation, resuspended in water/CH_3CN (1:1, 0.05% TFA) and immediately lyophilized.

[00682] The protected glycopeptide was then subjected to global acid deprotection by treatment with a TFA cocktail (94% TFA, 2.5% H_2O, 2.5% EDT, 1% TIPSH) (1 mL) for 2 hours. The residue was precipitated with ice-cold Et_2O (12 mL), and the suspension was centrifuged to give a white pellet. The supernant was decanted and the pellet was triturated with ice-cold diethyl ether (12 mL). This process was repeated three times in total, and the resulting precipitate was dissolved in water/CH_3CN (1:1, 0.05% TFA) and lyophilized. The corresponding crude glycopeptide was purified by RP-HPLC.

6.4.2.7 KLH-Conjugation of 15/18-mer Glycopeptides

[00683] KLH was first incubated with the heterobifunctional crosslinker sulfo-GMBS) in pH 7 phosphate buffer saline (PBS) for 2 hours. The unconjugated crosslinker was removed by size

exclusion chromatography (passage over Bio-Gel P-10 fine column, respectively) and maleimide-activated KLH was then obtained. The freshly deprotected (glyco)peptides bearing a terminal thiol functionality were mixed with maleimide-containing KLH in pH 7 PBS and incubated at room temperature for 6 hours. After this time, unreacted (glyco)peptide was removed using an Amicon Ultra-4 centrifugal filter (50 000 molecular weight cut off). Finally, the corresponding KLH conjugates were obtained as a PBS solution.

6.4.3 SYNTHESIS OF FULL-LENGTH MUC16 GLYCOPEPTIDES (55-MERS)

6.4.3.1 Synthesis of Chitobiose-bearing, Full-length Glycopeptide

[00684] Upon completion of the automated synthesis according to the methods of Section 6.4.2.1, the peptide-resin was subjected to N-acetylation and deallylation (*see* Section 6.4.2.2 and Section 6.4.2.3, respectively) to provide after cleavage from the resin (*see* Section 6.4.2.4) the partially protected peptide p55-mer[N1-S55] bearing the free carboxylic acid at Asp30 side chain. A fraction of this crude peptide was purified by silica gel column chromatography eluting with 5→12% MeOH/CH_2Cl_2 to give peptide p55-mer[N1-S55] (70 mg) as a white solid upon lyophilization. FIG. 27A depicts the side-chain protected N-acetylated 55-mer peptide amide. FIG. 27B depicts the ESI-MS and UV traces from UPLC analysis for glycopeptide p55-mer[N1-S55].

[00685] According to Section 6.4.2.6, peptide p55-mer[N1-S55] (20 mg, 2.0 μmol) and chitobiose ($GlcNAc_2$) anomeric amine (3.5 mg, 8.1 μmol) were combined and dissolved in anhydrous DMSO (100 μL). A solution of PyAOP (4.3 mg, 8.1 μmol) in DMSO (30 μL) was then added, followed by DIEA (2.0 μL, 12.2 μmol). The golden-yellow mixture was stirred for 3 hours, quenched by addition of 1 mL of ice-cold water (0.05% TFA), frozen and lyophilized.

[00686] The protected glycopeptide was then subjected to cocktail R (1.0 mL) for 2 hours, precipitated with ice-cold Et_2O, centrifuged, resuspended, and lyophilized as described in Section 6.4.2.6. The crude peptide was dissolved in 25% acetonitrile/water (0.05% TFA) (2 mL) and purified by HPLC on a X-Bridge C18 column, using a linear gradient of 25-35% acetonitrile in water (0.05% TFA) over 30 minutes. The fractions containing the desired product, which eluted at 20 minutes, were collected and lyophilized to provide glycopeptide "55-mer(chitobiose)[N1-S55]" ($GlcNAc_2$-55-mer) (3.0 mg, 22% yield) as a white solid (FIG. 28A). FIG. 28B provides the ESI-MS and UV traces from UPLC analysis for glycopeptide "55 mer(chitobiose) [N1-S55]" ($GlcNAc_2$-55-mer).

6.4.3.2 Synthesis of Pentasaccharide-bearing, Full-length Glycopeptide

[00687] According to Section 6.4.2.6, peptide p55-mer[N1-S55] (10 mg, 1.0 μmol) and pentasaccharide $Man_3GlcNAc_2$ anomeric amine (1.5 mg, 1.6 μmol) were combined and dissolved in anhydrous DMSO (30 μL). A solution of PyAOP (2.1 mg, 4.1 μmol) in DMSO (5 μL) was then added, followed by DIEA (1.0 μL, 6.1 μmol). The golden-yellow mixture was stirred for 3 hours, quenched by addition of 1 mL of ice-cold water (0.05% TFA), frozen and lyophilized.

[00688] The protected glycopeptide was then subjected to cocktail R (1.0 mL) for 2 hours, precipitated with ice-cold Et_2O, centrifuged, resuspended, and lyophilized as described in Section 6.4.2.6. The crude peptide was dissolved in 25% acetonitrile/water (0.05% TFA) (2 mL) and purified by HPLC on a X-Bridge C18 column, using a linear gradient of 25-35% acetonitrile in water (0.05% TFA) over 30 minutes. The fractions containing the desired product, which eluted at 18 minutes, were collected and lyophilized to provide glycopeptide "55-mer($Man_3GlcNAc_2$)[N1-S55]" ($Man_3GlcNAc_2$-55-mer) (1.5 mg, 20% yield) as a white solid. FIG. 29A depicts Man3GlcNAc2-bearing 55-mer glycopeptide: "55-mer($Man_3GlcNAc_2$)[N1-S55]" ($Man_3GlcNAc_2$-55-mer). FIG. 29B depicts the ESI-MS and UV traces from analytical HPLC analysis for glycopeptide "55 mer($Man_3GlcNAc_2$)[N1-S55]" ($Man_3GlcNAc_2$-55-mer).

6.4.4 SYNTHESIS OF SMALLER-SIZED GLYCOPEPTIDES (15-MER AND 18-MER)

6.4.4.1 Synthesis of Chitobiose-monoglycosylated 15-mer

[00689] Upon completion of the automated synthesis according to Section 6.4.2.1, the peptide-resin was subjected to *N*-acetylation and deallylation (*see* Section 6.4.2.2 and Section 6.4.2.3, respectively) to provide after cleavage from the resin (*see* Section 6.4.2.4) the partially protected peptide p15-mer[C-G25-V38] bearing the free carboxylic acid at Asp30 (corresponding to Asn1806 of SEQ ID NO: 150) side chain. FIG. 30A. This peptide was used in the next step without further purification.

[00690] Peptide p15-mer[C-G25-V38] (10 mg, 3.8 μmol) and chitobiose ($GlcNAc_2$) anomeric amine (4.8 mg, 11.3 μmol) were combined and dissolved in anhydrous DMSO (80 μL). A solution of PyAOP (5.9 mg, 11.3 μmol) in DMSO (20 μL) was added, followed by DIEA (2.6 μL, 15 μmol), and the golden-yellow mixture was stirred for 2.5 hours, frozen and lyophilized. The protected glycopeptide was then subjected to a TFA cocktail (1 mL) for 2 hours, precipitated

with ice-cold diethyl ether, centrifuged, resuspended, and lyophilized according to Section 6.4.2.6. The crude peptide was dissolved in 15% acetonitrile/water (0.05% TFA) (2 mL) and purified by HPLC on a C18 column, using a linear gradient of 15-35% acetonitrile in water (0.05% TFA) over 30 minutes. The fractions containing the desired product, which eluted at 17 minutes, were collected and lyophilized to provide glycopeptide "15-mer(chitobiose)[C-G25-V38]" (GlcNAc2-15-mer) (2.0 mg, 25% yield) as a white solid. *See* FIG. 30B for chitobiose-monoglycosylated 15-mer glycopeptide: 15-mer(chitobiose)[C-G25-V38] ($GlcNAc_2$-15-mer). FIG. 30C depicts the ESI-MS and UV traces from analytical HPLC analysis for glycopeptide "15 mer(chitobiose)[C-G25-V38]" ($GlcNAc_2$-15-mer).

6.4.4.2 Synthesis of Chitobiose-bisglycosylated 18-mer

[00691] Upon completion of the automated synthesis according to Section 6.4.2.1, the peptide-resin was subjected to N-acetylation (*see* 6.4.2.2). Then, cleavage from the resin and concomitant removal of the OPp protecting groups was effected following the methods set forth in Section 6.4.2.4 to afford the partially protected peptide p18-mer[C-T22-V38] bearing the free carboxylic acid at both Asp24 and Asp30 side chains (corresponding to Asn1800 and Asn1806, respectively, of SEQ ID NO: 150). This peptide was used in the next step without further purification. *See* FIG. 32A.

[00692] Peptide p18-mer[C-T22-V38] (30 mg, 9.1 μmol) and chitobiose (GlcNAc2) anomeric amine (27 mg, 63.4 μmol) were combined and dissolved in anhydrous DMSO (150 μL). PyAOP (28.5 mg, 54.6 μmol) was then added in DMSO (50 μL) followed by DIEA (2.6 μL, 15 μmol), and the golden-yellow mixture was stirred for 2.5 hours, frozen and lyophilized. The protected glycopeptide was then subjected to a TFA cocktail (1 mL) for 2 hours, precipitated with ice-cold diethyl ether, centrifuged, resuspended, and lyophilized according to Section 6.4.2.6. The crude peptide was dissolved in 15% acetonitrile/water (0.05% TFA) (6 mL) and purified by HPLC on a C8 column, using a linear gradient of 15-27% acetonitrile in water (0.05% TFA) over 30 minutes. The fractions containing the desired product, which eluted at 15 minutes, were collected and lyophilized to provide glycopeptide "18-mer(chitobiose)$_2$[C-T22-V38]" [$(GlcNAc_2)_2$-18-mer] (6.5 mg, 25% yield) as a white solid. *See* FIG. 32B. FIG. 32C depicts ESI-MS and UV traces from analytical HPLC analysis for glycopeptide "18 mer(chitobiose)$_2$[C-T22-V38]" [$(GlcNAc_2)_2$-18-mer].

6.5 KLH-CONJUGATION OF 15-MER AND 18-MER MUC16 GLYCOPEPTIDES

[00693] Glycopeptides "15-mer(chitobiose)[C-G25-V38]" and "18-mer(chitobiose)$_2$[C-T22-V38]" were conjugated to KLH following the procedure set forth in Section 6.4.2.7 to afford the corresponding KLH conjugates, $GlcNAc_2$-15-mer-KLH and $(GlcNAc_2)_2$-18-mer-KLH, respectively. *See* FIG. 33A and FIG. 33B.

7. TABLE OF SEQUENCES

[00694] **Table 13.** Table of Sequences.

SEQ ID NO	NAME	SEQ
1	10C6 VH	QVTLKESGPGILQPSQTLSLTCSFSGFSLNTLGMGVGWIRQPSGKGLEWLAHIWWDDDKYYNPALKSRLTISKDSSKNQVFLKIANVDTADIATYYCSRIGTAQATDALDYWGQGTSVTVSS
2	10C6 VL	DIVLTQSPASLAVSLGQRATISYRASKSVSTSGYSYMHWNQQKPGQPPRLLIYLVSNLESGVPARFSGSGSGTDFTLNIHPVEEEDAATYYCQHIRELTRSEGGPSWKN
3	10C6 HCDR1 (KABAT)	TLGMGVG
4	10C6 HCDR2 (KABAT)	HIWWDDDKYYNPALKS
5	10C6 HCDR3 (KABAT)	IGTAQATDALDY
6	10C6 LCDR1 (KABAT)	RASKSVSTSGYSYMH
7	10C6 LCDR2 (KABAT)	LVSNLES
8	10C6 LCDR3 (KABAT)	QHIRELTRS
9	10C6 HCDR1 (CHOTHIA)	GFSLNTLGM
10	10C6 HCDR2 (CHOTHIA)	WDD
11	10C6 HCDR3 (CHOTHIA)	GTAQATDALD
12	10C6 LCDR1 (CHOTHIA)	SKSVSTSGYSY
13	10C6 LCDR2 (CHOTHIA)	LVS
14	10C6 LCDR3 (CHOTHIA)	IRELTR

15	10C6 HCDR1 (IMGT)	GFSLNTLGMG
16	10C6 HCDR2 (IMGT)	IWWDDDK
17	10C6 HCDR3 (IMGT)	SRIGTAQATDALDY
18	10C6 LCDR1 (IMGT)	KSVSTSGYSY
19	10C6 LCDR2 (IMGT)	LVS
20	10C6 LCDR3 (IMGT)	QHIRELTRS
21	7B12 VH	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTVGMGVGWSRQPSG KGLEWLAHIWWDDEDKYYNPALKSRLTISKDTSKNQVFLKIA NVDTADSATYYCTRIGTAQATDALDYWGQGTSVTVSS
22	7B12 VL	DIVMTQAAPSVSVTPGESVSISCRSSKSLRKSNGNTYLYWFLQ RPGQSPQRLIYYMSNLASGVPDRFSGRGSGTDFTLRISRVEAED VGVYYCMQSLEYPLTFGGGTKLKIK
23	7B12 HCDR1 (KABAT)	TVGMGVG
24	7B12 HCDR2 (KABAT)	HIWWDDEDKYYNPALKS
25	7B12 HCDR3 (KABAT)	IGTAQATDALDY
26	7B12 LCDR1 (KABAT)	RSSKSLRKSNGNTYL Y
27	7B12 LCDR2 (KABAT)	YMSNLAS
28	7B12 LCDR3 (KABAT)	MQSLEYPLT
29	7B12 HCDR1 (CHOTHIA)	GFSLSTVGM
30	7B12 HCDR2 (CHOTHIA)	WDDE
31	7B12 HCDR3 (CHOTHIA)	GTAQATDALD
32	7B12 LCDR1 (CHOTHIA)	SKSLRKSNGNTY
33	7B12 LCDR2 (CHOTHIA)	YMS
34	7B12 LCDR3 (CHOTHIA)	SLEYPL
35	7B12 HCDR1 (IMGT)	GFSLSTVGMG

36	7B12 HCDR2 (IMGT)	IWWDDEDK
37	7B12 HCDR3 (IMGT)	TRIGTAQATDALDY
38	7B12 LCDR1 (IMGT)	KSLRKSNGNTY
39	7B12 LCDR2 (IMGT)	YMS
40	7B12 LCDR3 (IMGT)	MQSLEYPLT
41	19C11 VH	QVNLKESGPGKLQPSQTLSLTCSFSGFSLSTLGMGVGWIRQSS GKGLEWLAHIWWDDDKYYNPALKSRLTISRATSKNQVFLKIV NVGTADTATYYCARIGTAQATDALDYWGQGTSVTVSS
42	19C11 VL	DIVMTQAAPSIPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQR PGQSPQRLIYYMSNLASGVPDRFSGRGSGTDFTLKISRVEAGD VGVYYCMQGLEHPLTFGGGTKLEIK
43	19C11 HCDR1 (KABAT)	TLGMGVG
44	19C11 HCDR2 (KABAT)	HIWWDDDKYYNPALKS
45	19C11 HCDR3 (KABAT)	IGTAQATDALDY
46	19C11 LCDR1 (KABAT)	RSSKSLLHSNGNTYLY
47	19C11 LCDR2 (KABAT)	YMSNLAS
48	19C11 LCDR3 (KABAT)	MQGLEHPLT
49	19C11 HCDR1 (CHOTHIA)	GFSLSTLGM
50	19C11 HCDR2 (CHOTHIA)	WDD
51	19C11 HCDR3 (CHOTHIA)	GTAQATDALD
52	19C11 LCDR1 (CHOTHIA)	SKSLLHSNGNTY
53	19C11 LCDR2 (CHOTHIA)	YMS
54	19C11 LCDR3 (CHOTHIA)	GLEHPL
55	19C11 HCDR1 (IMGT)	GFSLSTLGMG
56	19C11 HCDR2 (IMGT)	IWWDDDK

57	19C11 HCDR3 (IMGT)	ARIGTAQATDALDY
58	19C11 LCDR1 (IMGT)	KSLLHSNGNTY
59	19C11 LCDR2 (IMGT)	YMS
60	19C11 LCDR3 (IMGT)	MQGLEHPLT
61	16C5 VH	QVTLKESGPGILQPSQTLSLTCSFSGFSLNTLGMGVGWIRQPSG KGLEWLAHIWWDDDKYYYPALKSRLTISRDTSKNQVFLKIAN VDTADTATYYCARIGTAQATDALDYWGQGTSVTV SS
62	16C5 VL	ELDMTQTPPSLSASVGETVRIRCLASEDIYSGISWYQQKPGKPP TLLIYGASNLESGVPPRFSGSGSGTDYTLTIGGVQAEDAATYYC LGGYSYSSTLTFGAGTNVEIK
63	16C5 HCDR1 (KABAT)	TLGMGVG
64	16C5 HCDR2 (KABAT)	HIWWDDDKYYYPALKS
65	16C5 HCDR3 (KABAT)	IGTAQATDALDY
66	16C5 LCDR1 (KABAT)	LASEDIYSGIS
67	16C5 LCDR2 (KABAT)	GASNLES
68	16C5 LCDR3 (KABAT)	LGGYSYSSTLT
69	16C5 HCDR1 (CHOTHIA)	GFSLNTLGM
70	16C5 HCDR2 (CHOTHIA)	WDD
71	16C5 HCDR3 (CHOTHIA)	GTAQATDALD
72	16C5 LCDR1 (CHOTHIA)	SEDIYSG
73	16C5 LCDR2 (CHOTHIA)	GAS
74	16C5 LCDR3 (CHOTHIA)	GYSYSSTL
75	16C5 HCDR1 (IMGT)	GFSLNTLGMG
76	16C5 HCDR2 (IMGT)	IWWDDDK
77	16C5 HCDR3 (IMGT)	ARIGTAQATDALDY

78	16C5 LCDR1 (IMGT)	EDIYSG
79	16C5 LCDR2 (IMGT)	GAS
80	16C5 LCDR3 (IMGT)	LGGYSYSSTLT
81	18C6 VH	QVTLKESGPGILQPSQTLSLTCSFSGFSLSTVGMGVGWSRQPSG KGLEWLAHIWWDDEDKYYNPALKSRLTISKDTSKNQVFLKIA NVDTADTATYYCTRIGTAQATDALDYWGQGTSVTVSS
82	18C6 VL	DIVMTQAAPSVPVTPGESVSISCRSSKSLLHSNGNTYLYWFLQR PGQSPQRLIYYMSNLASGVPDRFSGRGSGTDFTLRISRVEAEDV GVYYCMQSLEYPLTFGGGTKLEIK
83	18C6 HCDR1 (KABAT)	TVGMGVG
84	18C6 HCDR2 (KABAT)	HIWWDDEDKYYNPALKS
85	18C6 HCDR3 (KABAT)	IGTAQATDALDY
86	18C6 LCDR1 (KABAT)	RSSKSLLHSNGNTYLY
87	18C6 LCDR2 (KABAT)	YMSNLAS
88	18C6 LCDR3 (KABAT)	MQSLEYPLT
89	18C6 HCDR1 (CHOTHIA)	GFSLSTVGM
90	18C6 HCDR2 (CHOTHIA)	WDDE
91	18C6 HCDR3 (CHOTHIA)	GTAQATDALD
92	18C6 LCDR1 (CHOTHIA)	SKSLLHSNGNTY
93	18C6 LCDR2 (CHOTHIA)	YMS
94	18C6 LCDR3 (CHOTHIA)	SLEYPL
95	18C6 HCDR1 (IMGT)	GFSLSTVGMG
96	18C6 HCDR2 (IMGT)	IWWDDEDK
97	18C6 HCDR3 (IMGT)	TRIGTAQATDALDY
98	18C6 LCDR1 (IMGT)	KSLLHSNGNTY
99	18C6 LCDR2 (IMGT)	YMS

100	18C6 LCDR3 (IMGT)	MQSLEYPLT
101	10C6-18C6 VH consensus	QVX$_{21}$LKESGPGX$_{22}$LQPSQTLSLTCSFSGFSLX$_{23}$TX$_{24}$GMGVGW X$_{25}$RQX$_{26}$SGKGLEWLAHIWWDDX$_{27}$DKYYX$_{28}$PALKSRLTISX$_{29}$ X$_{30}$X$_{31}$SKNQVFLKIX$_{32}$NVX$_{33}$TADX$_{34}$ATYYCX$_{35}$RIGTAQATDAL DYWGQGTSVTVSS Wherein X$_{21}$ is T or N, X$_{22}$ is I or K, X$_{23}$ is N or S, X$_{24}$ is V or L, X$_{25}$ is S or I, X$_{26}$ is P or S, X$_{27}$ is E or absent, X$_{28}$ is N or Y, X$_{29}$ is K or R, X$_{30}$ is A or D, X$_{31}$ is T or S, X$_{32}$ is V or A, X$_{33}$ is G or D, X$_{34}$ is T, I, or S, and X$_{35}$ is T, S, or A
102	7B12, 19C11, 18C6 VL consensus	DIVMTQAAPSX$_{36}$X$_{37}$VTPGESVSISCRSSKSLX$_{38}$X$_{39}$SNGNTYLY WFLQRPGQSPQRLIYYMSNLASGVPDRFSGRGSGTDFTLX$_{40}$IS RVEAX$_{41}$DVGVYYCMQX$_{42}$LEX$_{43}$PLTFGGGTKLEIK Wherein X$_{36}$ is I or V, X$_{37}$ is P or S, X$_{38}$ is R or L, X$_{39}$ is K or H, X$_{40}$ is R or K, X$_{41}$ is E or G, X$_{42}$ is S or G, and X$_{43}$ is Y or H
103	HCDR1 KABAT CONSENSUS	TX$_1$GMGVG Wherein X$_1$ is L or V
104	HCDR2 KABAT CONSENSUS	HIWWDDX$_2$DKYYX$_3$PALKS Wherein X$_2$ is E or absent and X$_3$ is Y or N
105	HCDR3 KABAT CONSENSUS	IGTAQATDALDY
106	7B12, 19C11, 18C6 LCDR1 KABAT CONSENSUS	RSSKSLX$_4$X$_5$SNGNTYLY Wherein X$_4$ is R or L, and X$_5$ is K or H
107	7B12, 19C11, 18C6 LCDR2 KABAT CONSENSUS	YMSNLAS
108	7B12, 19C11, 18C6 LCDR3 KABAT CONSENSUS	MQX$_6$LEX$_7$PLT Wherein X6 is G or S and X7 is H or Y
109	10C6-18C6 HCDR1 CHOTHIA CONSENSUS	GFSLX$_8$TX$_9$GM Wherein X$_8$ is N or S, and X$_9$ is L or V
110	10C6-18C6	WDDX$_{10}$

	HCDR2 CHOTHIA CONSENSUS	Wherein X_{10} is E or absent
111	10C6-18C6 HCDR3 CHOTHIA CONSENSUS	GTAQATDALD
112	7B12, 19C11, 18C6 LCDR1 CHOTHIA CONSENSUS	SKSLX$_{11}$X$_{12}$SNGNTY Wherein X_{11} is L or R, and X_{12} is H or K
113	7B12, 19C11, 18C6 LCDR2 CHOTHIA CONSENSUS	YMS
114	7B12, 19C11, 18C6 LCDR3 CHOTHIA CONSENSUS	X$_{13}$LEX$_{14}$PL Wherein X_{13} is G or S, and X_{14} is H or Y
115	10C6-18C6 HCDR1 IMGT CONSENSUS	GFSLX$_{15}$TX$_{16}$GMG Wherein X_{15} is N or S, and X_{16} is V or L
116	10C6-18C6 HCDR2 IMGT CONSENSUS	IWWDDX$_{17}$DK Wherein X_{17} is E or absent
117	10C6-18C6 HCDR3 IMGT CONSENSUS	X$_{18}$RIGTAQATDALDY Wherein X_{18} is T, A, or S
118	7B12, 19C11, 18C6 LCDR1 IMGT CONSENSUS	KSLX$_{19}$X$_{20}$SNGNTY Wherein X_{19} is V or L, and X_{20} is H or K
119	7B12, 19C11, 18C6 LCDR2 IMGT CONSENSUS	YMS
120	7B12, 19C11, 18C6 LCDR3 IMGT CONSENSUS	MQSLEYPLT
121	MUC16c114 F primer	CCATGCGATATCGCCACCATGGTGAACTTCTCGCCACTGGC T
122	MUC16c114 R	TACGGCGGCCGCTTGCAGATCCTCCAGGTCTAGG

	primer	
123	MUC16c344 F primer	CCATGCGATATCGCCACCATGGTGACAGGCCCTGGGCTGGACAGA
124	MUC16c344 R primer	TACGGCGGCCGCTTGCAGATCCTCCAGGTCTAGG
125	MUC16c57-114 F primer	CCATGCGATATCAAACTTCTCGCCACTGGCT
126	MUC16c57-114 R primer	AGATCTAACCATGGGAAGGTCAGAATTCCCAGT
127	117-244LGALS3 F primer	CCATGCGATATCACCTTATAACCTGCCTTTG
128	117-244LGALS3 R primer	AGATCTAACCATGGTATATGAAGCACTGGT
129	55mer immunizing peptide	NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNS
130	18mer immunizing peptide	CTRNGTQLQNFTLDRSSV
131	15mer immunizing peptide	CGTQLQNFTLDRSSV
132	MUC16c344	WELSQLTHGVTQLGFYVLDRDSLFINGYAPQNLSIRGEYQINFHIVNQNLSNPDPTSSEYITLLRDIQDKVTTLYKGSQLHDTFRFCLVTNLTMDSVLVTVKALFSSNLDPSLVEQVFLDKTLNASFHQLGSTYQLVDIHVTEMESSVYQPTSSSSTQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQVSTFRSVPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRRKKEGEYNVQQQCPGYYQSHLDLEDLQ
133	MUC16c114	NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRRKKEGEYNVQQQCPGYYQSHLDLEDLQ
134	MUC16c86	NFSPLARRVDRVAIYEEFLRMDLPFWAVILIGLAGLLGLITCLICGVLVTTRRRKKEGEYNVQQQCPGYYQSHLDLEDLQ
135	MUC16c80	NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGDLEDLQ
136	Immature Human MUC16 amino acid sequence (NP_078966.2)	MLKPSGLPGSSSPTRSLMTGSRSTKATPEMDSGLTGATLSPKTSTGAIVVTEHTLPFTSPDKTLASPTSSVVGRTTQSLGVMSSALPESTSRGMTHSEQRTSPSLSPQVNGTPSRNYPATSMVSGLSSPRTRTSSTEGNFTKEASTYTLTVETTSGPVTEKYTVPTETSTTEGDSTETPWDTRYIPVKITSPMKTFADSTASKENAPVSMTPAETTVTDSHTPGRTNPSFGTLYSSFLDLSPKGTPNSRGETSLELILSTTGYPFSSPEPGSAGHSRISTSAPLSSSASVLDNKISETSIFSGQSLTSPLSP

		GVPEARASTMPNSAIPFSMTLSNAETSAERVRSTISSLGTPSIST KQTAETILTFHAFAETMDIPSTHIAKTLASEWLGSPGTLGGTST SALTTTSPSTTLVSEETNTHHSTSGKETEGTLNTSMTPLETSAP GEESEMTATLVPTLGFTTLDSKIRSPSQVSSSHPTRELRTTGSTS GRQSSSTAAHGSSDILRATTSSTSKASSWTSESTAQQFSEPQHT QWVETSPSMKTERPPASTSVAAPITTSVPSVVSGFTTLKTSSTK GIWLEETSADTLIGESTAGPTTHQFAVPTGISMTGGSSTRGSQG TTHLLTRATASSETSADLTLATNGVPVSVSPAVSKTAAGSSPPG GTKPSYTMVSSVIPETSSLQSSAFREGTSLGLTPLNTRHPFSSPE PDSAGHTKISTSIPLLSSASVLEDKVSATSTFSHHKATSSITTGTP EISTKTKPSSAVLSSMTLSNAATSPERVRNATSPLTHPSPSGEET AGSVLTLSTSAETTDSPNIHPTGTLTSESSESPSTLSLPSVSGVKT TFSSSTPSTHLFTSGEETEETSNPSVSQPETSVSRVRTTLASTSVP TPVFPTMDTWPTRSAQFSSSHLVSELRATSSTSVTNSTGSALPK ISHLTGTATMSQTNRDTFNDSAAPQSTTWPETSPRFKTGLPSAT TTVSTSATSLSATVMVSKFTSPATSSMEATSIREPSTTILTTETT NGPGSMAVASTNIPIGKGYITEGRLDTSHLPIGTTASSETSMDFT MAKESVSMSVSPSQSMDAAGSSTPGRTSQFVDTFSDDVYHLTS REITIPRDGTSSALTPQMTATHPPSPDPGSARSTWLGILSSSPSSP TPKVTMSSTFSTQRVTTSMIMDTVETSRWNMPNLPSTTSLTPS NIPTSGAIGKSTLVPLDTPSPATSLEASEGGLPTLSTYPESTNTPS IHLGAHASSESPSTIKLTMASVVKPGSYTPLTFPSIETHIHVSTA RMAYSSGSSPEMTAPGETNTGSTWDPTTYITTTDPKDTSSAQV STPHSVRTLRTTENHPKTESATPAAYSGSPKISSSPNLTSPATKA WTITDTTEHSTQLHYTKLAEKSSGFETQSAPGPVSVVIPTSPTIG SSTLELTSDVPGEPLVLAPSEQTTITLPMATWLSTSLTEEMAST DLDISSPSSPMSTFAIFPPMSTPSHELSKSEADTSAIRNTDSTTLD QHLGIRSLGRTGDLTTVPITPLTTTWTSVIEHSTQAQDTLSATM SPTHVTQSLKDQTSIPASASPSHLTEVYPELGTQGRSSSEATTF WKPSTDTLSREIETGPTNIQSTPPMDNTTTGSSSSGVTLGIAHLP IGTSSPAETSTNMALERRSSTATVSMAGTMGLLVTSAPGRSISQ SLGRVSSVLSESTTEGVTDSSKGSSPRLNTQGNTALSSSLEPSY AEGSQMSTSIPLTSSPTTPDVEFIGGSTFWTKEVTTVMTSDISKS SARTESSSATLMSTALGSTENTGKEKLRTASMDLPSPTPSMEV TPWISLTLSNAPNTTDSLDLSHGVHTSSAGTLATDRSL*N*TGVTR ASRLENGSDTSSKSLSMGNSTHTSMTYTEKSEVSSSIHPRPETS APGAETTLTSTPGNRAISLTLPFSSIPVEEVISTGITSGPDINSAPM THSPITPPTIVWTSTGTIEQSTQPLHAVSSEKVSVQTQSTPYVNS VAVSASPTHENSVSSGSSTSSPYSSASLESLDSTISRRNAITSWL WDLTTSLPTTTWPSTSLSEALSSGHSGVSNPSSTTTEFPLFSAAS TSAAKQRNPETETHGPQNTAASTLNTDASSVTGLSETPVGASIS SEVPLPMAITSRSDVSGLTSESTANPSLGTASSAGTKLTRTISLP TSESLVSFRMNKDPWTVSIPLGSHPTTNTETSIPVNSAGPPGLST VASDVIDTPSDGAESIPTVSFSPSPDTEVTTISHFPEKTTHSFRTIS SLTHELTSRVTPIPGDWMSSAMSTKPTGASPSITLGERRTITSAA PTTSPIVLTASFTETSTVSLDNETTVKTSDILDARKTNELPSDSSS

		SSDLINTSIASSTMDVTKTASISPTSISGMTASSSPSLFSSDRPQV PTSTTETNTATSPSVSSNTYSLDGGSNVGGTPSTLPPFTITHPVE TSSALLAWSRPVRTFSTMVSTDTASGENPTSSNSVVTSVPAPGT WTSVGSTTDLPAMGFLKTSPAGEAHSLLASTIEPATAFTPHLSA AVVTGSSATSEASLLTTSESKAIHSSPQTPTTPTSGANWETSATP ESLLVVTETSDTTLTSKILVTDTILFSTVSTPPSKFPSTGTLSGAS FPTLLPDTPAIPLTATEPTSSLATSFDSTPLVTIASDSLGTVPETT LTMSETSNGDALVLKTVSNPDRSIPGITIQGVTESPLHPSSTSPS KIVAPRNTTYEGSITVALSTLPAGTTGSLVFSQSSENSETTALVD SSAGLERASVMPLTTGSQGMASSGGIRSGSTHSTGTKTFSSLPL TMNPGEVTAMSEITTNRLTATQSTAPKGIPVKPTSAESGLLTPV SASSSPSKAFASLTTAPPTWGIPQSTLTFEFSEVPSLDTKSASLPT PGQSLNTIPDSDASTASSSLSKSPEKNPRARMMTSTKAISASSFQ STGFTETPEGSASPSMAGHEPRVPTSGTGDPRYASESMSYPDPS KASSAMTSTSLASKLTTLFSTGQAARSGSSSSPISLSTEKETSFL SPTASTSRKTSLFLGPSMARQPNILVHLQTSALTLSPTSTLNMS QEEPPELTSSQTIAEEEGTTAETQTLTFTPSETPTSLLPVSSPTEP TARRKSSPETWASSISVPAKTSLVETTDGTLVTTIKMSSQAAQG NSTWPAPAEETGSSPAGTSPGSPEMSTTLKIMSSKEPSISPEIRST VRNSPWKTPETTVPMETTVEPVTLQSTALGSGSTSISHLPTGTT SPTKSPTENMLATERVSLSPSPPEAWTNLYSGTPGGTRQSLAT MSSVSLESPTARSITGTGQQSSPELVSKTTGMEFSMWHGSTGG TTGDTHVSLSTSSNILEDPVTSPNSVSSLTDKSKHKTETWVSTT AIPSTVLNNKIMAAEQQTSRSVDEAYSSTSSWSDQTSGSDITLG ASPDVTNTLYITSTAQTTSLVSLPSGDQGITSLTNPSGGKTSSAS SVTSPSIGLETLRANVSAVKSDIAPTAGHLSQTSSPAEVSILDVT TAPTPGISTTITTMGTNSISTTTPNPEVGMSTMDSTPATERRTTS TEHPSTWSSTAASDSWTVTDMTSNLKVARSPGTISTMHTTSFL ASSTELDSMSTPHGRITVIGTSLVTPSSDASAVKTETSTSERTLS PSDTTASTPISTFSRVQRMSISVPDILSTSWTPSSTEAEDVPVSM VSTDHASTKTDPNTPLSTFLFDSLSTLDWDTGRSLSSATATTSA PQGATTPQELTLETMISPATSQLPFSIGHITSAVTPAAMARSSGV TFSRPDPTSKKAEQTSTQLPTTTSAHPGQVPRSAATTLDVIPHT AKTPDATFQRQGQTALTTEARATSDSWNEKEKSTPSAPWITE MMNSVSEDTIKEVTSSSSVLRTLNTLDINLESGTTSSPSWKSSP YERIAPSESTTDKEAIHPSTNTVETTGWVTSSEHASHSTIPAHSA SSKLTSPVVTTSTREQAIVSMSTTTWPESTRARTEPNSFLTIELR DVSPYMDTSSTTQTSIISSPGSTAITKGPRTEITSSKRISSSFLAQS MRSSDSPSEAITRLSNFPAMTESGGMILAMQTSPPGATSLSAPT LDTSATASWTGTPLATTQRFTYSEKTTLFSKGPEDTSQPSPPSV EETSSSSSLVPIHATTSPSNILLTSQGHSPSSTPPVTSVFLSETSGL GKTTDMSRISLEPGTSLPPNLSSTAGEALSTYEASRDTKAIHHS ADTAVTNMEATSSEYSPIPGHTKPSKATSPLVTSHIMGDITSSTS VFGSSETTEIETVSSVNQGLQERSTSQVASSATETSTVITHVSSG DATTHVTKTQATFSSGTSISSPHQFITSTNTFTDVSTNPSTSLIMT ESSGVTITTQTGPTGAATQGPYLLDTSTMPYLTETPLAVTPDFM

		QSEKTTLISKGPKDVSWTSPPSVAETSYPSSLTPFLVTTIPPATST LQGQHTSSPVSATSVLTSGLVKTTDMLNTSMEPVTNSPQNLNN PSNEILATLAATTDIETIHPSINKAVTNMGTASSAHVLHSTLPVS SEPSTATSPMVPASSMGDALASISIPGSETTDIEGEPTSSLTAGR KENSTLQEMNSTTESNIILSNVSVGAITEATKMEVPSFDATFIPT PAQSTKFPDIFSVASSRLSNSPPMTISTHMTTTQTGSSGATSKIP LALDTSTLETSAGTPSVVTEGFAHSKITTAMNNDVKDVSQTNP PFQDEASSPSSQAPVLVTTLPSSVAFTPQWHSTSSPVSMSSVLT SSLVKTAGKVDTSLETVTSSPQSMSNTLDDISVTSAATTDIETT HPSINTVVTNVGTTGSAFESHSTVSAYPEPSKVTSPNVTTSTME DTTISRSIPKSSKTTRTETETTSSLTPKLRETSISQEITSSTETSTVP YKELTGATTEVSRTDVTSSSSTSFPGPDQSTVSLDISTETNTRLS TSPIMTESAEITITTQTGPHGATSQDTFTMDPSNTTPQAGIHSAM THGFSQLDVTTLMSRIPQDVSWTSPPSVDKTSSPSSFLSSPAMT TPSLISSTLPEDKLSSPMTSLLTSGLVKITDILRTRLEPVTSSLPNF SSTSDKILATSKDSKDTKEIFPSINTEETNVKANNSGHESHSPAL ADSETPKATTQMVITTTVGDPAPSTSMPVHGSSETTNIKREPTY FLTPRLRETSTSQESSFPTDTSFLLSKVPTGTITEVSSTGVNSSSK ISTPDHDKSTVPPDTFTGEIPRVFTSSIKTKSAEMTITTQASPPES ASHSTLPLDTSTTLSQGGTHSTVTQGFPYSEVTTLMGMGPGNV SWMTTPPVEETSSVSSLMSSPAMTSPSPVSSTSPQSIPSSPLPVT ALPTSVLVTTTDVLGTTSPESVTSSPPNLSSITHERPATYKDTAH TEAAMHHSTNTAVTNVGTSGSGHKSQSSVLADSETSKATPLM STTSTLGDTSVSTSTPNISQTNQIQTEPTASLSPRLRESSTSEKTS STTETNTAFSYVPTGAITQASRTEISSSRTSISDLDRPTIAPDISTG MITRLFTSPIMTKSAEMTVTTQTTTPGATSQGILPWDTSTTLFQ GGTHSTVSQGFPHSEITTLRSRTPGDVSWMTTPPVEETSSGFSL MSPSMTSPSPVSSTSPESIPSSPLPVTALLTSVLVTTTNVLGTTSP EPVTSSPPNLSSPTQERLTTYKDTAHTEAMHASMHTNTAVAN VGTSISGHESQSSVPADSHTSKATSPMGITFAMGDTSVSTSTPA FFETRIQTESTSSLIPGLRDTRTSEEINTVTETSTVLSEVPTTTTTE VSRTEVITSSRTTISGPDHSKMSPYISTETITRLSTFPFVTGSTEM AITNQTGPIGTISQATLTLDTSSTASWEGTHSPVTQRFPHSEETT TMSRSTKGVSWQSPPSVEETSSPSSPVPLPAITSHSSLYSAVSGS SPTSALPVTSLLTSGRRKTIDMLDTHSELVTSSLPSASSFSGEILT SEASTNTETIHFSENTAETNMGTTNSMHKLHSSVSIHSQPSGHT PPKVTGSMMEDAIVSTSTPGSPETKNVDRDSTSPLTPELKEDST ALVMNSTTESNTVFSSVSLDAATEVSRAEVTYYDPTFMPASAQ STKSPDISPEASSSHSNSPPLTISTHKTIATQTGPSGVTSLGQLTL DTSTIATSAGTPSARTQDFVDSETTSVMNNDLNDVLKTSPFSAE EANSLSSQAPLLVTTSPSPVTSTLQEHSTSSLVSVTSVPTPTLAK ITDMDTNLEPVTRSPQNLRNTLATSEATTDTHTMHPSINTAVA NVGTTSSPNEFYFTVSPDSDPYKATSAVVITSTSGDSIVSTSMPR SSAMKKIESETTFSLIFRLRETSTSQKIGSSSDTSTVFDKAFTAAT TEVSRTELTSSSRTSIQGTEKPTMSPDTSTRSVTMLSTFAGLTKS EERTIATQTGPHRATSQGTLTWDTSITTSQAGTHSAMTHGFSQ

		LDLSTLTSRVPEYISGTSPPSVEKTSSSSSLLSLPAITSPSPVPTTL PESRPSSPVHLTSLPTSGLVKTTDMLASVASLPPNLGSTSHKIPT TSEDIKDTEKMYPSTNIAVTNVGTTTSEKESYSSVPAYSEPPKV TSPMVTSFNIRDTIVSTSMPGSSEITRIEMESTFSLAHGLKGTSTS QDPIVSTEKSAVLHKLTTGATETSRTEVASSRRTSIPGPDHSTES PDISTEVIPSLPISLGITESSNMTIITRTGPPLGSTSQGTFTLDTPTT SSRAGTHSMATQEFPHSEMTTVMNKDPEILSWTIPPSIEKTSFSS SLMPSPAMTSPPVSSTLPKTIHTTPSPMTSLLTPSLVMTTDTLGT SPEPTTSSPPNLSSTSHEILTTDEDTTAIEAMHPSTSTAATNVETT SSGHGSQSSVLADSEKTKATAPMDTTSTMGHTTVSTSMSVSSE TTKIKRESTYSLTPGLRETSISQNASFSTDTSIVLSEVPTGTTAEV SRTEVTSSGRTSIPGPSQSTVLPEISTRTMTRLFASPTMTESAEM TIPTQTGPSGSTSQDTLTLDTSTTKSQAKTHSTLTQRFPHSEMT TLMSRGPGDMSWQSSPSLENPSSLPSLLSLPATTSPPPISSTLPV TISSSPLPVTSLLTSSPVTTTDMLHTSPELVTSSPPKLSHTSDERL TTGKDTTNTEAVHPSTNTAASNVEIPSSGHESPSSALADSETSK ATSPMFITSTQEDTTVAISTPHFLETSRIQKESISSLSPKLRETGSS VETSSAIETSAVLSEVSIGATTEISRTEVTSSSRTSISGSAESTMLP EISTTRKIIKFPTSPILAESSEMTIKTQTSPPGSTSESTFTLDTSTTP SLVITHSTMTQRLPHSEITTLVSRGAGDVPRPSSLPVEETSPPSS QLSLSAMISPSPVSSTLPASSHSSSASVTSLLTPGQVKTTEVLDA SAEPETSSPPSLSSTSVEILATSEVTTDTEKIHPFSNTAVTKVGTS SSGHESPSSVLPDSETTKATSAMGTISIMGDTSVSTLTPALSNTR KIQSEPASSLTTRLRETSTSEETSLATEANTVLSKVSTGATTEVS RTEAISFSRTSMSGPEQSTMSQDISIGTIPRISASSVLTESAKMTI TTQTGPSESTLESTLNLNTATTPSWVETHSIVIQGFPHPEMTTS MGRGPGGVSWPSPPFVKETSPPSSPLSLPAVTSPHPVSTTFLAHI PPSPLPVTSLLTSGPATTTDILGTSTEPGTSSSSSLSTTSHERLTT YKDTAHTEAVHPSTNTGGTNVATTSSGYKSQSSVLADSSPMC TTSTMGDTSVLTSTPAFLETRRIQTELASSLTPGLRESSGSEGTS SGTKMSTVLSKVPTGATTEISKEDVTSIPGPAQSTISPDISTRTVS WFSTSPVMTESAEITMNTHTSPLGATTQGTSTLDTSSTTSLTMT HSTISQGFSHSQMSTLMRRGPEDVSWMSPPLLEKTRPSFSLMSS PATTSPSPVSSTLPESISSSPLPVTSLLTSGLAKTTDMLHKSSEPV TNSPANLSSTSVEILATSEVTTDTEKTHPSSNRTVTDVGTSSSG HESTSFVLADSQTSKVTSPMVITSTMEDTSVSTSTPGFFETSRIQ TEPTSSLTLGLRKTSSSEGTSLATEMSTVLSGVPTGATAEVSRT EVTSSSRTSISGFAQLTVSPETSTETITRLPTSSIMTESAEMMIKT QTDPPGSTPESTHTVDISTTPNWVETHSTVTQRFSHSEMTTLVS RSPGDMLWPSQSSVEETSSASSLLSLPATTSPSPVSSTLVEDFPS ASLPVTSLLNPGLVITTDRMGISREPGTSSTSNLSSTSHERLTTL EDTVDTEDMQPSTHTAVTNVRTSISGHESQSSVLSDSETPKATS PMGTTYTMGETSVSISTSDFFETSRIQIEPTSSLTSGLRETSSSERI SSATEGSTVLSEVPSGATTEVSRTEVISSRGTSMSGPDQFTISPDI STEAITRLSTSPIMTESAESAITIETGSPGATSEGTLTLDTSTTTF WSGTHSTASPGFSHSEMTTLMSRTPGDVPWPSLPSVEEASSVS

		SSLSSPAMTSTSFFSTLPESISSSPHPVTALLTLGPVKTTDMLRTS SEPETSSPPNLSSTSAEILATSEVTKDREKIHPSSNTPVVNVGTVI YKHLSPSSVLADLVTTKPTSPMATTSTLGNTSVSTSTPAFPETM MTQPTSSLTSGLREISTSQETSSATERSASLSGMPTGATTKVSRT EALSLGRTSTPGPAQSTISPEISTETITRISTPLTTTGSAEMTITPK TGHSGASSQGTFTLDTSSRASWPGTHSAATHRSPHSGMTTPMS RGPEDVSWPSRPSVEKTSPPSSLVSLSAVTSPSPLYSTPSESSHSS PLRVTSLFTPVMMKTTDMLDTSLEPVTTSPPSMNITSDESLATS KATMETEAIQLSENTAVTQMGTISARQEFYSSYPGLPEPSKVTS PVVTSSTIKDIVSTTIPASSEITRIEMESTSTLTPTPRETSTSQEIHS ATKPSTVPYKALTSATIEDSMTQVMSSSRGPSPDQSTMSQDIST EVITRLSTSPIKTESTEMTITTQTGSPGATSRGTLTLDTSTTFMS GTHSTASQGFSHSQMTALMSRTPGDVPWLSHPSVEEASSASFS LSSPVMTSSSPVSSTLPDSIHSSSLPVTSLLTSGLVKTTELLGTSS EPETSSPPNLSSTSAEILAITEVTTDTEKLEMTNVVTSGYTHESP SSVLADSVTTKATSSMGITYPTGDTNVLTSTPAFSDTSRIQTKS KLSLTPGLMETSISEETSSATEKSTVLSSVPTGATTEVSRTEAISS SRTSIPGPAQSTMSSDTSMETITRISTPLTRKESTDMAITPKTGPS GATSQGTFTLDSSSTASWPGTHSATTQRFPQSVVTTPMSRGPE DVSWPSPLSVEKNSPPSSLVSSSSVTSPSPLYSTPSGSSHSSPVPV TSLFTSIMMKATDMLDASLEPETTSAPNMNITSDESLAASKATT ETEAIHVFENTAASHVETTSATEELYSSSPGFSEPTKVISPVVTS SSIRDNMVSTTMPGSSGITRIEIESMSSLTPGLRETRTSQDITSST ETSTVLYKMPSGATPEVSRTEVMPSSRTSIPGPAQSTMSLDISD EVVTRLSTSPIMTESAEITITTQTGYSLATSQVTLPLGTSMTFLS GTHSTMSQGLSHSEMTNLMSRGPESLSWTSPRFVETTRSSSSLT SLPLTTSLSPVSSTLLDSSPSSPLPVTSLILPGLVKTTEVLDTSSEP KTSSSPNLSSTSVEIPATSEIMTDTEKIHPSSNTAVAKVRTSSSV HESHSSVLADSETTITIPSMGITSAVDDTTVFTSNPAFSETRRIPT EPTFSLTPGFRETSTSEETTSITETSAVLYGVPTSATTEVSMTEI MSSNRIHIPDSDQSTMSPDIITEVITRLSSSSMMSESTQMTITTQK SSPGATAQSTLTLATTTAPLARTHSTVPPRFLHSEMTTLMSRSP ENPSWKSSLFVEKTSSSSSLLSLPVTTSPSVSSTLPQSIPSSSFSVT SLLTPGMVKTTDTSTEPGTSLSPNLSGTSVEILAASEVTTDTEKI HPSSSMAVTNVGTTSSGHELYSSVSIHSEPSKATYPVGTPSSMA ETSISTSMPANFETTGFEAEPFSHLTSGFRKTNMSLDTSSVTPTN TPSSPGSTHLLQSSKTDFTSSAKTSSPDWPPASQYTEIPVDIITPF NASPSITESTGITSFPESRFTMSVTESTHHLSTDLLPSAETISTGT VMPSLSEAMTSFATTGVPRAISGSGSPFSRTESGPGDATLSTIAE SLPSSTPVPFSSSTFTTTDSSTIPALHEITSSSATPYRVDTSLGTES STTEGRLVMVSTLDTSSQPGRTSSSPILDTRMTESVELGTVTSA YQVPSLSTRLTRTDGIMEHITKIPNEAAHRGTIRPVKGPQTSTSP ASPKGLHTGGTKRMETTTTALKTTTTALKTTSRATLTTSVYTP TLGTLTPLNASMQMASTIPTEMMITTPYVFPDVPETTSSLATSL GAETSTALPRTTPSVFNRESETTASLVSRSGAERSPVIQTLDVSS SEPDTTASWVIHPAETIPTVSKTTPNFFHSELDTVSSTATSHGAD

		VSSAIPTNISPSELDALTPLVTISGTDTSTTFPTLTKSPHETETRTT WLTHPAETSSTIPRTIPNFSHHESDATPSIATSPGAETSSAIPIMT VSPGAEDLVTSQVTSSGTDRNMTIPTLTLSPGEPKTIASLVTHPE AQTSSAIPTSTISPAVSRLVTSMVTSLAAKTSTTNRALTNSPGEP ATTVSLVTHPAQTSPTVPWTTSIFFHSKSDTTPSMTTSHGAESS SAVPTPTVSTEVPGVVTPLVTSSRAVISTTIPILTLSPGEPETTPS MATSHGEEASSAIPTPTVSPGVPGVVTSLVTSSRAVTSTTIPILT FSLGEPETTPSMATSHGTEAGSAVPTVLPEVPGMVTSLVASSR AVTSTTLPTLTLSPGEPETTPSMATSHGAEASSTVPTVSPEVPG VVTSLVTSSSGVNSTSIPTLILSPGELETTPSMATSHGAEASSAV PTPTVSPGVSGVVTPLVTSSRAVTSTTIPILTLSSSEPETTPSMAT SHGVEASSAVLTVSPEVPGMVTSLVTSSRAVTSTTIPTLTISSDE PETTTSLVTHSEAKMISAIPTLAVSPTVQGLVTSLVTSSGSETSA FSNLTVASSQPETIDSWVAHPGTEASSVVPTLTVSTGEPFTNISL VTHPAESSSTLPRTTSRFSHSELDTMPSTVTSPEAESSSAISTTIS PGIPGVLTSLVTSSGRDISATFPTVPESPHESEATASWVTHPAVT STTVPRTTPNYSHSEPDTTPSIATSPGAEATSDFPTITVSPDVPD MVTSQVTSSGTDTSITIPTLTLSSGEPETTTSFITYSETHTSSAIPT LPVSPGASKMLTSLVISSGTDSTTTFPTLTETPYEPETTAIQLIHP AETNTMVPRTTPKFSHSKSDTTLPVAITSPGPEASSAVSTTTISP DMSDLVTSLVPSSGTDTSTTFPTLSETPYEPETTATWLTHPAET STTVSGTIPNFSHRGSDTAPSMVTSPGVDTRSGVPTTTIPPSIPG VVTSQVTSSATDTSTAIPTLTPSPGEPETTASSATHPGTQTGFTV PIRTVPSSEPDTMASWVTHPPQTSTPVSRTTSSFSHSSPDATPV MATSPRTEASSAVLTTISPGAPEMVTSQITSSGAATSTTVPTLTH SPGMPETTALLSTHPRTETSKTFPASTVFPQVSETTASLTIRPGA ETSTALPTQTTSSLFTLLVTGTSRVDLSPTASPGVSAKTAPLSTH PGTETSTMIPTSTLSLGLLETTGLLATSSSAETSTSTLTLTVSPAV SGLSSASITTDKPQTVTSWNTETSPSVTSVGPPEFSRTVTGTTM TLIPSEMPTPPKTSHGEGVSPTTILRTTMVEATNLATTGSSPTVA KTTTTFNTLAGSLFTPLTTPGMSTLASESVTSRTSYNHRSWIST TSSYNRRYWTPATSTPVTSTFSPGISTSSIPSSTAATVPFMVPFTL NFTITNLQYEEDMRHPGSRKFNATERELQGLLKPLFRNSSLEYL YSGCRLASLRPEKDSSATAVDAICTHRPDPEDLGLDRERLYWE LSNLTNGIQELGPYTLDRNSLYVNGFTHRSSMPTTSTPGTSTVD VGTSGTPSSSPSPTTAGPLLMPFTLNFTITNLQYEEDMRRTGSR KFNTMESVLQGLLKPLFKNTSVGPLYSGCRLTLLRPEKDGAAT GVDAICTHRLDPKSPGLNREQLYWELSKLTNDIEELGPYTLDR NSLYVNGFTHQSSVSTTSTPGTSTVDLRTSGTPSSLSSPTIMAA GPLLVPFTLNFTITNLQYGEDMGHPGSRKFNTTERVLQGLLGPI FKNTSVGPLYSGCRLTSLRSEKDGAATGVDAICIHHLDPKSPGL NRERLYWELSQLTNGIKELGPYTLDRNSLYVNGFTHRTSVPTS STPGTSTVDLGTSGTPFSLPSPATAGPLLVLFTLNFTITNLKYEE DMHRPGSRKFNTTERVLQTLLGPMFKNTSVGLLYSGCRLTLLR SEKDGAATGVDAICTHRLDPKSPGVDREQLYWELSQLTNGIKE LGPYTLDRNSLYVNGFTHWIPVPTSSTPGTSTVDLGSGTPSSLP

		SPTTAGPLLVPFTLNFTITNLKYEEDMHCPGSRKFNTTERVLQS LLGPMFKNTSVGPLYSGCRLTLLRSEKDGAATGVDAICTHRLD PKSPGVDREQLYWELSQLTNGIKELGPYTLDRNSLYVNGFTHQ TSAPNTSTPGTSTVDLGTSGTPSSLPSPTSAGPLLVPFTLNFTITN LQYEEDMHHPGSRKFNTTERVLQGLLGPMFKNTSVGLLYSGC RLTLLRPEKNGAATGMDAICSHRLDPKSPGLNREQLYWELSQL THGIKELGPYTLDRNSLYVNGFTHRSSVAPTSTPGTSTVDLGTS GTPSSLPSPTTAVPLLVPFTLNFTITNLQYGEDMRHPGSRKFNT TERVLQGLLGPLFKNSSVGPLYSGCRLISLRSEKDGAATGVDAI CTHHLNPQSPGLDREQLYWQLSQMTNGIKELGPYTLDRNSLY VNGFTHRSSGLTTSTPWTSTVDLGTSGTPSPVPSPTTTGPLLVPF TLNFTITNLQYEENMGHPGSRKFNITESVLQGLLKPLFKSTSVG PLYSGCRLTLLRPEKDGVATRVDAICTHRPDPKIPGLDRQQLY WELSQLTHSITELGPYTLDRDSLYVNGFTQRSSVPTTSTPGTFT VQPETSETPSSLPGPTATGPVLLPFTLNFTITNLQYEEDMRRPGS RKFNTTERVLQGLLMPLFKNTSVSSLYSGCRLTLLRPEKDGAA TRVDAVCTHRPDPKSPGLDRERLYWKLSQLTHGITELGPYTLD RHSLYVNGFTHQSSMTTTRTPDTSTMHLATSRTPASLSGPMTA SPLLVLFTINFTITNLRYEENMHHPGSRKFNTTERVLQGLLRPV FKNTSVGPLYSGCRLTLLRPKKDGAATKVDAICTYRPDPKSPG LDREQLYWELSQLTHSITELGPYTLDRDSLYVNGFTQRSSVPTT SIPGTPTVDLGTSGTPVSKPGPSAASPLLVLFTLNFTITNLRYEE NMQHPGSRKFNTTERVLQGLLRSLFKSTSVGPLYSGCRLTLLR PEKDGTATGVDAICTHHPDPKSPRLDREQLYWELSQLTHNITE LGPYALDNDSLFVNGFTHRSSVSTTSTPGTPTVYLGASKTPASI FGPSAASHLLILFTLNFTITNLRYEENMWPGSRKFNTTERVLQG LLRPLFKNTSVGPLYSGCRLTLLRPEKDGEATGVDAICTHRPDP TGPGLDREQLYLELSQLTHSITELGPYTLDRDSLYVNGFTHRSS VPTTSTGVVSEEPFTLNFTINNLRYMADMGQPGSLKFNITDNV MQHLLSPLFQRSSLGARYTGCRVIALRSVKNGAETRVDLLCTY LQPLSGPGLPIKQVFHELSQQTHGITRLGPYSLDKDSLYLNGYN EPGPDEPPTTPKPATTFLPPLSEATTAMGYHLKTLTLNFTISNLQ YSPDMGKGSATFNSTEGVLQHLLRPLFQKSSMGPFYLGCQLIS LRPEKDGAATGVDTTCTYHPDPVGPGLDIQQLYWELSQLTHG VTQLGFYVLDRDSLFINGYAPQNLSIRGEYQINFHIVNWNLSNP DPTSSEYITLLRDIQDKVTTLYKGSQLHDTFRFCLVTNLTMDSV LVTVKALFSSNLDPSLVEQVFLDKTLNASFHWLGSTYQLVDIH VTEMESSVYQPTSSSSTQHFYLNFTITNLPYSQDKAQPGTTNYQ RNKRNIEDALNQLFRNSSIKSYFSDCQVSTFRSVPNRHHTGVDS LCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVD GYSPNRNEPLTGNSDLPFWAVILIGLAGLLGVITCLICGVLVTT RRRKKEGEYNVQQQCPGYYQSHLDLEDLQ
137	Immature Human MUC16	AGCGTTGCACAATTCCCCCAACCTCCATACATACGGCAGCT CTTCTAGACACAGGTTTTCCCAGGTCAAATGCGGGGACCCC AGCCATATCTCCCACCCTGAGAAATTTTGGAGTTTCAGGGA

	nucleic acid sequence (NM_024690.2)	GCTCAGAAGCTCTGCAGAGGCCACCCTCTCTGAGGGGATTC TTCTTAGACCTCCATCCAGAGGCAAATGTTGACCTGTCCATG CTGAAACCCTCAGGCCTTCCTGGGTCATCTTCTCCCACCCGC TCCTTGATGACAGGGAGCAGGAGCACTAAAGCCACACCAG AAATGGATTCAGGACTGACAGGAGCCACCTTGTCACCTAAG ACATCTACAGGTGCAATCGTGGTGACAGAACATACTCTGCC CTTTACTTCCCCAGATAAGACCTTGGCCAGTCCTACATCTTC GGTTGTGGGAAGAACCACCCAGTCTTTGGGGGTGATGTCCT CTGCTCTCCCTGAGTCAACCTCTAGAGGAATGACACACTCC GAGCAAAGAACCAGCCCATCGCTGAGTCCCCAGGTCAATGG AACTCCCTCTAGGAACTACCCTGCTACAAGCATGGTTTCAG GATTGAGTTCCCCAAGGACCAGGACCAGTTCCACAGAAGGA AATTTTACCAAAGAAGCATCTACATACACACTCACTGTAGA GACCACAAGTGGCCCAGTCACTGAGAAGTACACAGTCCCCA CTGAGACCTCAACAACTGAAGGTGACAGCACAGAGACCCC CTGGGACACAAGATATATTCCTGTAAAAATCACATCTCCAA TGAAAACATTTGCAGATTCAACTGCATCCAAGGAAAATGCC CCAGTGTCTATGACTCCAGCTGAGACCACAGTTACTGACTC ACATACTCCAGGAAGGACAAACCCATCATTTGGGACACTTT ATTCTTCCTTCCTTGACCTATCACCTAAAGGGACCCCAAATT CCAGAGGTGAAACAAGCCTGGAACTGATTCTATCAACCACT GGATATCCCTTCTCCTCTCCTGAACCTGGCTCTGCAGGACAC AGCAGAATAAGTACCAGTGCGCCTTTGTCATCATCTGCTTC AGTTCTCGATAATAAAATATCAGAGACCAGCATATTCTCAG GCCAGAGTCTCACCTCCCCTCTGTCTCCTGGGGTGCCCGAG GCCAGAGCCAGCACAATGCCCAACTCAGCTATCCCTTTTTC CATGACACTAAGCAATGCAGAAACAAGTGCCGAAAGGGTC AGAAGCACAATTTCCTCTCTGGGGACTCCATCAATATCCAC AAAGCAGACAGCAGAGACTATCCTTACCTTCCATGCCTTCG CTGAGACCATGGATATACCCAGCACCCACATAGCCAAGACT TTGGCTTCAGAATGGTTGGGAAGTCCAGGTACCCTTGGTGG CACCAGCACTTCAGCGCTGACAACCACATCTCCATCTACCA CTTTAGTCTCAGAGGAGACCAACACCCATCACTCCACGAGT GGAAAGGAAACAGAAGGAACTTTGAATACATCTATGACTCC ACTTGAGACCTCTGCTCCTGGAGAAGAGTCCGAAATGACTG CCACCTTGGTCCCCACTCTAGGTTTTACAACTCTTGACAGCA AGATCAGAAGTCCATCTCAGGTCTCTTCATCCCACCCAACA AGAGAGCTCAGAACCACAGGCAGCACCTCTGGGAGGCAGA GTTCCAGCACAGCTGCCCACGGGAGCTCTGACATCCTGAGG GCAACCACTTCCAGCACCTCAAAAGCATCATCATGGACCAG TGAAAGCACAGCTCAGCAATTTAGTGAACCCCAGCACACAC AGTGGGTGGAGACAAGTCCTAGCATGAAAACAGAGAGACC CCCAGCATCAACCAGTGTGGCAGCCCCTATCACCACTTCTG TTCCCTCAGTGGTCTCTGGCTTCACCACCCTGAAGACCAGCT CCACAAAAGGGATTTGGCTTGAAGAAACATCTGCAGACACA CTCATCGGAGAATCCACAGCTGGCCCAACCACCCATCAGTT

		TGCTGTTCCCACTGGGATTTCAATGACAGGAGGCAGCAGCA CCAGGGGAAGCCAGGGCACAACCCACCTACTCACCAGAGC CACAGCATCATCTGAGACATCCGCAGATTTGACTCTGGCCA CGAACGGTGTCCCAGTCTCCGTGTCTCCAGCAGTGAGCAAG ACGGCTGCTGGCTCAAGTCCTCCAGGAGGGACAAAGCCATC ATATACAATGGTTTCTTCTGTCATCCCTGAGACATCATCTCT ACAGTCCTCAGCTTTCAGGGAAGGAACCAGCCTGGGACTGA CTCCATTAAACACTAGACATCCCTTCTCTTCCCCTGAACCAG ACTCTGCAGGACACACCAAGATAAGCACCAGCATTCCTCTG TTGTCATCTGCTTCAGTTCTTGAGGATAAAGTGTCAGCGACC AGCACATTCTCACACCACAAAGCCACCTCATCTATTACCAC AGGGACTCCTGAAATCTCAACAAAGACAAAGCCCAGCTCA GCCGTTCTTTCCTCCATGACCCTAAGCAATGCAGCAACAAG TCCTGAAAGAGTCAGAAATGCAACTTCCCCTCTGACTCATC CATCTCCATCAGGGGAAGAGACAGCAGGGAGTGTCCTCACT CTCAGCACCTCTGCTGAGACTACAGACTCACCTAACATCCA CCCAACTGGGACACTGACTTCAGAATCGTCAGAGAGTCCTA GCACTCTCAGCCTCCCAAGTGTCTCTGGAGTCAAAACCACA TTTTCTTCATCTACTCCTTCCACTCATCTATTTACTAGTGGAG AAGAAACAGAGGAAACTTCGAATCCATCTGTGTCTCAACCT GAGACTTCTGTTTCCAGAGTAAGGACCACCTTGGCCAGCAC CTCTGTCCCTACCCCAGTATTCCCCACCATGGACACCTGGCC TACACGTTCAGCTCAGTTCTCTTCATCCCACCTAGTGAGTGA GCTCAGAGCTACGAGCAGTACCTCAGTTACAAACTCAACTG GTTCAGCTCTTCCTAAAATATCTCACCTCACTGGGACGGCA ACAATGTCACAGACCAATAGAGACACGTTTAATGACTCTGC TGCACCCCAAAGCACAACTTGGCCAGAGACTAGTCCCAGAT TCAAGACAGGGTTACCTTCAGCAACAACCACTGTTTCAACC TCTGCCACTTCTCTCTCTGCTACTGTAATGGTCTCTAAATTC ACTTCTCCAGCAACTAGTTCCATGGAAGCAACTTCTATCAG GGAACCATCAACAACCATCCTCACAACAGAGACCACGAAT GGCCCAGGCTCTATGGCTGTGGCTTCTACCAACATCCCAATT GGAAAGGGCTACATTACTGAAGGAAGATTGGACACAAGCC ATCTGCCCATTGGAACCACAGCTTCCTCTGAGACATCTATG GATTTTACCATGGCCAAAGAAAGTGTCTCAATGTCAGTATC TCCATCTCAGTCCATGGATGCTGCTGGCTCAAGCACTCCAG GAAGGACAAGCCAATTCGTTGACACATTTTCTGATGATGTC TATCATTTAACATCCAGAGAAATTACAATACCTAGAGATGG AACAAGCTCAGCTCTGACTCCACAAATGACTGCAACTCACC CTCCATCTCCTGATCCTGGCTCTGCTAGAAGCACCTGGCTTG GCATCTTGTCCTCATCTCCTTCTTCTCCTACTCCCAAAGTCA CAATGAGCTCCACATTTTCAACTCAGAGAGTCACCACAAGC ATGATAATGGACACAGTTGAAACTAGTCGGTGGAACATGCC CAACTTACCTTCCACGACTTCCTTGACACCAAGTAATATTCC AACAAGTGGTGCCATAGGAAAAAGCACCCTGGTTCCCTTGG ACACTCCATCTCCAGCCACATCATTGGAGGCATCAGAAGGG

		GGACTTCCAACCCTCAGCACCTACCCTGAATCAACAAACAC ACCCAGCATCCACCTCGGAGCACACGCTAGTTCAGAAAGTC CAAGCACCATCAAACTTACCATGGCTTCAGTAGTAAAACCT GGCTCTTACACACCTCTCACCTTCCCCTCAATAGAGACCCAC ATTCATGTATCAACAGCCAGAATGGCTTACTCTTCTGGGTCT TCACCTGAGATGACAGCTCCTGGAGAGACTAACACTGGTAG TACCTGGGACCCCACCACCTACATCACCACTACGGATCCTA AGGATACAAGTTCAGCTCAGGTCTCTACACCCCACTCAGTG AGGACACTCAGAACCACAGAAAACCATCCAAAGACAGAGT CCGCCACCCCAGCTGCTTACTCTGGAAGTCCTAAAATCTCA AGTTCACCCAATCTCACCAGTCCGGCCACAAAAGCATGGAC CATCACAGACACAACTGAACACTCCACTCAATTACATTACA CAAAATTGGCAGAAAAATCATCTGGATTTGAGACACAGTCA GCTCCAGGACCTGTCTCTGTAGTAATCCCTACCTCCCCTACC ATTGGAAGCAGCACATTGGAACTAACTTCTGATGTCCCAGG GGAACCCCTGGTCCTTGCTCCCAGTGAGCAGACCACAATCA CTCTCCCCATGGCAACATGGCTGAGTACCAGTTTGACAGAG GAAATGGCTTCAACAGACCTTGATATTTCAAGTCCAAGTTC ACCCATGAGTACATTTGCTATTTTTCCACCTATGTCCACACC TTCTCATGAACTTTCAAAGTCAGAGGCAGATACCAGTGCCA TTAGAAATACAGATTCAACAACGTTGGATCAGCACCTAGGA ATCAGGAGTTTGGGCAGAACTGGGGACTTAACAACTGTTCC TATCACCCCACTGACAACCACGTGGACCAGTGTGATTGAAC ACTCAACACAAGCACAGGACACCCTTTCTGCAACGATGAGT CCTACTCACGTGACACAGTCACTCAAAGATCAAACATCTAT ACCAGCCTCAGCATCCCCTTCCCATCTTACTGAAGTCTACCC TGAGCTCGGGACACAAGGGAGAAGCTCCTCTGAGGCAACC ACTTTTTGGAAACCATCTACAGACACACTGTCCAGAGAGAT TGAGACTGGCCCAACAAACATTCAATCCACTCCACCCATGG ACAACACAACAACAGGGAGCAGTAGTAGTGGAGTCACCCT GGGCATAGCCCACCTTCCCATAGGAACATCCTCCCCAGCTG AGACATCCACAAACATGGCACTGGAAAGAAGAAGTTCTAC AGCCACTGTCTCTATGGCTGGGACAATGGGACTCCTTGTTA CTAGTGCTCCAGGAAGAAGCATCAGCCAGTCATTAGGAAGA GTTTCCTCTGTCCTTTCTGAGTCAACTACTGAAGGAGTCACA GATTCTAGTAAGGGAAGCAGCCCAAGGCTGAACACACAGG GAAATACAGCTCTCTCCTCCTCTCTTGAACCCAGCTATGCTG AAGGAAGCCAGATGAGCACAAGCATCCCTCTAACCTCATCT CCTACAACTCCTGATGTGGAATTCATAGGGGGCAGCACATT TTGGACCAAGGAGGTCACCACAGTTATGACCTCAGACATCT CCAAGTCTTCAGCAAGGACAGAGTCCAGCTCAGCTACCCTT ATGTCCACAGCTTTGGGAAGCACTGAAAATACAGGAAAAG AAAAACTCAGAACTGCCTCTATGGATCTTCCATCTCCAACTC CATCAATGGAGGTGACACCATGGATTTCTCTCACTCTCAGT AATGCCCCCAATACCACAGATTCACTTGACCTCAGCCATGG GGTGCACACCAGCTCTGCAGGGACTTTGGCCACTGACAGGT

		CATTGAATACTGGTGTCACTAGAGCCTCCAGATTGGAAAAC GGCTCTGATACCTCTTCTAAGTCCCTGTCTATGGGAAACAGC ACTCACACTTCCATGACTTACACAGAGAAGAGTGAAGTGTC TTCTTCAATCCATCCCCGACCTGAGACCTCAGCTCCTGGAGC AGAGACCACTTTGACTTCCACTCCTGGAAACAGGGCCATAA GCTTAACATTGCCTTTTTCATCCATTCCAGTGGAAGAAGTCA TTTCTACAGGCATAACCTCAGGACCAGACATCAACTCAGCA CCCATGACACATTCTCCCATCACCCCACCAACAATTGTATG GACCAGTACAGGCACAATTGAACAGTCCACTCAACCACTAC ATGCAGTTTCTTCAGAAAAAGTTTCTGTGCAGACACAGTCA ACTCCATATGTCAACTCTGTGGCAGTGTCTGCTTCCCCTACC CATGAGAATTCAGTCTCTTCTGGAAGCAGCACATCCTCTCC ATATTCCTCAGCCTCACTTGAATCCTTGGATTCCACAATCAG TAGGAGGAATGCAATCACTTCCTGGCTATGGGACCTCACTA CATCTCTCCCCACTACAACTTGGCCAAGTACTAGTTTATCTG AGGCACTGTCCTCAGGCCATTCTGGGGTTTCAAACCCAAGT TCAACTACGACTGAATTTCCACTCTTTTCAGCTGCATCCACA TCTGCTGCTAAGCAAAGAAATCCAGAAACAGAGACCCATG GTCCCCAGAATACAGCCGCGAGTACTTTGAACACTGATGCA TCCTCGGTCACAGGTCTTTCTGAGACTCCTGTGGGGGCAAG TATCAGCTCTGAAGTCCCTCTTCCAATGGCCATAACTTCTAG ATCAGATGTTTCTGGCCTTACATCTGAGAGTACTGCTAACCC GAGTTTAGGCACAGCCTCTTCAGCAGGGACCAAATTAACTA GGACAATATCCCTGCCCACTTCAGAGTCTTTGGTTTCCTTTA GAATGAACAAGGATCCATGGACAGTGTCAATCCCTTTGGGG TCCCATCCAACTACTAATACAGAAACAAGCATCCCAGTAAA CAGCGCAGGTCCACCTGGCTTGTCCACAGTAGCATCAGATG TAATTGACACACCTTCAGATGGGGCTGAGAGTATTCCCACT GTCTCCTTTTCCCCCTCCCCTGATACTGAAGTGACAACTATC TCACATTTCCCAGAAAAGACAACTCATTCATTTAGAACCAT TTCATCTCTCACTCATGAGTTGACTTCAAGAGTGACACCTAT TCCTGGGGATTGGATGAGTTCAGCTATGTCTACAAAGCCCA CAGGAGCCAGTCCCTCCATTACACTGGGAGAGAGAAGGAC AATCACCTCTGCTGCTCCAACCACTTCCCCCATAGTTCTCAC TGCTAGTTTCACAGAGACCAGCACAGTTTCACTGGATAATG AAACTACAGTAAAAACCTCAGATATCCTTGACGCACGGAAA ACAAATGAGCTCCCCTCAGATAGCAGTTCTTCTTCTGATCTG ATCAACACCTCCATAGCTTCTTCAACTATGGATGTCACTAAA ACAGCCTCCATCAGTCCCACTAGCATCTCAGGAATGACAGC AAGTTCCTCCCCATCTCTCTTCTCTTCAGATAGACCCCAGGT TCCCACATCTACAACAGAGACAAATACAGCCACCTCTCCAT CTGTTTCCAGTAACACCTATTCTCTTGATGGGGGCTCCAATG TGGGTGGCACTCCATCCACTTTACCACCCTTTACAATCACCC ACCCTGTCGAGACAAGCTCGGCCCTATTAGCCTGGTCTAGA CCAGTAAGAACTTTCAGCACCATGGTCAGCACTGACACTGC CTCCGGAGAAAATCCTACCTCTAGCAATTCTGTGGTGACTTC

		TGTTCCAGCACCAGGTACATGGACCAGTGTAGGCAGTACTA CTGACTTACCTGCCATGGGCTTTCTCAAGACAAGTCCTGCA GGAGAGGCACACTCACTTCTAGCATCAACTATTGAACCAGC CACTGCCTTCACTCCCCATCTCTCAGCAGCAGTGGTCACTGG ATCCAGTGCTACATCAGAAGCCAGTCTTCTCACTACGAGTG AAAGCAAAGCCATTCATTCTTCACCACAGACCCCAACTACA CCCACCTCTGGAGCAAACTGGGAAACTTCAGCTACTCCTGA GAGCCTTTTGGTAGTCACTGAGACTTCAGACACAACACTTA CCTCAAAGATTTTGGTCACAGATACCATCTTGTTTTCAACTG TGTCCACGCCACCTTCTAAATTTCCAAGTACGGGGACTCTGT CTGGAGCTTCCTTCCCTACTTTACTCCCGGACACTCCAGCCA TCCCTCTCACTGCCACTGAGCCAACAAGTTCATTAGCTACAT CCTTTGATTCCACCCCACTGGTGACTATAGCTTCGGATAGTC TTGGCACAGTCCCAGAGACTACCCTGACCATGTCAGAGACC TCAAATGGTGATGCACTGGTTCTTAAGACAGTAAGTAACCC AGATAGGAGCATCCCTGGAATCACTATCCAAGGAGTAACAG AAAGTCCACTCCATCCTTCTTCCACTTCCCCCTCTAAGATTG TTGCTCCACGGAATACAACCTATGAAGGTTCGATCACAGTG GCACTTTCTACTTTGCCTGCGGGAACTACTGGTTCCCTTGTA TTCAGTCAGAGTTCTGAAAACTCAGAGACAACGGCTTTGGT AGACTCATCAGCTGGGCTTGAGAGGGCATCTGTGATGCCAC TAACCACAGGAAGCCAGGGTATGGCTAGCTCTGGAGGAATC AGAAGTGGGTCCACTCACTCAACTGGAACCAAAACATTTTC TTCTCTCCCTCTGACCATGAACCCAGGTGAGGTTACAGCCAT GTCTGAAATCACCACGAACAGACTGACAGCTACTCAATCAA CAGCACCCAAAGGGATACCTGTGAAGCCCACCAGTGCTGAG TCAGGCCTCCTAACACCTGTCTCTGCCTCCTCAAGCCCATCA AAGGCCTTTGCCTCACTGACTACAGCTCCCCCAACTTGGGG GATCCCACAGTCTACCTTGACATTTGAGTTTTCTGAGGTCCC AAGTTTGGATACTAAGTCCGCTTCTTTACCAACTCCTGGACA GTCCCTGAACACCATTCCAGACTCAGATGCAAGCACAGCAT CTTCCTCACTGTCCAAGTCTCCAGAAAAAAACCCAAGGGCA AGGATGATGACTTCCACAAAGGCCATAAGTGCAAGCTCATT TCAATCAACAGGTTTTACTGAAACCCCTGAGGGATCTGCCT CCCCTTCTATGGCAGGGCATGAACCCAGAGTCCCCACTTCA GGAACAGGGGACCCTAGATATGCCTCAGAGAGCATGTCTTA TCCAGACCCAAGCAAGGCATCATCAGCTATGACATCGACCT CTCTTGCATCAAAACTCACAACTCTCTTCAGCACAGGTCAA GCAGCAAGGTCTGGTTCTAGTTCCTCTCCCATAAGCCTATCC ACTGAGAAAGAAACAAGCTTCCTTTCCCCCACTGCATCCAC CTCCAGAAAGACTTCACTATTTCTTGGGCCTTCCATGGCAAG GCAGCCCAACATATTGGTGCATCTTCAGACTTCAGCTCTGA CACTTTCTCCAACATCCACTCTAAATATGTCCCAGGAGGAG CCTCCTGAGTTAACCTCAAGCCAGACCATTGCAGAAGAAGA GGGAACAACAGCTGAAACACAGACGTTAACCTTCACACCAT CTGAGACCCCAACATCCTTGTTACCTGTCTCTTCTCCCACAG

		AACCCACAGCCAGAAGAAAGAGTTCTCCAGAAACATGGGC AAGCTCTATTTCAGTTCCTGCCAAGACCTCCTTGGTTGAAAC AACTGATGGAACGCTAGTGACCACCATAAAGATGTCAAGCC AGGCAGCACAAGGAAATTCCACGTGGCCTGCCCCAGCAGA GGAGACGGGGAGCAGTCCAGCAGGCACATCCCCAGGAAGC CCAGAAATGTCTACCACTCTCAAAATCATGAGCTCCAAGGA ACCCAGCATCAGCCCAGAGATCAGGTCCACTGTGAGAAATT CTCCTTGGAAGACTCCAGAAACAACTGTTCCCATGGAGACC ACAGTGGAACCAGTCACCCTTCAGTCCACAGCCCTAGGAAG TGGCAGCACCAGCATCTCTCACCTGCCCACAGGAACCACAT CACCAACCAAGTCACCAACAGAAAATATGTTGGCTACAGAA AGGGTCTCCCTCTCCCCATCCCCACCTGAGGCTTGGACCAA CCTTTATTCTGGAACTCCAGGAGGGACCAGGCAGTCACTGG CCACAATGTCCTCTGTCTCCCTAGAGTCACCAACTGCTAGA AGCATCACAGGGACTGGTCAGCAAAGCAGTCCAGAACTGG TTTCAAAGACAACTGGAATGGAATTCTCTATGTGGCATGGC TCTACTGGAGGGACCACAGGGGACACACATGTCTCTCTGAG CACATCTTCCAATATCCTTGAAGACCCTGTAACCAGCCCAA ACTCTGTGAGCTCATTGACAGATAAATCCAAACATAAAACC GAGACATGGGTAAGCACCACAGCCATTCCCTCCACTGTCCT GAATAATAAGATAATGGCAGCTGAACAACAGACAAGTCGA TCTGTGGATGAGGCTTATTCATCAACTAGTTCTTGGTCAGAT CAGACATCTGGGAGTGACATCACCCTTGGTGCATCTCCTGA TGTCACAAACACATTATACATCACCTCCACAGCACAAACCA CCTCACTAGTGTCTCTGCCCTCTGGAGACCAAGGCATTACA AGCCTCACCAATCCCTCAGGAGGAAAAACAAGCTCTGCGTC ATCTGTCACATCTCCTTCAATAGGGCTTGAGACTCTGAGGG CCAATGTAAGTGCAGTGAAAAGTGACATTGCCCCTACTGCT GGGCATCTATCTCAGACTTCATCTCCTGCGGAAGTGAGCAT CCTGGACGTAACCACAGCTCCTACTCCAGGTATCTCCACCA CCATCACCACCATGGGAACCAACTCAATCTCAACTACCACA CCCAACCCAGAAGTGGGTATGAGTACCATGGACAGCACCCC GGCCACAGAGAGGCGCACAACTTCTACAGAACACCCTTCCA CCTGGTCTTCCACAGCTGCATCAGATTCCTGGACTGTCACAG ACATGACTTCAAACTTGAAAGTTGCAAGATCTCCTGGAACA ATTTCCACAATGCATACAACTTCATTCTTAGCCTCAAGCACT GAATTAGACTCCATGTCTACTCCCCATGGCCGTATAACTGTC ATTGGAACCAGCCTGGTCACTCCATCCTCTGATGCTTCAGCT GTAAAGACAGAGACCAGTACAAGTGAAAGAACATTGAGTC CTTCAGACACAACTGCATCTACTCCCATCTCAACTTTTTCTC GTGTCCAGAGGATGAGCATCTCAGTTCCTGACATTTTAAGT ACAAGTTGGACTCCCAGTAGTACAGAAGCAGAAGATGTGCC TGTTTCAATGGTTTCTACAGATCATGCTAGTACAAAGACTG ACCCAAATACGCCCCTGTCCACTTTTCTGTTTGATTCTCTGT CCACTCTTGACTGGGACACTGGGAGATCTCTGTCATCAGCC ACAGCCACTACCTCAGCTCCTCAGGGGGCCACAACTCCCCA

		GGAACTCACTTTGGAAACCATGATCAGCCCAGCTACCTCAC AGTTGCCCTTCTCTATAGGGCACATTACAAGTGCAGTCACA CCAGCTGCAATGGCAAGGAGCTCTGGAGTTACTTTTTCAAG ACCAGATCCCACAAGCAAAAAGGCAGAGCAGACTTCCACT CAGCTTCCCACCACCACTTCTGCACATCCAGGGCAGGTGCC CAGATCAGCAGCAACAACTCTGGATGTGATCCCACACACAG CAAAAACTCCAGATGCAACTTTTCAGAGACAAGGGCAGAC AGCTCTTACAACAGAGGCAAGAGCTACATCTGACTCCTGGA ATGAGAAAGAAAAATCAACCCCAAGTGCACCTTGGATCACT GAGATGATGAATTCTGTCTCAGAAGATACCATCAAGGAGGT TACCAGCTCCTCCAGTGTATTAAGGACCCTGAATACGCTGG ACATAAACTTGGAATCTGGGACGACTTCATCCCCAAGTTGG AAAAGCAGCCCATATGAGAGAATTGCCCCTTCTGAGTCCAC CACAGACAAAGAGGCAATTCACCCTTCTACAAACACAGTAG AGACCACAGGCTGGGTCACAAGTTCCGAACATGCTTCTCAT TCCACTATCCCAGCCCACTCAGCGTCATCCAAACTCACATCT CCAGTGGTTACAACCTCCACCAGGGAACAAGCAATAGTTTC TATGTCAACAACCACATGGCCAGAGTCTACAAGGGCTAGAA CAGAGCCTAATTCCTTCTTGACTATTGAACTGAGGGACGTC AGCCCTTACATGGACACCAGCTCAACCACACAAACAAGTAT TATCTCTTCCCCAGGTTCCACTGCGATCACCAAGGGGCCTA GAACAGAAATTACCTCCTCTAAGAGAATATCCAGCTCATTC CTTGCCCAGTCTATGAGGTCGTCAGACAGCCCCTCAGAAGC CATCACCAGGCTGTCTAACTTTCCTGCCATGACAGAATCTG GAGGAATGATCCTTGCTATGCAAACAAGTCCACCTGGCGCT ACATCACTAAGTGCACCTACTTTGGATACATCAGCCACAGC CTCCTGGACAGGGACTCCACTGGCTACGACTCAGAGATTTA CATACTCAGAGAAGACCACTCTCTTTAGCAAAGGTCCTGAG GATACATCACAGCCAAGCCCTCCCTCTGTGGAAGAAACCAG CTCTTCCTCTTCCCTGGTACCTATCCATGCTACAACCTCGCC TTCCAATATTTTGTTGACATCACAAGGGCACAGTCCCTCCTC TACTCCACCTGTGACCTCAGTTTTCTTGTCTGAGACCTCTGG CCTGGGGAAGACCACAGACATGTCGAGGATAAGCTTGGAA CCTGGCACAAGTTTACCTCCCAATTTGAGCAGTACAGCAGG TGAGGCGTTATCCACTTATGAAGCCTCCAGAGATACAAAGG CAATTCATCATTCTGCAGACACAGCAGTGACGAATATGGAG GCAACCAGTTCTGAATATTCTCCTATCCCAGGCCATACAAA GCCATCCAAAGCCACATCTCCATTGGTTACCTCCCACATCAT GGGGGACATCACTTCTTCCACATCAGTATTTGGCTCCTCCGA GACCACAGAGATTGAGACAGTGTCCTCTGTGAACCAGGGAC TTCAGGAGAGAAGCACATCCCAGGTGGCCAGCTCTGCTACA GAGACAAGCACTGTCATTACCCATGTGTCTAGTGGTGATGC TACTACTCATGTCACCAAGACACAAGCCACTTTCTCTAGCG GAACATCCATCTCAAGCCCTCATCAGTTTATAACTTCTACCA ACACATTTACAGATGTGAGCACCAACCCCTCCACCTCTCTG ATAATGACAGAATCTTCAGGAGTGACCATCACCACCCAAAC

		AGGTCCTACTGGAGCTGCAACACAGGGTCCATATCTCTTGG ACACATCAACCATGCCTTACTTGACAGAGACTCCATTAGCT GTGACTCCAGATTTTATGCAATCAGAGAAGACCACTCTCAT AAGCAAAGGTCCCAAGGATGTGTCCTGGACAAGCCCTCCCT CTGTGGCAGAAACCAGCTATCCCTCTTCCCTGACACCTTTCT TGGTCACAACCATACCTCCTGCCACTTCCACGTTACAAGGG CAACATACATCCTCTCCTGTTTCTGCGACTTCAGTTCTTACC TCTGGACTGGTGAAGACCACAGATATGTTGAACACAAGCAT GGAACCTGTGACCAATTCACCTCAAAATTTGAACAATCCAT CAAATGAGATACTGGCCACTTTGGCAGCCACCACAGATATA GAGACTATTCATCCTTCCATAAACAAAGCAGTGACCAATAT GGGGACTGCCAGTTCAGCACATGTACTGCATTCCACTCTCC CAGTCAGCTCAGAACCATCTACAGCCACATCTCCAATGGTT CCTGCCTCCAGCATGGGGGACGCTCTTGCTTCTATATCAATA CCTGGTTCTGAGACCACAGACATTGAGGGAGAGCCAACATC CTCCCTGACTGCTGGACGAAAAGAGAACAGCACCCTCCAGG AGATGAACTCAACTACAGAGTCAAACATCATCCTCTCCAAT GTGTCTGTGGGGGCTATTACTGAAGCCACAAAAATGGAAGT CCCCTCTTTTGATGCAACATTCATACCAACTCCTGCTCAGTC AACAAAGTTCCCAGATATTTTCTCAGTAGCCAGCAGTAGAC TTTCAAACTCTCCTCCCATGACAATATCTACCCACATGACCA CCACCCAGACAGGGTCTTCTGGAGCTACATCAAAGATTCCA CTTGCCTTAGACACATCAACCTTGGAAACCTCAGCAGGGAC TCCATCAGTGGTGACTGAGGGGTTTGCCCACTCAAAAATAA CCACTGCAATGAACAATGATGTCAAGGACGTGTCACAGACA AACCCTCCCTTTCAGGATGAAGCCAGCTCTCCCTCTTCTCAA GCACCTGTCCTTGTCACAACCTTACCTTCTTCTGTTGCTTTCA CACCGCAATGGCACAGTACCTCCTCTCCTGTTTCTATGTCCT CAGTTCTTACTTCTTCACTGGTAAAGACCGCAGGCAAGGTG GATACAAGCTTAGAAACAGTGACCAGTTCACCTCAAAGTAT GAGCAACACTTTGGATGACATATCGGTCACTTCAGCAGCCA CCACAGATATAGAGACAACGCATCCTTCCATAAACACAGTA GTTACCAATGTGGGGACCACCGGTTCAGCATTTGAATCACA TTCTACTGTCTCAGCTTACCCAGAGCCATCTAAAGTCACATC TCCAAATGTTACCACCTCCACCATGGAAGACACCACAATTT CCAGATCAATACCTAAATCCTCTAAGACTACAAGAACTGAG ACTGAGACAACTTCCTCCCTGACTCCTAAACTGAGGGAGAC CAGCATCTCCCAGGAGATCACCTCGTCCACAGAGACAAGCA CTGTTCCTTACAAAGAGCTCACTGGTGCCACTACCGAGGTA TCCAGGACAGATGTCACTTCCTCTAGCAGTACATCCTTCCCT GGCCCTGATCAGTCCACAGTGTCACTAGACATCTCCACAGA AACCAACACCAGGCTGTCTACCTCCCCAATAATGACAGAAT CTGCAGAAATAACCATCACCACCCAAACAGGTCCTCATGGG GCTACATCACAGGATACTTTTACCATGGACCCATCAAATAC AACCCCCCAGGCAGGGATCCACTCAGCTATGACTCATGGAT TTTCACAATTGGATGTGACCACTCTTATGAGCAGAATTCCAC

		AGGATGTATCATGGACAAGTCCTCCCTCTGTGGATAAAACC AGCTCCCCCTCTTCCTTTCTGTCCTCACCTGCAATGACCACA CCTTCCCTGATTTCTTCTACCTTACCAGAGGATAAGCTCTCC TCTCCTATGACTTCACTTCTCACCTCTGGCCTAGTGAAGATT ACAGACATATTACGTACACGCTTGGAACCTGTGACCAGCTC ACTTCCAAATTTCAGCAGCACCTCAGATAAGATACTGGCCA CTTCTAAAGACAGTAAAGACACAAAGGAAATTTTTCCTTCT ATAAACACAGAAGAGACCAATGTGAAAGCCAACAACTCTG GACATGAATCCCATTCCCCTGCACTGGCTGACTCAGAGACA CCCAAAGCCACAACTCAAATGGTTATCACCACCACTGTGGG AGATCCAGCTCCTTCCACATCAATGCCAGTGCATGGTTCCTC TGAGACTACAAACATTAAGAGAGAGCCAACATATTTCTTGA CTCCTAGACTGAGAGAGACCAGTACCTCTCAGGAGTCCAGC TTTCCCACGGACACAAGTTTTCTACTTTCCAAAGTCCCCACT GGTACTATTACTGAGGTCTCCAGTACAGGGGTCAACTCTTCT AGCAAAATTTCCACCCCAGACCATGATAAGTCCACAGTGCC ACCTGACACCTTCACAGGAGAGATCCCCAGGGTCTTCACCT CCTCTATTAAGACAAAATCTGCAGAAATGACGATCACCACC CAAGCAAGTCCTCCTGAGTCTGCATCGCACAGTACCCTTCC CTTGGACACATCAACCACACTTTCCCAGGGAGGGACTCATT CAACTGTGACTCAGGGATTCCCATACTCAGAGGTGACCACT CTCATGGGCATGGGTCCTGGGAATGTGTCATGGATGACAAC TCCCCCTGTGGAAGAAACCAGCTCTGTGTCTTCCCTGATGTC TTCACCTGCCATGACATCCCCTTCTCCTGTTTCCTCCACATC ACCACAGAGCATCCCCTCCTCTCCTCTTCCTGTGACTGCACT TCCTACTTCTGTTCTGGTGACAACCACAGATGTGTTGGGCAC AACAAGCCCAGAGTCTGTAACCAGTTCACCTCCAAATTTGA GCAGCATCACTCATGAGAGACCGGCCACTTACAAAGACACT GCACACACAGAAGCCGCCATGCATCATTCCACAAACACCGC AGTGACCAATGTAGGGACTTCCGGGTCTGGACATAAATCAC AATCCTCTGTCCTAGCTGACTCAGAGACATCGAAAGCCACA CCTCTGATGAGTACCACCTCCACCCTGGGGGACACAAGTGT TTCCACATCAACTCCTAATATCTCTCAGACTAACCAAATTCA AACAGAGCCAACAGCATCCCTGAGCCCTAGACTGAGGGAG AGCAGCACGTCTGAGAAGACCAGCTCAACAACAGAGACAA ATACTGCCTTTTCTTATGTGCCCACAGGTGCTATTACTCAGG CCTCCAGAACAGAAATCTCCTCTAGCAGAACATCCATCTCA GACCTTGATCGGCCCACAATAGCACCCGACATCTCCACAGG AATGATCACCAGGCTCTTCACCTCCCCCATCATGACAAAAT CTGCAGAAATGACCGTCACCACTCAAACAACTACTCCTGGG GCTACATCACAGGGTATCCTTCCCTGGGACACATCAACCAC ACTTTTCCAGGGAGGGACTCATTCAACCGTGTCTCAGGGAT TCCCACACTCAGAGATAACCACTCTTCGGAGCAGAACCCCT GGAGATGTGTCATGGATGACAACTCCCCCTGTGGAAGAAAC CAGCTCTGGGTTTTCCCTGATGTCACCTTCCATGACATCCCC TTCTCCTGTTTCCTCCACATCACCAGAGAGCATCCCCTCCTC

		TCCTCTCCCTGTGACTGCACTTCTTACTTCTGTTCTGGTGAC AACCACAAATGTATTGGGCACAACAAGCCCAGAGCCCGTA ACGAGTTCACCTCCAAATTTAAGCAGCCCCACACAGGAGAG ACTGACCACTTACAAAGACACTGCGCACACAGAAGCCATGC ATGCTTCCATGCATACAAACACTGCAGTGGCCAACGTGGGG ACCTCCATTTCTGGACATGAATCACAATCTTCTGTCCCAGCT GATTCACACACATCCAAAGCCACATCTCCAATGGGTATCAC CTTCGCCATGGGGGATACAAGTGTTTCTACATCAACTCCTGC CTTCTTTGAGACTAGAATTCAGACTGAATCAACATCCTCTTT GATTCCTGGATTAAGGGACACCAGGACGTCTGAGGAGATCA ACACTGTGACAGAGACCAGCACTGTCCTTTCAGAAGTGCCC ACTACTACTACTACTGAGGTCTCCAGGACAGAAGTTATCAC TTCCAGCAGAACAACCATCTCAGGGCCTGATCATTCCAAAA TGTCACCCTACATCTCCACAGAAACCATCACCAGGCTCTCC ACTTTTCCTTTTGTAACAGGATCCACAGAAATGGCCATCACC AACCAAACAGGTCCTATAGGGACTATCTCACAGGCTACCCT TACCCTGGACACATCAAGCACAGCTTCCTGGGAAGGGACTC ACTCACCTGTGACTCAGAGATTTCCACACTCAGAGGAGACC ACTACTATGAGCAGAAGTACTAAGGGCGTGTCATGGCAAAG CCCTCCCTCTGTGGAAGAAACCAGTTCTCCTTCTTCCCCAGT GCCTTTACCTGCAATAACCTCACATTCATCTCTTTATTCCGC AGTATCAGGAAGTAGCCCCACTTCTGCTCTCCCTGTGACTTC CCTTCTCACCTCTGGCAGGAGGAAGACCATAGACATGTTGG ACACACACTCAGAACTTGTGACCAGCTCCTTACCAAGTGCA AGTAGCTTCTCAGGTGAGATACTCACTTCTGAAGCCTCCAC AAATACAGAGACAATTCACTTTTCAGAGAACACAGCAGAA ACCAATATGGGGACCACCAATTCTATGCATAAACTACATTC CTCTGTCTCAATCCACTCCCAGCCATCCGGACACACACCTCC AAAGGTTACTGGATCTATGATGGAGGACGCTATTGTTTCCA CATCAACACCTGGTTCTCCTGAGACTAAAAATGTTGACAGA GACTCAACATCCCCTCTGACTCCTGAACTGAAAGAGGACAG CACCGCCCTGGTGATGAACTCAACTACAGAGTCAAACACTG TTTTCTCCAGTGTGTCCCTGGATGCTGCTACTGAGGTCTCCA GGGCAGAAGTCACCTACTATGATCCTACATTCATGCCAGCT TCTGCTCAGTCAACAAAGTCCCCAGACATTTCACCTGAAGC CAGCAGCAGTCATTCTAACTCTCCTCCCTTGACAATATCTAC ACACAAGACCATCGCCACACAAACAGGTCCTTCTGGGGTGA CATCTCTTGGCCAACTGACCCTGGACACATCAACCATAGCC ACCTCAGCAGGAACTCCATCAGCCAGAACTCAGGATTTTGT AGATTCAGAAACAACCAGTGTCATGAACAATGATCTCAATG ATGTGTTGAAGACAAGCCCTTTCTCTGCAGAAGAAGCCAAC TCTCTCTCTTCTCAGGCACCTCTCCTTGTGACAACCTCACCT TCTCCTGTAACTTCCACATTGCAAGAGCACAGTACCTCCTCT CTTGTTTCTGTGACCTCAGTACCCACCCCTACACTGGCGAAG ATCACAGACATGGACACAAACTTAGAACCTGTGACTCGTTC ACCTCAAAATTTAAGGAACACCTTGGCCACTTCAGAAGCCA

		CCACAGATACACACACAATGCATCCTTCTATAAACACAGCA GTGGCCAATGTGGGGACCACCAGTTCACCAAATGAATTCTA TTTTACTGTCTCACCTGACTCAGACCCATATAAAGCCACATC CGCAGTAGTTATCACTTCCACCTCGGGGGACTCAATAGTTTC CACATCAATGCCTAGATCCTCTGCGATGAAAAAGATTGAGT CTGAGACAACTTTCTCCCTGATATTTAGACTGAGGGAGACT AGCACCTCCCAGAAAATTGGCTCATCCTCAGACACAAGCAC GGTCTTTGACAAAGCATTCACTGCTGCTACTACTGAGGTCTC CAGAACAGAACTCACCTCCTCTAGCAGAACATCCATCCAAG GCACTGAAAAGCCCACAATGTCACCGGACACCTCCACAAGA TCTGTCACCATGCTTTCTACTTTTGCTGGCCTGACAAAATCC GAAGAAAGGACCATTGCCACCCAAACAGGTCCTCATAGGG CGACATCACAGGGTACCCTTACCTGGGACACATCAATCACA ACCTCACAGGCAGGGACCCACTCAGCTATGACTCATGGATT TTCACAATTAGATTTGTCCACTCTTACGAGTAGAGTTCCTGA GTACATATCAGGGACAAGCCCACCCTCTGTGGAAAAAACCA GCTCTTCCTCTTCCCTTCTGTCTTTACCAGCAATAACCTCAC CGTCCCCTGTACCTACTACATTACCAGAAAGTAGGCCGTCTT CTCCTGTTCATCTGACTTCACTCCCCACCTCTGGCCTAGTGA AGACCACAGATATGCTGGCATCTGTGGCCAGTTTACCTCCA AACTTGGGCAGCACCTCACATAAGATACCGACTACTTCAGA AGACATTAAAGATACAGAGAAAATGTATCCTTCCACAAACA TAGCAGTAACCAATGTGGGGACCACCACTTCTGAAAAGGAA TCTTATTCGTCTGTCCCAGCCTACTCAGAACCACCCAAAGTC ACCTCTCCAATGGTTACCTCTTTCAACATAAGGGACACCATT GTTTCCACATCCATGCCTGGCTCCTCTGAGATTACAAGGATT GAGATGGAGTCAACATTCTCCCTGGCTCATGGGCTGAAGGG AACCAGCACCTCCCAGGACCCCATCGTATCCACAGAGAAAA GTGCTGTCCTTCACAAGTTGACCACTGGTGCTACTGAGACCT CTAGGACAGAAGTTGCCTCTTCTAGAAGAACATCCATTCCA GGCCCTGATCATTCCACAGAGTCACCAGACATCTCCACTGA AGTGATCCCCAGCCTGCCTATCTCCCTTGGCATTACAGAATC TTCAAATATGACCATCATCACTCGAACAGGTCCTCCTCTTGG CTCTACATCACAGGGCACATTTACCTTGGACACACCAACTA CATCCTCCAGGGCAGGAACACACTCGATGGCGACTCAGGAA TTTCCACACTCAGAAATGACCACTGTCATGAACAAGGACCC TGAGATTCTATCATGGACAATCCCTCCTTCTATAGAGAAAA CCAGCTTCTCCTCTTCCCTGATGCCTTCACCAGCCATGACTT CACCTCCTGTTTCCTCAACATTACCAAAGACCATTCACACCA CTCCTTCTCCTATGACCTCACTGCTCACCCCTAGCCTAGTGA TGACCACAGACACATTGGGCACAAGCCCAGAACCTACAACC AGTTCACCTCCAAATTTGAGCAGTACCTCACATGAGATACT GACAACAGATGAAGACACCACAGCTATAGAAGCCATGCAT CCTTCCACAAGCACAGCAGCGACTAATGTGGAAACCACCAG TTCTGGACATGGGTCACAATCCTCTGTCCTAGCTGACTCAGA AAAAACCAAGGCCACAGCTCCAATGGATACCACCTCCACCA

		TGGGGCATACAACTGTTTCCACATCAATGTCTGTTTCCTCTG AGACTACAAAAATTAAGAGAGAGTCAACATATTCCTTGACT CCTGGACTGAGAGAGACCAGCATTTCCCAAAATGCCAGCTT TTCCACTGACACAAGTATTGTTCTTTCAGAAGTCCCCACTGG TACTACTGCTGAGGTCTCCAGGACAGAAGTCACCTCCTCTG GTAGAACATCCATCCCTGGCCCTTCTCAGTCCACAGTTTTGC CAGAAATATCCACAAGAACAATGACAAGGCTCTTTGCCTCG CCCACCATGACAGAATCAGCAGAAATGACCATCCCCACTCA AACAGGTCCTTCTGGGTCTACCTCACAGGATACCCTTACCTT GGACACATCCACCACAAAGTCCCAGGCAAAGACTCATTCAA CTTTGACTCAGAGATTTCCACACTCAGAGATGACCACTCTC ATGAGCAGAGGTCCTGGAGATATGTCATGGCAAAGCTCTCC CTCTCTGGAAAATCCCAGCTCTCTCCCTTCCCTGCTGTCTTT ACCTGCCACAACCTCACCTCCTCCCATTTCCTCCACATTACC AGTGACTATCTCCTCCTCTCCTCTTCCTGTGACTTCACTTCTC ACCTCTAGCCCGGTAACGACCACAGACATGTTACACACAAG CCCAGAACTTGTAACCAGTTCACCTCCAAAGCTGAGCCACA CTTCAGATGAGAGACTGACCACTGGCAAGGACACCACAAAT ACAGAAGCTGTGCATCCTTCCACAAACACAGCAGCGTCCAA TGTGGAGATTCCCAGCTCTGGACATGAATCCCCTTCCTCTGC CTTAGCTGACTCAGAGACATCCAAAGCCACATCACCAATGT TTATTACCTCCACCCAGGAGGATACAACTGTTGCCATATCA ACCCCTCACTTCTTGGAGACTAGCAGAATTCAGAAAGAGTC AATTTCCTCCCTGAGCCCTAAATTGAGGGAGACAGGCAGTT CTGTGGAGACAAGCTCAGCCATAGAGACAAGTGCTGTCCTT TCTGAAGTGTCCATTGGTGCTACTACTGAGATCTCCAGGAC AGAAGTCACCTCCTCTAGCAGAACATCCATCTCTGGTTCTGC TGAGTCCACAATGTTGCCAGAAATATCCACCACAAGAAAAA TCATTAAGTTCCCTACTTCCCCCATCCTGGCAGAATCATCAG AAATGACCATCAAGACCCAAACAAGTCCTCCTGGGTCTACA TCAGAGAGTACCTTTACATTAGACACATCAACCACTCCCTC CTTGGTAATAACCCATTCGACTATGACTCAGAGATTGCCAC ACTCAGAGATAACCACTCTTGTGAGTAGAGGTGCTGGGGAT GTGCCACGGCCCAGCTCTCTCCCTGTGGAAGAAACAAGCCC TCCATCTTCCCAGCTGTCTTTATCTGCCATGATCTCACCTTCT CCTGTTTCTTCCACATTACCAGCAAGTAGCCACTCCTCTTCT GCTTCTGTGACTTCACTTCTCACACCAGGCCAAGTGAAGAC TACTGAGGTGTTGGACGCAAGTGCAGAACCTGAAACCAGTT CACCTCCAAGTTTGAGCAGCACCTCAGTTGAAATACTGGCC ACCTCTGAAGTCACCACAGATACGGAGAAAATTCATCCTTT CTCAAACACGGCAGTAACCAAAGTTGGAACTTCCAGTTCTG GACATGAATCCCCTTCCTCTGTCCTACCTGACTCAGAGACA ACCAAAGCCACATCGGCAATGGGTACCATCTCCATTATGGG GGATACAAGTGTTTCTACATTAACTCCTGCCTTATCTAACAC TAGGAAAATTCAGTCAGAGCCAGCTTCCTCACTGACCACCA GATTGAGGGAGACCAGCACCTCTGAAGAGACCAGCTTAGCC

		ACAGAAGCAAACACTGTTCTTTCTAAAGTGTCCACTGGTGC TACTACTGAGGTCTCCAGGACAGAAGCCATCTCCTTTAGCA GAACATCCATGTCAGGCCCTGAGCAGTCCACAATGTCACAA GACATCTCCATAGGAACCATCCCCAGGATTTCTGCCTCCTCT GTCCTGACAGAATCTGCAAAAATGACCATCACAACCCAAAC AGGTCCTTCGGAGTCTACACTAGAAAGTACCCTTAATTTGA ACACAGCAACCACACCCTCTTGGGTGGAAACCCACTCTATA GTAATTCAGGGATTTCCACACCCAGAGATGACCACTTCCAT GGGCAGAGGTCCTGGAGGTGTGTCATGGCCTAGCCCTCCCT TTGTGAAAGAAACCAGCCCTCCATCCTCCCCGCTGTCTTTAC CTGCCGTGACCTCACCTCATCCTGTTTCCACCACATTCCTAG CACATATCCCCCCCTCTCCCCTTCCTGTGACTTCACTTCTCA CCTCTGGCCCGGCGACAACCACAGATATCTTGGGTACAAGC ACAGAACCTGGAACCAGTTCATCTTCAAGTTTGAGCACCAC CTCCCATGAGAGACTGACCACTTACAAAGACACTGCACATA CAGAAGCCGTGCATCCTTCCACAAACACAGGAGGGACCAAT GTGGCAACCACCAGCTCTGGATATAAATCACAGTCCTCTGT CCTAGCTGACTCATCTCCAATGTGTACCACCTCCACCATGGG GGATACAAGTGTTCTCACATCAACTCCTGCCTTCCTTGAGAC TAGGAGGATTCAGACAGAGCTAGCTTCCTCCCTGACCCCTG GATTGAGGGAGTCCAGCGGCTCTGAAGGGACCAGCTCAGG CACCAAGATGAGCACTGTCCTCTCTAAAGTGCCCACTGGTG CTACTACTGAGATCTCCAAGGAAGACGTCACCTCCATCCCA GGTCCCGCTCAATCCACAATATCACCAGACATCTCCACAAG AACCGTCAGCTGGTTCTCTACATCCCCTGTCATGACAGAATC AGCAGAAATAACCATGAACACCCATACAAGTCCTTTAGGGG CCACAACACAAGGCACCAGTACTTTGGACACGTCAAGCACA ACCTCTTTGACAATGACACACTCAACTATATCTCAAGGATTT TCACACTCACAGATGAGCACTCTTATGAGGAGGGGTCCTGA GGATGTATCATGGATGAGCCCTCCCCTTCTGGAAAAAACTA GACCTTCCTTTTCTCTGATGTCTTCACCAGCCACAACTTCAC CTTCTCCTGTTTCCTCCACATTACCAGAGAGCATCTCTTCCT CTCCTCTTCCTGTGACTTCACTCCTCACGTCTGGCTTGGCAA AAACTACAGATATGTTGCACAAAAGCTCAGAACCTGTAACC AACTCACCTGCAAATTTGAGCAGCACCTCAGTTGAAATACT GGCCACCTCTGAAGTCACCACAGATACAGAGAAAACTCATC CTTCTTCAAACAGAACAGTGACCGATGTGGGGACCTCCAGT TCTGGACATGAATCCACTTCCTTTGTCCTAGCTGACTCACAG ACATCCAAAGTCACATCTCCAATGGTTATTACCTCCACCATG GAGGATACGAGTGTCTCCACATCAACTCCTGGCTTTTTTGAG ACTAGCAGAATTCAGACAGAACCAACATCCTCCCTGACCCT TGGACTGAGAAAGACCAGCAGCTCTGAGGGGACCAGCTTA GCCACAGAGATGAGCACTGTCCTTTCTGGAGTGCCCACTGG TGCCACTGCTGAAGTCTCCAGGACAGAAGTCACCTCCTCTA GCAGAACATCCATCTCAGGCTTTGCTCAGCTCACAGTGTCA CCAGAGACTTCCACAGAAACCATCACCAGACTCCCTACCTC

		CAGCATAATGACAGAATCAGCAGAAATGATGATCAAGACA CAAACAGATCCTCCTGGGTCTACACCAGAGAGTACTCATAC TGTGGACATATCAACAACACCCAACTGGGTAGAAACCCACT CGACTGTGACTCAGAGATTTTCACACTCAGAGATGACCACT CTTGTGAGCAGAAGCCCTGGTGATATGTTATGGCCTAGTCA ATCCTCTGTGGAAGAAACCAGCTCTGCCTCTTCCCTGCTGTC TCTGCCTGCCACGACCTCACCTTCTCCTGTTTCCTCTACATT AGTAGAGGATTTCCCTTCCGCTTCTCTTCCTGTGACTTCTCTT CTCAACCCTGGCCTGGTGATAACCACAGACAGGATGGGCAT AAGCAGAGAACCTGGAACCAGTTCCACTTCAAATTTGAGCA GCACCTCCCATGAGAGACTGACCACTTTGGAAGACACTGTA GATACAGAAGACATGCAGCCTTCCACACACACAGCAGTGAC CAACGTGAGGACCTCCATTTCTGGACATGAATCACAATCTT CTGTCCTATCTGACTCAGAGACACCCAAAGCCACATCTCCA ATGGGTACCACCTACACCATGGGGGAAACGAGTGTTTCCAT ATCCACTTCTGACTTCTTTGAGACCAGCAGAATTCAGATAG AACCAACATCCTCCCTGACTTCTGGATTGAGGGAGACCAGC AGCTCTGAGAGGATCAGCTCAGCCACAGAGGGAAGCACTG TCCTTTCTGAAGTGCCCAGTGGTGCTACCACTGAGGTCTCCA GGACAGAAGTGATATCCTCTAGGGGAACATCCATGTCAGGG CCTGATCAGTTCACCATATCACCAGACATCTCTACTGAAGC GATCACCAGGCTTTCTACTTCCCCCATTATGACAGAATCAGC AGAAAGTGCCATCACTATTGAGACAGGTTCTCCTGGGGCTA CATCAGAGGGTACCCTCACCTTGGACACCTCAACAACAACC TTTTGGTCAGGGACCCACTCAACTGCATCTCCAGGATTTTCA CACTCAGAGATGACCACTCTTATGAGTAGAACTCCTGGAGA TGTGCCATGGCCGAGCCTTCCCTCTGTGGAAGAAGCCAGCT CTGTCTCTTCCTCACTGTCTTCACCTGCCATGACCTCAACTT CTTTTTTCTCCACATTACCAGAGAGCATCTCCTCCTCTCCTC ATCCTGTGACTGCACTTCTCACCCTTGGCCCAGTGAAGACC ACAGACATGTTGCGCACAAGCTCAGAACCTGAAACCAGTTC ACCTCCAAATTTGAGCAGCACCTCAGCTGAAATATTAGCCA CGTCTGAAGTCACCAAAGATAGAGAGAAAATTCATCCCTCC TCAAACACACCTGTAGTCAATGTAGGGACTGTGATTTATAA ACATCTATCCCCTTCCTCTGTTTTGGCTGACTTAGTGACAAC AAAACCCACATCTCCAATGGCTACCACCTCCACTCTGGGGA ATACAAGTGTTTCCACATCAACTCCTGCCTTCCCAGAAACTA TGATGACACAGCCAACTTCCTCCCTGACTTCTGGATTAAGG GAGATCAGTACCTCTCAAGAGACCAGCTCAGCAACAGAGA GAAGTGCTTCTCTTTCTGGAATGCCCACTGGTGCTACTACTA AGGTCTCCAGAACAGAAGCCCTCTCCTTAGGCAGAACATCC ACCCCAGGTCCTGCTCAATCCACAATATCACCAGAAATCTC CACGGAAACCATCACTAGAATTTCTACTCCCCTCACCACGA CAGGATCAGCAGAAATGACCATCACCCCCAAAACAGGTCAT TCTGGGGCATCCTCACAAGGTACCTTTACCTTGGACACATC AAGCAGAGCCTCCTGGCCAGGAACTCACTCAGCTGCAACTC

		ACAGATCTCCACACTCAGGGATGACCACTCCTATGAGCAGA GGTCCTGAGGATGTGTCATGGCCAAGCCGCCCATCAGTGGA AAAAACTAGCCCTCCATCTTCCCTGGTGTCTTTATCTGCAGT AACCTCACCTTCGCCACTTTATTCCACACCATCTGAGAGTAG CCACTCATCTCCTCTCCGGGTGACTTCTCTTTTCACCCCTGTC ATGATGAAGACCACAGACATGTTGGACACAAGCTTGGAACC TGTGACCACTTCACCTCCCAGTATGAATATCACCTCAGATG AGAGTCTGGCCACTTCTAAAGCCACCATGGAGACAGAGGCA ATTCAGCTTTCAGAAAACACAGCTGTGACTCAGATGGGCAC CATCAGCGCTAGACAAGAATTCTATTCCTCTTATCCAGGCCT CCCAGAGCCATCCAAAGTGACATCTCCAGTGGTCACCTCTT CCACCATAAAAGACATTGTTTCTACAACCATACCTGCTTCCT CTGAGATAACAAGAATTGAGATGGAGTCAACATCCACCCTG ACCCCCACACCAAGGGAGACCAGCACCTCCCAGGAGATCC ACTCAGCCACAAAGCCAAGCACTGTTCCTTACAAGGCACTC ACTAGTGCCACGATTGAGGACTCCATGACACAAGTCATGTC CTCTAGCAGAGGACCTAGCCCTGATCAGTCCACAATGTCAC AAGACATATCCACTGAAGTGATCACCAGGCTCTCTACCTCC CCCATCAAGACAGAATCTACAGAAATGACCATTACCACCCA AACAGGTTCTCCTGGGGCTACATCAAGGGGTACCCTTACCT TGGACACTTCAACAACTTTTATGTCAGGGACCCACTCAACT GCATCTCAAGGATTTTCACACTCACAGATGACCGCTCTTATG AGTAGAACTCCTGGAGATGTGCCATGGCTAAGCCATCCCTC TGTGGAAGAAGCCAGCTCTGCCTCTTTCTCACTGTCTTCACC TGTCATGACCTCATCTTCTCCCGTTTCTTCCACATTACCAGA CAGCATCCACTCTTCTTCGCTTCCTGTGACATCACTTCTCAC CTCAGGGCTGGTGAAGACCACAGAGCTGTTGGGCACAAGCT CAGAACCTGAAACCAGTTCACCCCCAAATTTGAGCAGCACC TCAGCTGAAATACTGGCCATCACTGAAGTCACTACAGATAC AGAGAAACTGGAGATGACCAATGTGGTAACCTCAGGTTATA CACATGAATCTCCTTCCTCTGTCCTAGCTGACTCAGTGACAA CAAAGGCCACATCTTCAATGGGTATCACCTACCCCACAGGA GATACAAATGTTCTCACATCAACCCCTGCCTTCTCTGACACC AGTAGGATTCAAACAAAGTCAAAGCTCTCACTGACTCCTGG GTTGATGGAGACCAGCATCTCTGAAGAGACCAGCTCTGCCA CAGAAAAAAGCACTGTCCTTTCTAGTGTGCCCACTGGTGCT ACTACTGAGGTCTCCAGGACAGAAGCCATCTCTTCTAGCAG AACATCCATCCCAGGCCCTGCTCAATCCACAATGTCATCAG ACACCTCCATGGAAACCATCACTAGAATTTCTACCCCCCTC ACAAGGAAAGAATCAACAGACATGGCCATCACCCCCAAAA CAGGTCCTTCTGGGGCTACCTCGCAGGGTACCTTTACCTTGG ACTCATCAAGCACAGCCTCCTGGCCAGGAACTCACTCAGCT ACAACTCAGAGATTTCCACAGTCAGTGGTGACAACTCCTAT GAGCAGAGGTCCTGAGGATGTGTCATGGCCAAGCCCGCTGT CTGTGGAAAAAAACAGCCCTCCATCTTCCCTGGTATCTTCAT CTTCAGTAACCTCACCTTCGCCACTTTATTCCACACCATCTG

		GGAGTAGCCACTCCTCTCCTGTCCCTGTCACTTCTCTTTTCA CCTCTATCATGATGAAGGCCACAGACATGTTGGATGCAAGT TTGGAACCTGAGACCACTTCAGCTCCCAATATGAATATCAC CTCAGATGAGAGTCTGGCCGCTTCTAAAGCCACCACGGAGA CAGAGGCAATTCACGTTTTTGAAAATACAGCAGCGTCCCAT GTGGAAACCACCAGTGCTACAGAGGAACTCTATTCCTCTTC CCCAGGCTTCTCAGAGCCAACAAAAGTGATATCTCCAGTGG TCACCTCTTCCTCTATAAGAGACAACATGGTTTCCACAACA ATGCCTGGCTCCTCTGGCATTACAAGGATTGAGATAGAGTC AATGTCATCTCTGACCCCTGGACTGAGGGAGACCAGAACCT CCCAGGACATCACCTCATCCACAGAGACAAGCACTGTCCTT TACAAGATGCCCTCTGGTGCCACTCCTGAGGTCTCCAGGAC AGAAGTTATGCCCTCTAGCAGAACATCCATTCCTGGCCCTG CTCAGTCCACAATGTCACTAGACATCTCCGATGAAGTTGTC ACCAGGCTGTCTACCTCTCCCATCATGACAGAATCTGCAGA AATAACCATCACCACCCAAACAGGTTATTCTCTGGCTACAT CCCAGGTTACCCTTCCCTTGGGCACCTCAATGACCTTTTTGT CAGGGACCCACTCAACTATGTCTCAAGGACTTTCACACTCA GAGATGACCAATCTTATGAGCAGGGGTCCTGAAAGTCTGTC ATGGACGAGCCCTCGCTTTGTGGAAACAACTAGATCTTCCT CTTCTCTGACATCATTACCTCTCACGACCTCACTTTCTCCTGT GTCCTCCACATTACTAGACAGTAGCCCCTCCTCTCCTCTTCC TGTGACTTCACTTATCCTCCCAGGCCTGGTGAAGACTACAG AAGTGTTGGATACAAGCTCAGAGCCTAAAACCAGTTCATCT CCAAATTTGAGCAGCACCTCAGTTGAAATACCGGCCACCTC TGAAATCATGACAGATACAGAGAAAATTCATCCTTCCTCAA ACACAGCGGTGGCCAAAGTGAGGACCTCCAGTTCTGTTCAT GAATCTCATTCCTCTGTCCTAGCTGACTCAGAAACAACCAT AACCATACCTTCAATGGGTATCACCTCCGCTGTGGACGATA CCACTGTTTTCACATCAAATCCTGCCTTCTCTGAGACTAGGA GGATTCCGACAGAGCCAACATTCTCATTGACTCCTGGATTC AGGGAGACTAGCACCTCTGAAGAGACCACCTCAATCACAG AAACAAGTGCAGTCCTTTATGGAGTGCCCACTAGTGCTACT ACTGAAGTCTCCATGACAGAAATCATGTCCTCTAATAGAAT ACACATCCCTGACTCTGATCAGTCCACGATGTCTCCAGACA TCATCACTGAAGTGATCACCAGGCTCTCTTCCTCATCCATGA TGTCAGAATCAACACAAATGACCATCACCACCCAAAAAAGT TCTCCTGGGGCTACAGCACAGAGTACTCTTACCTTGGCCAC AACAACAGCCCCCTTGGCAAGGACCCACTCAACTGTTCCTC CTAGATTTTTACACTCAGAGATGACAACTCTTATGAGTAGG AGTCCTGAAAATCCATCATGGAAGAGCTCTCTCTTTGTGGA AAAAACTAGCTCTTCATCTTCTCTGTTGTCCTTACCTGTCAC GACCTCACCTTCTGTTTCTTCCACATTACCGCAGAGTATCCC TTCCTCCTCTTTTTCTGTGACTTCACTCCTCACCCCAGGCATG GTGAAGACTACAGACACAAGCACAGAACCTGGAACCAGTT TATCTCCAAATCTGAGTGGCACCTCAGTTGAAATACTGGCT

		GCCTCTGAAGTCACCACAGATACAGAGAAAATTCATCCTTC TTCAAGCATGGCAGTGACCAATGTGGGAACCACCAGTTCTG GACATGAACTATATTCCTCTGTTTCAATCCACTCGGAGCCAT CCAAGGCTACATACCCAGTGGGTACTCCCTCTTCCATGGCT GAAACCTCTATTTCCACATCAATGCCTGCTAATTTTGAGACC ACAGGATTTGAGGCTGAGCCATTTTCTCATTTGACTTCTGGA TTTAGGAAGACAAACATGTCCCTGGACACCAGCTCAGTCAC ACCAACAAATACACCTTCTTCTCCTGGGTCCACTCACCTTTT ACAGAGTTCCAAGACTGATTTCACCTCTTCTGCAAAAACAT CATCCCCAGACTGGCCTCCAGCCTCACAGTATACTGAAATT CCAGTGGACATAATCACCCCCTTTAATGCTTCTCCATCTATT ACGGAGTCCACTGGGATAACCTCCTTCCCAGAATCCAGGTT TACTATGTCTGTAACAGAAAGTACTCATCATCTGAGTACAG ATTTGCTGCCTTCAGCTGAGACTATTTCCACTGGCACAGTGA TGCCTTCTCTATCAGAGGCCATGACTTCATTTGCCACCACTG GAGTTCCACGAGCCATCTCAGGTTCAGGTAGTCCATTCTCTA GGACAGAGTCAGGCCCTGGGGATGCTACTCTGTCCACCATT GCAGAGAGCCTGCCTTCATCCACTCCTGTGCCATTCTCCTCT TCAACCTTCACTACCACTGATTCTTCAACCATCCCAGCCCTC CATGAGATAACTTCCTCTTCAGCTACCCCATATAGAGTGGA CACCAGTCTTGGGACAGAGAGCAGCACTACTGAAGGACGCT TGGTTATGGTCAGTACTTTGGACACTTCAAGCCAACCAGGC AGGACATCTTCATCACCCATTTTGGATACCAGAATGACAGA GAGCGTTGAGCTGGGAACAGTGACAAGTGCTTATCAAGTTC CTTCACTCTCAACACGGTTGACAAGAACTGATGGCATTATG GAACACATCACAAAAATACCCAATGAAGCAGCACACAGAG GTACCATAAGACCAGTCAAAGGCCCTCAGACATCCACTTCG CCTGCCAGTCCTAAAGGACTACACACAGGAGGGACAAAAA GAATGGAGACCACCACCACAGCTCTGAAGACCACCACCAC AGCTCTGAAGACCACTTCCAGAGCCACCTTGACCACCAGTG TCTATACTCCCACTTTGGGAACACTGACTCCCCTCAATGCAT CAATGCAAATGGCCAGCACAATCCCCACAGAAATGATGATC ACAACCCCATATGTTTTCCCTGATGTTCCAGAAACGACATCC TCATTGGCTACCAGCCTGGGAGCAGAAACCAGCACAGCTCT TCCCAGGACAACCCCATCTGTTTTCAATAGAGAATCAGAGA CCACAGCCTCACTGGTCTCTCGTTCTGGGGCAGAGAGAAGT CCGGTTATTCAAACTCTAGATGTTTCTTCTAGTGAGCCAGAT ACAACAGCTTCATGGGTTATCCATCCTGCAGAGACCATCCC AACTGTTTCCAAGACAACCCCCAATTTTTTCCACAGTGAATT AGACACTGTATCTTCCACAGCCACCAGTCATGGGGCAGACG TCAGCTCAGCCATTCCAACAAATATCTCACCTAGTGAACTA GATGCACTGACCCCACTGGTCACTATTTCGGGGACAGATAC TAGTACAACATTCCCAACACTGACTAAGTCCCCACATGAAA CAGAGACAAGAACCACATGGCTCACTCATCCTGCAGAGACC AGCTCAACTATTCCCAGAACAATCCCCAATTTTTCTCATCAT GAATCAGATGCCACACCTTCAATAGCCACCAGTCCTGGGGC

		AGAAACCAGTTCAGCTATTCCAATTATGACTGTCTCACCTG GTGCAGAAGATCTGGTGACCTCACAGGTCACTAGTTCTGGG ACAGACAGAAATATGACTATTCCAACTTTGACTCTTTCTCCT GGTGAACCAAAGACGATAGCCTCATTAGTCACCCATCCTGA AGCACAGACAAGTTCGGCCATTCCAACTTCAACTATCTCGC CTGCTGTATCACGGTTGGTGACCTCAATGGTCACCAGTTTGG CGGCAAAGACAAGTACAACTAATCGAGCTCTGACAAACTCC CCTGGTGAACCAGCTACAACAGTTTCATTGGTCACGCATCC TGCACAGACCAGCCCAACAGTTCCCTGGACAACTTCCATTT TTTTCCATAGTAAATCAGACACCACACCTTCAATGACCACC AGTCATGGGGCAGAATCCAGTTCAGCTGTTCCAACTCCAAC TGTTTCAACTGAGGTACCAGGAGTAGTGACCCCTTTGGTCA CCAGTTCTAGGGCAGTGATCAGTACAACTATTCCAATTCTG ACTCTTTCTCCTGGTGAACCAGAGACCACACCTTCAATGGC CACCAGTCATGGGGAAGAAGCCAGTTCTGCTATTCCAACTC CAACTGTTTCACCTGGGGTACCAGGAGTGGTGACCTCTCTG GTCACTAGTTCTAGGGCAGTGACTAGTACAACTATTCCAAT TCTGACTTTTTCTCTTGGTGAACCAGAGACCACACCTTCAAT GGCCACCAGTCATGGGACAGAAGCTGGCTCAGCTGTTCCAA CTGTTTTACCTGAGGTACCAGGAATGGTGACCTCTCTGGTTG CTAGTTCTAGGGCAGTAACCAGTACAACTCTTCCAACTCTG ACTCTTTCTCCTGGTGAACCAGAGACCACACCTTCAATGGC CACCAGTCATGGGGCAGAAGCCAGCTCAACTGTTCCAACTG TTTCACCTGAGGTACCAGGAGTGGTGACCTCTCTGGTCACT AGTTCTAGTGGAGTAAACAGTACAAGTATTCCAACTCTGAT TCTTTCTCCTGGTGAACTAGAAACCACACCTTCAATGGCCAC CAGTCATGGGGCAGAAGCCAGCTCAGCTGTTCCAACTCCAA CTGTTTCACCTGGGGTATCAGGAGTGGTGACCCCTCTGGTC ACTAGTTCCAGGGCAGTGACCAGTACAACTATTCCAATTCT AACTCTTTCTTCTAGTGAGCCAGAGACCACACCTTCAATGG CCACCAGTCATGGGGTAGAAGCCAGCTCAGCTGTTCTAACT GTTTCACCTGAGGTACCAGGAATGGTGACCTCTCTGGTCAC TAGTTCTAGAGCAGTAACCAGTACAACTATTCCAACTCTGA CTATTTCTTCTGATGAACCAGAGACCACAACTTCATTGGTCA CCCATTCTGAGGCAAAGATGATTTCAGCCATTCCAACTTTA GCTGTCTCCCCTACTGTACAAGGGCTGGTGACTTCACTGGTC ACTAGTTCTGGGTCAGAGACCAGTGCGTTTTCAAATCTAAC TGTTGCCTCAAGTCAACCAGAGACCATAGACTCATGGGTCG CTCATCCTGGGACAGAAGCAAGTTCTGTTGTTCCAACTTTGA CTGTCTCCACTGGTGAGCCGTTTACAAATATCTCATTGGTCA CCCATCCTGCAGAGAGTAGCTCAACTCTTCCCAGGACAACC TCAAGGTTTTCCCACAGTGAATTAGACACTATGCCTTCTACA GTCACCAGTCCTGAGGCAGAATCCAGCTCAGCCATTTCAAC AACTATTTCACCTGGTATACCAGGTGTGCTGACATCACTGGT CACTAGCTCTGGGAGAGACATCAGTGCAACTTTTCCAACAG TGCCTGAGTCCCCACATGAATCAGAGGCAACAGCCTCATGG

		GTTACTCATCCTGCAGTCACCAGCACAACAGTTCCCAGGAC AACCCCTAATTATTCTCATAGTGAACCAGACACCACACCAT CAATAGCCACCAGTCCTGGGGCAGAAGCCACTTCAGATTTT CCAACAATAACTGTCTCACCTGATGTACCAGATATGGTAAC CTCACAGGTCACTAGTTCTGGGACAGACACCAGTATAACTA TTCCAACTCTGACTCTTTCTTCTGGTGAGCCAGAGACCACAA CCTCATTTATCACCTATTCTGAGACACACACAAGTTCAGCCA TTCCAACTCTCCCTGTCTCCCCTGGTGCATCAAAGATGCTGA CCTCACTGGTCATCAGTTCTGGGACAGACAGCACTACAACT TTCCCAACACTGACGGAGACCCCATATGAACCAGAGACAAC AGCCATACAGCTCATTCATCCTGCAGAGACCAACACAATGG TTCCCAGGACAACTCCCAAGTTTTCCCATAGTAAGTCAGAC ACCACACTCCCAGTAGCCATCACCAGTCCTGGGCCAGAAGC CAGTTCAGCTGTTTCAACGACAACTATCTCACCTGATATGTC AGATCTGGTGACCTCACTGGTCCCTAGTTCTGGGACAGACA CCAGTACAACCTTCCCAACATTGAGTGAGACCCCATATGAA CCAGAGACTACAGCCACGTGGCTCACTCATCCTGCAGAAAC CAGCACAACGGTTTCTGGGACAATTCCCAACTTTTCCCATA GGGGATCAGACACTGCACCCTCAATGGTCACCAGTCCTGGA GTAGACACGAGGTCAGGTGTTCCAACTACAACCATCCCACC CAGTATACCAGGGGTAGTGACCTCACAGGTCACTAGTTCTG CAACAGACACTAGTACAGCTATTCCAACTTTGACTCCTTCTC CTGGTGAACCAGAGACCACAGCCTCATCAGCTACCCATCCT GGGACACAGACTGGCTTCACTGTTCCAATTCGGACTGTTCC CTCTAGTGAGCCAGATACAATGGCTTCCTGGGTCACTCATC CTCCACAGACCAGCACACCTGTTTCCAGAACAACCTCCAGT TTTTCCCATAGTAGTCCAGATGCCACACCTGTAATGGCCACC AGTCCTAGGACAGAAGCCAGTTCAGCTGTACTGACAACAAT CTCACCTGGTGCACCAGAGATGGTGACTTCACAGATCACTA GTTCTGGGGCAGCAACCAGTACAACTGTTCCAACTTTGACT CATTCTCCTGGTATGCCAGAGACCACAGCCTTATTGAGCAC CCATCCCAGAACAGAGACAAGTAAAACATTTCCTGCTTCAA CTGTGTTTCCTCAAGTATCAGAGACCACAGCCTCACTCACC ATTAGACCTGGTGCAGAGACTAGCACAGCTCTCCCAACTCA GACAACATCCTCTCTCTTCACCCTACTTGTAACTGGAACCAG CAGAGTTGATCTAAGTCCAACTGCTTCACCTGGTGTTTCTGC AAAAACAGCCCCACTTTCCACCCATCCAGGGACAGAAACCA GCACAATGATTCCAACTTCAACTCTTTCCCTTGGTTTACTAG AGACTACAGGCTTACTGGCCACCAGCTCTTCAGCAGAGACC AGCACGAGTACTCTAACTCTGACTGTTTCCCCTGCTGTCTCT GGGCTTTCCAGTGCCTCTATAACAACTGATAAGCCCCAAAC TGTGACCTCCTGGAACACAGAAACCTCACCATCTGTAACTT CAGTTGGACCCCCAGAATTTTCCAGGACTGTCACAGGCACC ACTATGACCTTGATACCATCAGAGATGCCAACACCACCTAA AACCAGTCATGGAGAAGGAGTGAGTCCAACCACTATCTTGA GAACTACAATGGTTGAAGCCACTAATTTAGCTACCACAGGT

		TCCAGTCCCACTGTGGCCAAGACAACAACCACCTTCAATAC ACTGGCTGGAAGCCTCTTTACTCCTCTGACCACACCTGGGAT GTCCACCTTGGCCTCTGAGAGTGTGACCTCAAGAACAAGTT ATAACCATCGGTCCTGGATCTCCACCACCAGCAGTTATAAC CGTCGGTACTGGACCCCTGCCACCAGCACTCCAGTGACTTC TACATTCTCCCCAGGGATTTCCACATCCTCCATCCCCAGCTC CACAGCAGCCACAGTCCCATTCATGGTGCCATTCACCCTCA ACTTCACCATCACCAACCTGCAGTACGAGGAGGACATGCGG CACCCTGGTTCCAGGAAGTTCAACGCCACAGAGAGAGAACT GCAGGGTCTGCTCAAACCCTTGTTCAGGAATAGCAGTCTGG AATACCTCTATTCAGGCTGCAGACTAGCCTCACTCAGGCCA GAGAAGGATAGCTCAGCCACGGCAGTGGATGCCATCTGCAC ACATCGCCCTGACCCTGAAGACCTCGGACTGGACAGAGAGC GACTGTACTGGGAGCTGAGCAATCTGACAAATGGCATCCAG GAGCTGGGCCCCTACACCCTGGACCGGAACAGTCTCTATGT CAATGGTTTCACCCATCGAAGCTCTATGCCCACCACCAGCA CTCCTGGGACCTCCACAGTGGATGTGGGAACCTCAGGGACT CCATCCTCCAGCCCCAGCCCCACGACTGCTGGCCCTCTCCTG ATGCCGTTCACCCTCAACTTCACCATCACCAACCTGCAGTAC GAGGAGGACATGCGTCGCACTGGCTCCAGGAAGTTCAACAC CATGGAGAGTGTCCTGCAGGGTCTGCTCAAGCCCTTGTTCA AGAACACCAGTGTTGGCCCTCTGTACTCTGGCTGCAGATTG ACCTTGCTCAGGCCCGAGAAAGATGGGGCAGCCACTGGAGT GGATGCCATCTGCACCCACCGCCTTGACCCCAAAAGCCCTG GACTCAACAGGGAGCAGCTGTACTGGGAGCTAAGCAAACT GACCAATGACATTGAAGAGCTGGGCCCCTACACCCTGGACA GGAACAGTCTCTATGTCAATGGTTTCACCCATCAGAGCTCT GTGTCCACCACCAGCACTCCTGGGACCTCCACAGTGGATCT CAGAACCTCAGGGACTCCATCCTCCCTCTCCAGCCCCACAA TTATGGCTGCTGGCCCTCTCCTGGTACCATTCACCCTCAACT TCACCATCACCAACCTGCAGTATGGGGAGGACATGGGTCAC CCTGGCTCCAGGAAGTTCAACACCACAGAGAGGGTCCTGCA GGGTCTGCTTGGTCCCATATTCAAGAACACCAGTGTTGGCC CTCTGTACTCTGGCTGCAGACTGACCTCTCTCAGGTCTGAGA AGGATGGAGCAGCCACTGGAGTGGATGCCATCTGCATCCAT CATCTTGACCCCAAAAGCCCTGGACTCAACAGAGAGCGGCT GTACTGGGAGCTGAGCCAACTGACCAATGGCATCAAAGAG CTGGGCCCCTACACCCTGGACAGGAACAGTCTCTATGTCAA TGGTTTCACCCATCGGACCTCTGTGCCCACCAGCAGCACTCC TGGGACCTCCACAGTGGACCTTGGAACCTCAGGGACTCCAT TCTCCCTCCCAAGCCCCGCAACTGCTGGCCCTCTCCTGGTGC TGTTCACCCTCAACTTCACCATCACCAACCTGAAGTATGAG GAGGACATGCATCGCCCTGGCTCCAGGAAGTTCAACACCAC TGAGAGGGTCCTGCAGACTCTGCTTGGTCCTATGTTCAAGA ACACCAGTGTTGGCCTTCTGTACTCTGGCTGCAGACTGACCT TGCTCAGGTCCGAGAAGGATGGAGCAGCCACTGGAGTGGA

		TGCCATCTGCACCCACCGTCTTGACCCCAAAAGCCCTGGAG TGGACAGGGAGCAGCTATACTGGGAGCTGAGCCAGCTGAC CAATGGCATCAAAGAGCTGGGCCCCTACACCCTGGACAGGA ACAGTCTCTATGTCAATGGTTTCACCCATTGGATCCCTGTGC CCACCAGCAGCACTCCTGGGACCTCCACAGTGGACCTTGGG TCAGGGACTCCATCCTCCCTCCCCAGCCCCACAACTGCTGG CCCTCTCCTGGTGCCGTTCACCCTCAACTTCACCATCACCAA CCTGAAGTACGAGGAGGACATGCATTGCCCTGGCTCCAGGA AGTTCAACACCACAGAGAGAGTCCTGCAGAGTCTGCTTGGT CCCATGTTCAAGAACACCAGTGTTGGCCCTCTGTACTCTGGC TGCAGACTGACCTTGCTCAGGTCCGAGAAGGATGGAGCAGC CACTGGAGTGGATGCCATCTGCACCCACCGTCTTGACCCCA AAAGCCCTGGAGTGGACAGGGAGCAGCTATACTGGGAGCT GAGCCAGCTGACCAATGGCATCAAAGAGCTGGGTCCCTACA CCCTGGACAGAAACAGTCTCTATGTCAATGGTTTCACCCAT CAGACCTCTGCGCCCAACACCAGCACTCCTGGGACCTCCAC AGTGGACCTTGGGACCTCAGGGACTCCATCCTCCCTCCCCA GCCCTACATCTGCTGGCCCTCTCCTGGTGCCATTCACCCTCA ACTTCACCATCACCAACCTGCAGTACGAGGAGGACATGCAT CACCCAGGCTCCAGGAAGTTCAACACCACGGAGCGGGTCCT GCAGGGTCTGCTTGGTCCCATGTTCAAGAACACCAGTGTCG GCCTTCTGTACTCTGGCTGCAGACTGACCTTGCTCAGGCCTG AGAAGAATGGGGCAGCCACTGGAATGGATGCCATCTGCAG CCACCGTCTTGACCCCAAAAGCCCTGGACTCAACAGAGAGC AGCTGTACTGGGAGCTGAGCCAGCTGACCCATGGCATCAAA GAGCTGGGCCCCTACACCCTGGACAGGAACAGTCTCTATGT CAATGGTTTCACCCATCGGAGCTCTGTGGCCCCCACCAGCA CTCCTGGGACCTCCACAGTGGACCTTGGGACCTCAGGGACT CCATCCTCCCTCCCCAGCCCCACAACAGCTGTTCCTCTCCTG GTGCCGTTCACCCTCAACTTTACCATCACCAATCTGCAGTAT GGGGAGGACATGCGTCACCCTGGCTCCAGGAAGTTCAACAC CACAGAGAGGGTCCTGCAGGGTCTGCTTGGTCCCTTGTTCA AGAACTCCAGTGTCGGCCCTCTGTACTCTGGCTGCAGACTG ATCTCTCTCAGGTCTGAGAAGGATGGGGCAGCCACTGGAGT GGATGCCATCTGCACCCACCACCTTAACCCTCAAAGCCCTG GACTGGACAGGGAGCAGCTGTACTGGCAGCTGAGCCAGAT GACCAATGGCATCAAAGAGCTGGGCCCCTACACCCTGGACC GGAACAGTCTCTACGTCAATGGTTTCACCCATCGGAGCTCT GGGCTCACCACCAGCACTCCTTGGACTTCCACAGTTGACCTT GGAACCTCAGGGACTCCATCCCCCGTCCCCAGCCCCACAAC CACCGGCCCTCTCCTGGTGCCATTCACACTCAACTTCACCAT CACTAACCTACAGTATGAGGAGAACATGGGTCACCCTGGCT CCAGGAAGTTCAACATCACGGAGAGTGTTCTGCAGGGTCTG CTCAAGCCCTTGTTCAAGAGCACCAGTGTTGGCCCTCTGTAT TCTGGCTGCAGACTGACCTTGCTCAGGCCTGAGAAGGATGG AGTAGCCACCAGAGTGGACGCCATCTGCACCCACCGCCCTG

		ACCCCAAAATCCCTGGGCTAGACAGACAGCAGCTATACTGG GAGCTGAGCCAGCTGACCCACAGCATCACTGAGCTGGGACC CTACACCCTGGATAGGGACAGTCTCTATGTCAATGGTTTCA CCCAGCGGAGCTCTGTGCCCACCACCAGCACTCCTGGGACT TTCACAGTACAGCCGGAAACCTCTGAGACTCCATCATCCCT CCCTGGCCCCACAGCCACTGGCCCTGTCCTGCTGCCATTCAC CCTCAATTTTACCATCACTAACCTGCAGTATGAGGAGGACA TGCGTCGCCCTGGCTCCAGGAAGTTCAACACCACGGAGAGG GTCCTTCAGGGTCTGCTTATGCCCTTGTTCAAGAACACCAGT GTCAGCTCTCTGTACTCTGGTTGCAGACTGACCTTGCTCAGG CCTGAGAAGGATGGGGCAGCCACCAGAGTGGATGCTGTCTG CACCCATCGTCCTGACCCCAAAAGCCCTGGACTGGACAGAG AGCGGCTGTACTGGAAGCTGAGCCAGCTGACCCACGGCATC ACTGAGCTGGGCCCCTACACCCTGGACAGGCACAGTCTCTA TGTCAATGGTTTCACCCATCAGAGCTCTATGACGACCACCA GAACTCCTGATACCTCCACAATGCACCTGGCAACCTCGAGA ACTCCAGCCTCCCTGTCTGGACCCATGACCGCCAGCCCTCTC CTGGTGCTATTCACAATTAACTTCACCATCACTAACCTGCGG TATGAGGAGAACATGCATCACCCTGGCTCTAGAAAGTTTAA CACCACGGAGAGAGTCCTTCAGGGTCTGCTCAGGCCTGTGT TCAAGAACACCAGTGTTGGCCCTCTGTACTCTGGCTGCAGA CTGACCTTGCTCAGGCCCAAGAAGGATGGGGCAGCCACCAA AGTGGATGCCATCTGCACCTACCGCCCTGATCCCAAAAGCC CTGGACTGGACAGAGAGCAGCTATACTGGGAGCTGAGCCA GCTGACCCACAGCATCACTGAGCTGGGCCCCTACACCCTGG ACAGGGACAGTCTCTATGTCAATGGTTTCACACAGCGGAGC TCTGTGCCCACCACTAGCATTCCTGGGACCCCCACAGTGGA CCTGGGAACATCTGGGACTCCAGTTTCTAAACCTGGTCCCTC GGCTGCCAGCCCTCTCCTGGTGCTATTCACTCTCAACTTCAC CATCACCAACCTGCGGTATGAGGAGAACATGCAGCACCCTG GCTCCAGGAAGTTCAACACCACGGAGAGGGTCCTTCAGGGC CTGCTCAGGTCCCTGTTCAAGAGCACCAGTGTTGGCCCTCTG TACTCTGGCTGCAGACTGACTTTGCTCAGGCCTGAAAAGGA TGGGACAGCCACTGGAGTGGATGCCATCTGCACCCACCACC CTGACCCCAAAAGCCCTAGGCTGGACAGAGAGCAGCTGTAT TGGGAGCTGAGCCAGCTGACCCACAATATCACTGAGCTGGG CCCCTATGCCCTGGACAACGACAGCCTCTTTGTCAATGGTTT CACTCATCGGAGCTCTGTGTCCACCACCAGCACTCCTGGGA CCCCCACAGTGTATCTGGGAGCATCTAAGACTCCAGCCTCG ATATTTGGCCCTTCAGCTGCCAGCCATCTCCTGATACTATTC ACCCTCAACTTCACCATCACTAACCTGCGGTATGAGGAGAA CATGTGGCCTGGCTCCAGGAAGTTCAACACTACAGAGAGGG TCCTTCAGGGCCTGCTAAGGCCCTTGTTCAAGAACACCAGT GTTGGCCCTCTGTACTCTGGCTGCAGGCTGACCTTGCTCAGG CCAGAGAAAGATGGGGAAGCCACCGGAGTGGATGCCATCT GCACCCACCGCCCTGACCCCACAGGCCCTGGGCTGGACAGA

		GAGCAGCTGTATTTGGAGCTGAGCCAGCTGACCCACAGCAT CACTGAGCTGGGCCCCTACACACTGGACAGGGACAGTCTCT ATGTCAATGGTTTCACCCATCGGAGCTCTGTACCCACCACC AGCACCGGGGTGGTCAGCGAGGAGCCATTCACACTGAACTT CACCATCAACAACCTGCGCTACATGGCGGACATGGGCCAAC CCGGCTCCCTCAAGTTCAACATCACAGACAACGTCATGCAG CACCTGCTCAGTCCTTTGTTCCAGAGGAGCAGCCTGGGTGC ACGGTACACAGGCTGCAGGGTCATCGCACTAAGGTCTGTGA AGAACGGTGCTGAGACACGGGTGGACCTCCTCTGCACCTAC CTGCAGCCCCTCAGCGGCCCAGGTCTGCCTATCAAGCAGGT GTTCCATGAGCTGAGCCAGCAGACCCATGGCATCACCCGGC TGGGCCCCTACTCTCTGGACAAAGACAGCCTCTACCTTAAC GGTTACAATGAACCTGGTCCAGATGAGCCTCCTACAACTCC CAAGCCAGCCACCACATTCCTGCCTCCTCTGTCAGAAGCCA CAACAGCCATGGGGTACCACCTGAAGACCCTCACACTCAAC TTCACCATCTCCAATCTCCAGTATTCACCAGATATGGGCAA GGGCTCAGCTACATTCAACTCCACCGAGGGGGTCCTTCAGC ACCTGCTCAGACCCTTGTTCCAGAAGAGCAGCATGGGCCCC TTCTACTTGGGTTGCCAACTGATCTCCCTCAGGCCTGAGAAG GATGGGGCAGCCACTGGTGTGGACACCACCTGCACCTACCA CCCTGACCCTGTGGGCCCCGGGCTGGACATACAGCAGCTTT ACTGGGAGCTGAGTCAGCTGACCCATGGTGTCACCCAACTG GGCTTCTATGTCCTGGACAGGGATAGCCTCTTCATCAATGG CTATGCACCCCAGAATTTATCAATCCGGGGCGAGTACCAGA TAAATTTCCACATTGTCAACTGGAACCTCAGTAATCCAGAC CCCACATCCTCAGAGTACATCACCCTGCTGAGGGACATCCA GGACAAGGTCACCACACTCTACAAAGGCAGTCAACTACATG ACACATTCCGCTTCTGCCTGGTCACCAACTTGACGATGGACT CCGTGTTGGTCACTGTCAAGGCATTGTTCTCCTCCAATTTGG ACCCCAGCCTGGTGGAGCAAGTCTTTCTAGATAAGACCCTG AATGCCTCATTCCATTGGCTGGGCTCCACCTACCAGTTGGTG GACATCCATGTGACAGAAATGGAGTCATCAGTTTATCAACC AACAAGCAGCTCCAGCACCCAGCACTTCTACCTGAATTTCA CCATCACCAACCTACCATATTCCCAGGACAAAGCCCAGCCA GGCACCACCAATTACCAGAGGAACAAAAGGAATATTGAGG ATGCGCTCAACCAACTCTTCCGAAACAGCAGCATCAAGAGT TATTTTTCTGACTGTCAAGTTTCAACATTCAGGTCTGTCCCC AACAGGCACCACACCGGGGTGGACTCCCTGTGTAACTTCTC GCCACTGGCTCGGAGAGTAGACAGAGTTGCCATCTATGAGG AATTTCTGCGGATGACCCGGAATGGTACCCAGCTGCAGAAC TTCACCCTGGACAGGAGCAGTGTCCTTGTGGATGGGTATTC TCCCAACAGAAATGAGCCCTTAACTGGGAATTCTGACCTTC CCTTCTGGGCTGTCATCCTCATCGGCTTGGCAGGACTCCTGG GAGTCATCACATGCCTGATCTGCGGTGTCCTGGTGACCACC CGCCGGCGGAAGAAGGAAGGAGAATACAACGTCCAGCAAC AGTGCCCAGGCTACTACCAGTCACACCTAGACCTGGAGGAT

		CTGCAATGACTGGAACTTGCCGGTGCCTGGGGTGCCTTTCC CCCAGCCAGGGTCCAAAGAAGCTTGGCTGGGGCAGAAATA AACCATATTGGTCGGA
138	Bispecific	EIVMTQTPATLSVSAGERVTITCKASQSVSNDVTWYQQKPGQ APRLLIYSASNRYSGVPARFSGSGYGTEFTFTISSVQSEDFAVYF CQQDYSSFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGECGGGG SGGGGSQVQLVQSGGGLTLSKADYEKHKVYACEVTHQGLSSP VTKSFNRGECGGGGSGGGGSQVQLVQSGGGVVQPGRSLRLSC KASGYTFTRYTMHWVRQAPGKCLEWIGYINPSRGYTNYNQKF KDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYCL DYWGQGTPVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSAS VGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASG VPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGCG TKLQITR
139	MUC16c114-N3	NFSPLARRVDRVAIYEEFLRMTRNGTQLQAFTLDRSSVLVDGY SPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRR KKEGEYNVQQQCPGYYQSHLDLEDLQ
140	10C6 VH NUCLEIC ACID	CAGGTAACTCTGAAAGAGTCTGGCCCTGGGATATTGCAGCC CTCCCAGACCCTCAGTCTGACTTGTTCTTTCTCTGGGTTTTC ACTGAACACTCTTGGTATGGGTGTAGGCTGGATTCGGCAGC CTTCAGGGAAGGGTCTGGAGTGGCTGGCACACATTTGGTGG GATGATGATAAGTACTATAACCCAGCCCTGAAGAGTCGGCT CACAATCTCCAAGGATTCCTCCAAAAACCAGGTTTTCCTCA AGATCGCCAATGTGGACACTGCAGATATTGCCACATACTAC TGTTCTCGAATCGGGACAGCTCAGGCTACGGATGCTCTGGA CTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA
141	10C6 VL NUCLEIC ACID	GACATTGTGCTGACACAGTCTCCTGCTTCCTTAGCTGTATCT CTGGGGCAGAGGGCCACCATCTCATACAGGGCCAGCAAAA GTGTCAGTACATCTGGCTATAGTTATATGCACTGGAACCAA CAGAAACCAGGACAGCCACCCAGACTCCTCATCTATCTTGT ATCCAACCTAGAATCTGGGGTCCCTGCCAGGTTCAGTGGCA GTGGGTCTGGGACAGACTTCACCCTCAACATCCATCCTGTG GAGGAGGAGGATGCTGCAACCTATTACTGTCAGCACATTAG GGAGCTTACACGTTCGGAGGGGGGACCAAGCTGGAAATAA AAC
142	7B12 VH NUCLEIC ACID	CAGGTTACTCTGAAAGAGTCTGGCCCTGGGATATTGCAGCC CTCCCAGACCCTCAGTCTGACTTGTTCTTTCTCTGGGTTTTC ACTGAGCACTGTTGGTATGGGTGTAGGCTGGAGTCGTCAGC CCTCAGGGAAGGGTCTGGAGTGGCTGGCACACATCTGGTGG GATGATGAAGATAAGTATTATAATCCAGCCCTGAAGAGTCG GCTCACAATCTCCAAGGATACCTCCAAAAACCAGGTCTTCC TCAAGATCGCCAATGTGGACACTGCAGATAGTGCCACATAC TACTGTACTCGAATCGGGACAGCTCAGGCTACGGATGCTTT

		GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA
143	7B12 VL NUCLEIC ACID	GATATTGTGATGACTCAGGCTGCACCCTCTGTATCTGTCACT CCTGGAGAGTCAGTATCCATCTCCTGCAGGTCTAGTAAGAG TCTTCGGAAAAGTAATGGCAACACTTACTTGTATTGGTTCCT GCAGAGGCCAGGCCAGTCTCCTCAGCGCCTGATATATTATA TGTCCAACCTTGCCTCAGGAGTCCCAGACAGGTTCAGTGGC AGAGGGTCAGGAACTGATTTCACACTGAGAATCAGTAGAGT GGAGGCTGAAGATGTGGGTGTTTATTACTGTATGCAAAGTC TAGAATATCCTCTCACGTTCGGAGGGGGGACTAAGCTAAAA ATAAAA
144	19C11 VH NUCLEIC ACID	CAGGTTAATCTGAAAGAGTCTGGCCCTGGGAAATTGCAGCC CTCCCAGACCCTCAGTCTGACTTGTTCTTTCTCTGGGTTTTC ACTGAGCACTCTTGGTATGGGTGTAGGTTGGATTCGTCAGT CTTCAGGGAAGGGTCTGGAGTGGCTGGCACACATTTGGTGG GATGATGATAAGTACTATAACCCAGCCCTGAAGAGTCGGCT CACAATCTCCAGGGCTACCTCCAAAAACCAGGTTTTCCTCA AGATCGTCAATGTGGGCACTGCAGATACTGCCACATATTAC TGTGCTCGAATCGGGACAGCTCAGGCTACGGATGCTTTGGA CTATTGGGGTCAGGGAACCTCAGTCACCGTTTCCTCA
145	19C11 VL NUCLEIC ACID	GATATTGTGATGACTCAGGCTGCACCCTCTATCCCTGTCACT CCTGGAGAGTCAGTATCCATCTCCTGCAGGTCTAGTAAGAG TCTTCTGCATAGTAATGGCAACACTTATTTGTATTGGTTCCT GCAGAGGCCAGGCCAGTCTCCTCAGCGCCTGATATATTATA TGTCCAACCTTGCCTCAGGAGTCCCAGACAGGTTCAGTGGC AGAGGGTCAGGAACTGATTTCACACTGAAAATCAGTAGAGT GGAGGCTGGGGATGTGGGTGTTTATTACTGTATGCAGGGTC TAGAGCATCCTCTCACGTTCGGAGGGGGGACCAAGCTGGAA ATAAAA
146	16C5 VH NUCLEIC ACID	CAGGTTACTCTGAAAGAGTCTGGCCCTGGAATATTGCAGCC CTCCCAGACCCTCAGTCTGACTTGTTCTTTCTCTGGGTTTTC ACTGAACACTCTTGGTATGGGTGTAGGCTGGATTCGTCAGC CTTCAGGGAAGGGTCTGGAGTGGCTGGCACACATTTGGTGG GATGATGATAAGTACTATTACCCAGCCCTGAAGAGTCGGCT CACAATCTCCAGGGATACCTCCAAAAACCAGGTATTCCTCA AGATCGCCAATGTGGACACTGCAGATACTGCCACATACTAC TGTGCTCGAATCGGGACAGCTCAGGCTACGGATGCTCTGGA CTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA
147	16C5 VL NUCLEIC ACID	GAGCTCGATATGACCCAGACTCCACCCTCCCTGTCTGCATCT GTGGGAGAAACTGTCAGGATTAGGTGCCTGGCCAGTGAGG ACATTTATAGTGGTATATCCTGGTATCAACAGAAGCCAGGG AAACCTCCTACACTCCTGATCTATGGTGCATCCAATTTAGAA TCTGGGGTCCCACCACGGTTCAGTGGCAGTGGATCTGGGAC AGATTACACCCTCACCATTGGCGGCGTGCAGGCTGAAGATG CTGCCACCTACTACTGTCTAGGCGGTTATAGTTATAGTAGTA CCTTGACTTTTGGAGCTGGCACCAATGTGGAAATCAAA
148	18C6 VH	CAGGTTACTCTGAAAGAGTCTGGCCCTGGGATATTGCAGCC

	NUCLEIC ACID	CTCCCAGACCCTCAGTCTGACTTGTTCTTTCTCTGGGTTTTC ACTGAGCACTGTTGGTATGGGTGTAGGCTGGAGTCGTCAGC CTTCAGGGAAGGGTCTGGAGTGGCTGGCACACATTTGGTGG GATGATGAGGATAAGTATTATAACCCAGCCCTGAAGAGTCG GCTCACAATCTCCAAGGATACCTCCAAAAACCAGGTATTCC TCAAGATCGCCAATGTGGACACTGCAGATACTGCCACATAC TACTGTACTCGAATCGGGACAGCTCAGGCTACGGATGCTTT GGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA
149	18C6 VL NUCLEIC ACID	GATATTGTGATGACTCAGGCTGCACCCTCTGTACCTGTCACT CCTGGAGAGTCAGTATCCATCTCCTGCAGGTCTAGTAAGAG TCTTCTGCATAGTAATGGCAACACTTACTTGTATTGGTTCCT GCAGAGGCCAGGCCAGTCTCCTCAGCGCCTGATATATTATA TGTCCAACCTTGCCTCAGGAGTCCCAGACAGGTTCAGTGGC AGAGGGTCAGGAACTGATTTCACACTGAGAATCAGTAGAGT GGAGGCTGAGGATGTGGGTGTTTATTACTGTATGCAAAGTC TAGAATATCCTCTCACGTTCGGAGGGGGGACCAAGCTGGAA ATAAAA
150	Mature Human MUC16 amino acid sequence	DKTLASPTSSVVGRTTQSLGVMSSALPESTSRGMTHSEQRTSPS LSPQVNGTPSRNYPATSMVSGLSSPRTRTSSTEGNFTKEASTYT LTVETTSGPVTEKYTVPTETSTTEGDSTETPWDTRYIPVKITSP MKTFADSTASKENAPVSMTPAETTVTDSHTPGRTNPSFGTLYS SFLDLSPKGTPNSRGETSLELILSTTGYPFSSPEPGSAGHSRISTS APLSSSASVLDNKISETSIFSGQSLTSPLSPGVPEARASTMPNSAI PFSMTLSNAETSAERVRSTISSLGTPSISTKQTAETILTFHAFAET MDIPSTHIAKTLASEWLGSPGTLGGTSTSALTTTSPSTTLVSEET NTHHSTSGKETEGTLNTSMTPLETSAPGEESEMTATLVPTLGFT TLDSKIRSPSQVSSSHPTRELRTTGSTSGRQSSSTAAHGSSDILR ATTSSTSKASSWTSESTAQQFSEPQHTQWVETSPSMKTERPPAS TSVAAPITTSVPSVVSGFTTLKTSSTKGIWLEETSADTLIGESTA GPTTHQFAVPTGISMTGGSSTRGSQGTTHLLTRATASSETSADL TLATNGVPVSVSPAVSKTAAGSSPPGGTKPSYTMVSSVIPETSS LQSSAFREGTSLGLTPLNTRHPFSSPEPDSAGHTKISTSIPLLSSA SVLEDKVSATSTFSHHKATSSITTGTPEISTKTKPSSAVLSSMTL SNAATSPERVRNATSPLTHPSPSGEETAGSVLTLSTSAETTDSP NIHPTGTLTSESSESPSTLSLPSVSGVKTTFSSSTPSTHLFTSGEE TEETSNPSVSQPETSVSRVRTTLASTSVPTPVFPTMDTWPTRSA QFSSSHLVSELRATSSTSVTNSTGSALPKISHLTGTATMSQTNR DTFNDSAAPQSTTWPETSPRFKTGLPSATTTVSTSATSLSATVM VSKFTSPATSSMEATSIREPSTTILTTETTNGPGSMAVASTNIPIG KGYITEGRLDTSHLPIGTTASSETSMDFTMAKESVSMSVSPSQS MDAAGSSTPGRTSQFVDTFSDDVYHLTSREITIPRDGTSSALTP QMTATHPPSPDPGSARSTWLGILSSSPSSPTPKVTMSSTFSTQR VTTSMIMDTVETSRWNMPNLPSTTSLTPSNIPTSGAIGKSTLVP LDTPSPATSLEASEGGLPTLSTYPESTNTPSIHLGAHASSESPSTI KLTMASVVKPGSYTPLTFPSIETHIHVSTARMAYSSGSSPEMTA PGETNTGSTWDPTTYITTTDPKDTSSAQVSTPHSVRTLRTTENH

		PKTESATPAAYSGSPKISSSPNLTSPATKAWTITDTTEHSTQLHY TKLAEKSSGFETQSAPGPVSVVIPTSPTIGSSTLELTSDVPGEPL VLAPSEQTTITLPMATWLSTSLTEEMASTDLDISSPSSPMSTFAI FPPMSTPSHELSKSEADTSAIRNTDSTTLDQHLGIRSLGRTGDLT TVPITPLTTTWTSVIEHSTQAQDTLSATMSPTHVTQSLKDQTSIP ASASPSHLTEVYPELGTQGRSSSEATTFWKPSTDTLSREIETGPT NIQSTPPMDNTTTGSSSSGVTLGIAHLPIGTSSPAETSTNMALER RSSTATVSMAGTMGLLVTSAPGRSISQSLGRVSSVLSESTTEGV TDSSKGSSPRLNTQGNTALSSSLEPSYAEGSQMSTSIPLTSSPTT PDVEFIGGSTFWTKEVTTVMTSDISKSSARTESSSATLMSTALG STENTGKEKLRTASMDLPSPTPSMEVTPWISLTLSNAPNTTDSL DLSHGVHTSSAGTLATDRSLNTGVTRASRLENGSDTSSKSLSM GNSTHTSMTYTEKSEVSSSIHPRPETSAPGAETTLTSTPGNRAIS LTLPFSSIPVEEVISTGITSGPDINSAPMTHSPITPPTIVWTSTGTIE QSTQPLHAVSSEKVSVQTQSTPYVNSVAVSASPTHENSVSSGSS TSSPYSSASLESLDSTISRRNAITSWLWDLTTSLPTTTWPSTSLS EALSSGHSGVSNPSSTTTEFPLFSAASTSAAKQRNPETETHGPQ NTAASTLNTDASSVTGLSETPVGASISSEVPLPMAITSRSDVSGL TSESTANPSLGTASSAGTKLTRTISLPTSESLVSFRMNKDPWTV SIPLGSHPTTNTETSIPVNSAGPPGLSTVASDVIDTPSDGAESIPT VSFSPSPDTEVTTISHFPEKTTHSFRTISSLTHELTSRVTPIPGDW MSSAMSTKPTGASPSITLGERRTITSAAPTTSPIVLTASFTETSTV SLDNETTVKTSDILDARKTNELPSDSSSSSDLINTSIASSTMDVT KTASISPTSISGMTASSSPSLFSSDRPQVPTSTTETNTATSPSVSS NTYSLDGGSNVGGTPSTLPPFTITHPVETSSALLAWSRPVRTFS TMVSTDTASGENPTSSNSVVTSVPAPGTWTSVGSTTDLPAMGF LKTSPAGEAHSLLASTIEPATAFTPHLSAAVVTGSSATSEASLLT TSESKAIHSSPQTPTTPTSGANWETSATPESLLVVTETSDTTLTS KILVTDTILFSTVSTPPSKFPSTGTLSGASFPTLLPDTPAIPLTATE PTSSLATSFDSTPLVTIASDSLGTVPETTLTMSETSNGDALVLKT VSNPDRSIPGITIQGVTESPLHPSSTSPSKIVAPRNTTYEGSITVA LSTLPAGTTGSLVFSQSSENSETTALVDSSAGLERASVMPLTTG SQGMASSGGIRSGSTHSTGTKTFSSLPLTMNPGEVTAMSEITTN RLTATQSTAPKGIPVKPTSAESGLLTPVSASSSPSKAFASLTTAP PTWGIPQSTLTFEFSEVPSLDTKSASLPTPGQSLNTIPDSDASTA SSSLSKSPEKNPRARMMTSTKAISASSFQSTGFTETPEGSASPSM AGHEPRVPTSGTGDPRYASESMSYPDPSKASSAMTSTSLASKL TTLFSTGQAARSGSSSSPISLSTEKETSFLSPTASTSRKTSLFLGP SMARQPNILVHLQTSALTLSPTSTLNMSQEEPPELTSSQTIAEEE GTTAETQTLTFTPSETPTSLLPVSSPTEPTARRKSSPETWASSISV PAKTSLVETTDGTLVTTIKMSSQAAQGNSTWPAPAEETGSSPA GTSPGSPEMSTTLKIMSSKEPSISPEIRSTVRNSPWKTPETTVPM ETTVEPVTLQSTALGSGSTSISHLPTGTTSPTKSPTENMLATERV SLSPSPPEAWTNLYSGTPGGTRQSLATMSSVSLESPTARSITGT GQQSSPELVSKTTGMEFSMWHGSTGGTTGDTHVSLSTSSNILE DPVTSPNSVSSLTDKSKHKTETWVSTTAIPSTVLNNKIMAAEQ

		QTSRSVDEAYSSTSSWSDQTSGSDITLGASPDVTNTLYITSTAQ TTSLVSLPSGDQGITSLTNPSGGKTSSASSVTSPSIGLETLRANV SAVKSDIAPTAGHLSQTSSPAEVSILDVTTAPTPGISTTITTMGT NSISTTTPNPEVGMSTMDSTPATERRTTSTEHPSTWSSTAASDS WTVTDMTSNLKVARSPGTISTMHTTSFLASSTELDSMSTPHGRI TVIGTSLVTPSSDASAVKTETSTSERTLSPSDTTASTPISTFSRVQ RMSISVPDILSTSWTPSSTEAEDVPVSMVSTDHASTKTDPNTPL STFLFDSLSTLDWDTGRSLSSATATTSAPQGATTPQELTLETMI SPATSQLPFSIGHITSAVTPAAMARSSGVTFSRPDPTSKKAEQTS TQLPTTTSAHPGQVPRSAATTLDVIPHTAKTPDATFQRQGQTA LTTEARATSDSWNEKEKSTPSAPWITEMMNSVSEDTIKEVTSSS SVLRTLNTLDINLESGTTSSPSWKSSPYERIAPSESTTDKEAIHPS TNTVETTGWVTSSEHASHSTIPAHSASSKLTSPVVTTSTREQAI VSMSTTTWPESTRARTEPNSFLTIELRDVSPYMDTSSTTQTSIIS SPGSTAITKGPRTEITSSKRISSSFLAQSMRSSDSPSEAITRLSNFP AMTESGGMILAMQTSPPGATSLSAPTLDTSATASWTGTPLATT QRFTYSEKTTLFSKGPEDTSQPSPPSVEETSSSSSLVPIHATTSPS NILLTSQGHSPSSTPPVTSVFLSETSGLGKTTDMSRISLEPGTSLP PNLSSTAGEALSTYEASRDTKAIHHSADTAVTNMEATSSEYSPI PGHTKPSKATSPLVTSHIMGDITSSTSVFGSSETTEIETVSSVNQ GLQERSTSQVASSATETSTVITHVSSGDATTHVTKTQATFSSGT SISSPHQFITSTNTFTDVSTNPSTSLIMTESSGVTITTQTGPTGAA TQGPYLLDTSTMPYLTETPLAVTPDFMQSEKTTLISKGPKDVS WTSPPSVAETSYPSSLTPFLVTTIPPATSTLQGQHTSSPVSATSV LTSGLVKTTDMLNTSMEPVTNSPQNLNNPSNEILATLAATTDIE TIHPSINKAVTNMGTASSAHVLHSTLPVSSEPSTATSPMVPASS MGDALASISIPGSETTDIEGEPTSSLTAGRKENSTLQEMNSTTES NIILSNVSVGAITEATKMEVPSFDATFIPTPAQSTKFPDIFSVASS RLSNSPPMTISTHMTTTQTGSSGATSKIPLALDTSTLETSAGTPS VVTEGFAHSKITTAMNNDVKDVSQTNPPFQDEASSPSSQAPVL VTTLPSSVAFTPQWHSTSSPVSMSSVLTSSLVKTAGKVDTSLET VTSSPQSMSNTLDDISVTSAATTDIETTHPSINTVVTNVGTTGS AFESHSTVSAYPEPSKVTSPNVTTSTMEDTTISRSIPKSSKTTRT ETETTSSLTPKLRETSISQEITSSTETSTVPYKELTGATTEVSRTD VTSSSSTSFPGPDQSTVSLDISTETNTRLSTSPIMTESAEITITTQT GPHGATSQDTFTMDPSNTTPQAGIHSAMTHGFSQLDVTTLMSR IPQDVSWTSPPSVDKTSSPSSFLSSPAMTTPSLISSTLPEDKLSSP MTSLLTSGLVKITDILRTRLEPVTSSLPNFSSTSDKILATSKDSK DTKEIFPSINTEETNVKANNSGHESHSPALADSETPKATTQMVI TTTVGDPAPSTSMPVHGSSETTNIKREPTYFLTPRLRETSTSQES SFPTDTSFLLSKVPTGTITEVSSTGVNSSSKISTPDHDKSTVPPDT FTGEIPRVFTSSIKTKSAEMTITTQASPPESASHSTLPLDTSTTLS QGGTHSTVTQGFPYSEVTTLMGMGPGNVSWMTTPPVEETSSV SSLMSSPAMTSPSPVSSTSPQSIPSSPLPVTALPTSVLVTTTDVLG TTSPESVTSSPPNLSSITHERPATYKDTAHTEAAMHHSTNTAVT NVGTSGSGHKSQSSVLADSETSKATPLMSTTSTLGDTSVSTSTP

		NISQTNQIQTEPTASLSPRLRESSTSEKTSSTTETNTAFSYVPTG AITQASRTEISSSRTSISDLDRPTIAPDISTGMITRLFTSPIMTKSA EMTVTTQTTTPGATSQGILPWDTSTTLFQGGTHSTVSQGFPHSE ITTLRSRTPGDVSWMTTPPVEETSSGFSLMSPSMTSPSPVSSTSP ESIPSSPLPVTALLTSVLVTTTNVLGTTSPEPVTSSPPNLSSPTQE RLTTYKDTAHTEAMHASMHTNTAVANVGTSISGHESQSSVPA DSHTSKATSPMGITFAMGDTSVSTSTPAFFETRIQTESTSSLIPG LRDTRTSEEINTVTETSTVLSEVPTTTTTEVSRTEVITSSRTTISG PDHSKMSPYISTETITRLSTFPFVTGSTEMAITNQTGPIGTISQAT LTLDTSSTASWEGTHSPVTQRFPHSEETTTMSRSTKGVSWQSP PSVEETSSPSSPVPLPAITSHSSLYSAVSGSSPTSALPVTSLLTSG RRKTIDMLDTHSELVTSSLPSASSFSGEILTSEASTNTETIHFSEN TAETNMGTTNSMHKLHSSVSIHSQPSGHTPPKVTGSMMEDAIV STSTPGSPETKNVDRDSTSPLTPELKEDSTALVMNSTTESNTVF SSVSLDAATEVSRAEVTYYDPTFMPASAQSTKSPDISPEASSSH SNSPPLTISTHKTIATQTGPSGVTSLGQLTLDTSTIATSAGTPSAR TQDFVDSETTSVMNNDLNDVLKTSPFSAEEANSLSSQAPLLVT TSPSPVTSTLQEHSTSSLVSVTSVPTPTLAKITDMDTNLEPVTRS PQNLRNTLATSEATTDTHTMHPSINTAVANVGTTSSPNEFYFT VSPDSDPYKATSAVVITSTSGDSIVSTSMPRSSAMKKIESETTFS LIFRLRETSTSQKIGSSSDTSTVFDKAFTAATTEVSRTELTSSSRT SIQGTEKPTMSPDTSTRSVTMLSTFAGLTKSEERTIATQTGPHR ATSQGTLTWDTSITTSQAGTHSAMTHGFSQLDLSTLTSRVPEYI SGTSPPSVEKTSSSSSLLSLPAITSPSPVPTTLPESRPSSPVHLTSL PTSGLVKTTDMLASVASLPPNLGSTSHKIPTTSEDIKDTEKMYP STNIAVTNVGTTTSEKESYSSVPAYSEPPKVTSPMVTSFNIRDTI VSTSMPGSSEITRIEMESTFSLAHGLKGTSTSQDPIVSTEKSAVL HKLTTGATETSRTEVASSRRTSIPGPDHSTESPDISTEVIPSLPISL GITESSNMTIITRTGPPLGSTSQGTFTLDTPTTSSRAGTHSMATQ EFPHSEMTTVMNKDPEILSWTIPPSIEKTSFSSSLMPSPAMTSPP VSSTLPKTIHTTPSPMTSLLTPSLVMTTDTLGTSPEPTTSSPPNLS STSHEILTTDEDTTAIEAMHPSTSTAATNVETTSSGHGSQSSVL ADSEKTKATAPMDTTSTMGHTTVSTSMSVSSETTKIKRESTYS LTPGLRETSISQNASFSTDTSIVLSEVPTGTTAEVSRTEVTSSGR TSIPGPSQSTVLPEISTRTMTRLFASPTMTESAEMTIPTQTGPSGS TSQDTLTLDTSTTKSQAKTHSTLTQRFPHSEMTTLMSRGPGDM SWQSSPSLENPSSLPSLLSLPATTSPPPISSTLPVTISSSPLPVTSLL TSSPVTTTDMLHTSPELVTSSPPKLSHTSDERLTTGKDTTNTEA VHPSTNTAASNVEIPSSGHESPSSALADSETSKATSPMFITSTQE DTTVAISTPHFLETSRIQKESISSLSPKLRETGSSVETSSAIETSAV LSEVSIGATTEISRTEVTSSSRTSISGSAESTMLPEISTTRKIIKFPT SPILAESSEMTIKTQTSPPGSTSESTFTLDTSTTPSLVITHSTMTQ RLPHSEITTLVSRGAGDVPRPSSLPVEETSPPSSQLSLSAMISPSP VSSTLPASSHSSSASVTSLLTPGQVKTTEVLDASAEPETSSPPSL SSTSVEILATSEVTTDTEKIHPFSNTAVTKVGTSSSGHESPSSVL PDSETTKATSAMGTISIMGDTSVSTLTPALSNTRKIQSEPASSLT

		TRLRETSTSEETSLATEANTVLSKVSTGATTEVSRTEAISFSRTS MSGPEQSTMSQDISIGTIPRISASSVLTESAKMTITTQTGPSESTL ESTLNLNTATTPSWVETHSIVIQGFPHPEMTTSMGRGPGGVSW PSPPFVKETSPPSSPLSLPAVTSPHPVSTTFLAHIPPSPLPVTSLLT SGPATTTDILGTSTEPGTSSSSSLSTTSHERLTTYKDTAHTEAVH PSTNTGGTNVATTSSGYKSQSSVLADSSPMCTTSTMGDTSVLT STPAFLETRRIQTELASSLTPGLRESSGSEGTSSGTKMSTVLSKV PTGATTEISKEDVTSIPGPAQSTISPDISTRTVSWFSTSPVMTESA EITMNTHTSPLGATTQGTSTLDTSSTTSLTMTHSTISQGFSHSQ MSTLMRRGPEDVSWMSPPLLEKTRPSFSLMSSPATTSPSPVSST LPESISSSPLPVTSLLTSGLAKTTDMLHKSSEPVTNSPANLSSTS VEILATSEVTTDTEKTHPSSNRTVTDVGTSSSGHESTSFVLADS QTSKVTSPMVITSTMEDTSVSTSTPGFFETSRIQTEPTSSLTLGL RKTSSSEGTSLATEMSTVLSGVPTGATAEVSRTEVTSSSRTSISG FAQLTVSPETSTETITRLPTSSIMTESAEMMIKTQTDPPGSTPEST HTVDISTTPNWVETHSTVTQRFSHSEMTTLVSRSPGDMLWPSQ SSVEETSSASSLLSLPATTSPSPVSSTLVEDFPSASLPVTSLLNPG LVITTDRMGISREPGTSSTSNLSSTSHERLTTLEDTVDTEDMQPS THTAVTNVRTSISGHESQSSVLSDSETPKATSPMGTTYTMGETS VSISTSDFFETSRIQIEPTSSLTSGLRETSSSERISSATEGSTVLSEV PSGATTEVSRTEVISSRGTSMSGPDQFTISPDISTEAITRLSTSPIM TESAESAITIETGSPGATSEGTLTLDTSTTTFWSGTHSTASPGFS HSEMTTLMSRTPGDVPWPSLPSVEEASSVSSSLSSPAMTSTSFF STLPESISSSPHPVTALLTLGPVKTTDMLRTSSEPETSSPPNLSST SAEILATSEVTKDREKIHPSSNTPVVNVGTVIYKHLSPSSVLAD LVTTKPTSPMATTSTLGNTSVSTSTPAFPETMMTQPTSSLTSGL REISTSQETSSATERSASLSGMPTGATTKVSRTEALSLGRTSTPG PAQSTISPEISTETITRISTPLTTTGSAEMTITPKTGHSGASSQGTF TLDTSSRASWPGTHSAATHRSPHSGMTTPMSRGPEDVSWPSRP SVEKTSPPSSLVSLSAVTSPSPLYSTPSESSHSSPLRVTSLFTPVM MKTTDMLDTSLEPVTTSPPSMNITSDESLATSKATMETEAIQLS ENTAVTQMGTISARQEFYSSYPGLPEPSKVTSPVVTSSTIKDIVS TTIPASSEITRIEMESTSTLTPTPRETSTSQEIHSATKPSTVPYKAL TSATIEDSMTQVMSSSRGPSPDQSTMSQDISTEVITRLSTSPIKT ESTEMTITTQTGSPGATSRGTLTLDTSTTFMSGTHSTASQGFSH SQMTALMSRTPGDVPWLSHPSVEEASSASFSLSSPVMTSSSPVS STLPDSIHSSSLPVTSLLTSGLVKTTELLGTSSEPETSSPPNLSSTS AEILAITEVTTDTEKLEMTNVVTSGYTHESPSSVLADSVTTKAT SSMGITYPTGDTNVLTSTPAFSDTSRIQTKSKLSLTPGLMETSIS EETSSATEKSTVLSSVPTGATTEVSRTEAISSSRTSIPGPAQSTMS SDTSMETITRISTPLTRKESTDMAITPKTGPSGATSQGTFTLDSS STASWPGTHSATTQRFPQSVVTTPMSRGPEDVSWPSPLSVEKN SPPSSLVSSSSVTSPSPLYSTPSGSSHSSPVPVTSLFTSIMMKATD MLDASLEPETTSAPNMNITSDESLAASKATTETEAIHVFENTAA SHVETTSATEELYSSSPGFSEPTKVISPVVTSSSIRDNMVSTTMP GSSGITRIEIESMSSLTPGLRETRTSQDITSSTETSTVLYKMPSGA

		TPEVSRTEVMPSSRTSIPGPAQSTMSLDISDEVVTRLSTSPIMTE SAEITITTQTGYSLATSQVTLPLGTSMTFLSGTHSTMSQGLSHSE MTNLMSRGPESLSWTSPRFVETTRSSSSLTSLPLTTSLSPVSSTL LDSSPSSPLPVTSLILPGLVKTTEVLDTSSEPKTSSSPNLSSTSVEI PATSEIMTDTEKIHPSSNTAVAKVRTSSSVHESHSSVLADSETTI TIPSMGITSAVDDTTVFTSNPAFSETRRIPTEPTFSLTPGFRETST SEETTSITETSAVLYGVPTSATTEVSMTEIMSSNRIHIPDSDQST MSPDIITEVITRLSSSSMMSESTQMTITTQKSSPGATAQSTLTLA TTTAPLARTHSTVPPRFLHSEMTTLMSRSPENPSWKSSLFVEKT SSSSSLLSLPVTTSPSVSSTLPQSIPSSSFSVTSLLTPGMVKTTDTS TEPGTSLSPNLSGTSVEILAASEVTTDTEKIHPSSSMAVTNVGTT SSGHELYSSVSIHSEPSKATYPVGTPSSMAETSISTSMPANFETT GFEAEPFSHLTSGFRKTNMSLDTSSVTPTNTPSSPGSTHLLQSSK TDFTSSAKTSSPDWPPASQYTEIPVDIITPFNASPSITESTGITSFP ESRFTMSVTESTHHLSTDLLPSAETISTGTVMPSLSEAMTSFAT TGVPRAISGSGSPFSRTESGPGDATLSTIAESLPSSTPVPFSSSTFT TTDSSTIPALHEITSSSATPYRVDTSLGTESSTTEGRLVMVSTLD TSSQPGRTSSSPILDTRMTESVELGTVTSAYQVPSLSTRLTRTD GIMEHITKIPNEAAHRGTIRPVKGPQTSTSPASPKGLHTGGTKR METTTTALKTTTTALKTTSRATLTTSVYTPTLGTLTPLNASMQ MASTIPTEMMITTPYVFPDVPETTSSLATSLGAETSTALPRTTPS VFNRESETTASLVSRSGAERSPVIQTLDVSSSEPDTTASWVIHP AETIPTVSKTTPNFFHSELDTVSSTATSHGADVSSAIPTNISPSEL DALTPLVTISGTDTSTTFPTLTKSPHETETRTTWLTHPAETSSTIP RTIPNFSHHESDATPSIATSPGAETSSAIPIMTVSPGAEDLVTSQV TSSGTDRNMTIPTLTLSPGEPKTIASLVTHPEAQTSSAIPTSTISP AVSRLVTSMVTSLAAKTSTTNRALTNSPGEPATTVSLVTHPAQ TSPTVPWTTSIFFHSKSDTTPSMTTSHGAESSSAVPTPTVSTEVP GVVTPLVTSSRAVISTTIPILTLSPGEPETTPSMATSHGEEASSAI PTPTVSPGVPGVVTSLVTSSRAVTSTTIPILTFSLGEPETTPSMAT SHGTEAGSAVPTVLPEVPGMVTSLVASSRAVTSTTLPTLTLSPG EPETTPSMATSHGAEASSTVPTVSPEVPGVVTSLVTSSSGVNST SIPTLILSPGELETTPSMATSHGAEASSAVPTPTVSPGVSGVVTP LVTSSRAVTSTTIPILTLSSSEPETTPSMATSHGVEASSAVLTVSP EVPGMVTSLVTSSRAVTSTTIPTLTISSDEPETTTSLVTHSEAKM ISAIPTLAVSPTVQGLVTSLVTSSGSETSAFSNLTVASSQPETIDS WVAHPGTEASSVVPTLTVSTGEPFTNISLVTHPAESSSTLPRTTS RFSHSELDTMPSTVTSPEAESSSAISTTISPGIPGVLTSLVTSSGR DISATFPTVPESPHESEATASWVTHPAVTSTTVPRTTPNYSHSEP DTTPSIATSPGAEATSDFPTITVSPDVPDMVTSQVTSSGTDTSITI PTLTLSSGEPETTTSFITYSETHTSSAIPTLPVSPGASKMLTSLVIS SGTDSTTTFPTLTETPYEPETTAIQLIHPAETNTMVPRTTPKFSH SKSDTTLPVAITSPGPEASSAVSTTTISPDMSDLVTSLVPSSGTD TSTTFPTLSETPYEPETTATWLTHPAETSTTVSGTIPNFSHRGSD TAPSMVTSPGVDTRSGVPTTTIPPSIPGVVTSQVTSSATDTSTAI PTLTPSPGEPETTASSATHPGTQTGFTVPIRTVPSSEPDTMASW

		VTHPPQTSTPVSRTTSSFSHSSPDATPVMATSPRTEASSAVLTTI SPGAPEMVTSQITSSGAATSTTVPTLTHSPGMPETTALLSTHPR TETSKTFPASTVFPQVSETTASLTIRPGAETSTALPTQTTSSLFTL LVTGTSRVDLSPTASPGVSAKTAPLSTHPGTETSTMIPTSTLSLG LLETTGLLATSSSAETSTSTLTLTVSPAVSGLSSASITTDKPQTV TSWNTETSPSVTSVGPPEFSRTVTGTTMTLIPSEMPTPPKTSHGE GVSPTTILRTTMVEATNLATTGSSPTVAKTTTTFNTLAGSLFTP LTTPGMSTLASESVTSRTSYNHRSWISTTSSYNRRYWTPATSTP VTSTFSPGISTSSIPSSTAATVPFMVPFTLNFTITNLQYEEDMRHP GSRKFNATERELQGLLKPLFRNSSLEYLYSGCRLASLRPEKDSS ATAVDAICTHRPDPEDLGLDRERLYWELSNLTNGIQELGPYTL DRNSLYVNGFTHRSSMPTTSTPGTSTVDVGTSGTPSSSPSPTTA GPLLMPFTLNFTITNLQYEEDMRRTGSRKFNTMESVLQGLLKP LFKNTSVGPLYSGCRLTLLRPEKDGAATGVDAICTHRLDPKSP GLNREQLYWELSKLTNDIEELGPYTLDRNSLYVNGFTHQSSVS TTSTPGTSTVDLRTSGTPSSLSSPTIMAAGPLLVPFTLNFTITNLQ YGEDMGHPGSRKFNTTERVLQGLLGPIFKNTSVGPLYSGCRLT SLRSEKDGAATGVDAICIHHLDPKSPGLNRERLYWELSQLTNG IKELGPYTLDRNSLYVNGFTHRTSVPTSSTPGTSTVDLGTSGTP FSLPSPATAGPLLVLFTLNFTITNLKYEEDMHRPGSRKFNTTER VLQTLLGPMFKNTSVGLLYSGCRLTLLRSEKDGAATGVDAICT HRLDPKSPGVDREQLYWELSQLTNGIKELGPYTLDRNSLYVN GFTHWIPVPTSSTPGTSTVDLGSGTPSSLPSPTTAGPLLVPFTLN FTITNLKYEEDMHCPGSRKFNTTERVLQSLLGPMFKNTSVGPL YSGCRLTLLRSEKDGAATGVDAICTHRLDPKSPGVDREQLYW ELSQLTNGIKELGPYTLDRNSLYVNGFTHQTSAPNTSTPGTSTV DLGTSGTPSSLPSPTSAGPLLVPFTLNFTITNLQYEEDMHHPGSR KFNTTERVLQGLLGPMFKNTSVGLLYSGCRLTLLRPEKNGAAT GMDAICSHRLDPKSPGLNREQLYWELSQLTHGIKELGPYTLDR NSLYVNGFTHRSSVAPTSTPGTSTVDLGTSGTPSSLPSPTTAVPL LVPFTLNFTITNLQYGEDMRHPGSRKFNTTERVLQGLLGPLFK NSSVGPLYSGCRLISLRSEKDGAATGVDAICTHHLNPQSPGLDR EQLYWQLSQMTNGIKELGPYTLDRNSLYVNGFTHRSSGLTTST PWTSTVDLGTSGTPSPVPSPTTTGPLLVPFTLNFTITNLQYEEN MGHPGSRKFNITESVLQGLLKPLFKSTSVGPLYSGCRLTLLRPE KDGVATRVDAICTHRPDPKIPGLDRQQLYWELSQLTHSITELG PYTLDRDSLYVNGFTQRSSVPTTSTPGTFTVQPETSETPSSLPGP TATGPVLLPFTLNFTITNLQYEEDMRRPGSRKFNTTERVLQGLL MPLFKNTSVSSLYSGCRLTLLRPEKDGAATRVDAVCTHRPDPK SPGLDRERLYWKLSQLTHGITELGPYTLDRHSLYVNGFTHQSS MTTTRTPDTSTMHLATSRTPASLSGPMTASPLLVLFTINFTITNL RYEENMHHPGSRKFNTTERVLQGLLRPVFKNTSVGPLYSGCRL TLLRPKKDGAATKVDAICTYRPDPKSPGLDREQLYWELSQLTH SITELGPYTLDRDSLYVNGFTQRSSVPTTSIPGTPTVDLGTSGTP VSKPGPSAASPLLVLFTLNFTITNLRYEENMQHPGSRKFNTTER VLQGLLRSLFKSTSVGPLYSGCRLTLLRPEKDGTATGVDAICT

		HHPDPKSPRLDREQLYWELSQLTHNITELGPYALDNDSLFVNG FTHRSSVSTTSTPGTPTVYLGASKTPASIFGPSAASHLLILFTLNF TITNLRYEENMWPGSRKFNTTERVLQGLLRPLFKNTSVGPLYS GCRLTLLRPEKDGEATGVDAICTHRPDPTGPGLDREQLYLELS QLTHSITELGPYTLDRDSLYVNGFTHRSSVPTTSTGVVSEEPFT LNFTINNLRYMADMGQPGSLKFNITDNVMQHLLSPLFQRSSLG ARYTGCRVIALRSVKNGAETRVDLLCTYLQPLSGPGLPIKQVF HELSQQTHGITRLGPYSLDKDSLYLNGYNEPGPDEPPTTPKPAT TFLPPLSEATTAMGYHLKTLTLNFTISNLQYSPDMGKGSATFNS TEGVLQHLLRPLFQKSSMGPFYLGCQLISLRPEKDGAATGVDT TCTYHPDPVGPGLDIQQLYWELSQLTHGVTQLGFYVLDRDSLF INGYAPQNLSIRGEYQINFHIVNWNLSNPDPTSSEYITLLRDIQD KVTTLYKGSQLHDTFRFCLVTNLTMDSVLVTVKALFSSNLDPS LVEQVFLDKTLNASFHWLGSTYQLVDIHVTEMESSVYQPTSSS STQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQLF RNSSIKSYFSDCQVSTFRSVPNRHHTGVDSLCNFSPLARRVDRV AIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNS DLPFWAVILIGLAGLLGVITCLICGVLVTTRRRKKEGEYNVQQ QCPGYYQSHLDLEDLQ
151	MUC16c114-N1	AFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGY SPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRR KKEGEYNVQQQCPGYYQSHLDLEDLQ
152	MUC16c114-N2	NFSPLARRVDRVAIYEEFLRMTRAGTQLQNFTLDRSSVLVDGY SPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRR KKEGEYNVQQQCPGYYQSHLDLEDLQ
153	MUC16c114-N12	AFSPLARRVDRVAIYEEFLRMTRAGTQLQNFTLDRSSVLVDGY SPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRR KKEGEYNVQQQCPGYYQSHLDLEDLQ
154	MUC16c114-N123	AFSPLARRVDRVAIYEEFLRMTRAGTQLQAFTLDRSSVLVDGY SPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRR KKEGEYNVQQQCPGYYQSHLDLEDLQ
155	MUC16c344 N-term of first tandem repeat	WELSQL
156	MUC16c344 C-term of first tandem repeat	TGVDSLC
157	MUC16c344 N-term of ectodomain	NFSPLAR
158	MUC16c344 C-term of ectodomain	TGNSDLP
159	Transmembrane	FWAVILIGLAGLLGLITCLICGVLV
160	Cytoplasmic	TTRRRKKEGEYNVQQQCPGYYQSHLDLEDLQ

	tail	
161	MUC16c114 ectodomain	NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGY SPNRNEPLTGNSDLP
162	MUC16c80 ectodomain	NFSPLARRVDRVAIYEEFLRMDLP
163	MUC16c86 ectodomain	NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGY SPNRNEPLTGNSDLP
164	MUC16c86 transmembrane	FWAVILIGLAGLLGLITCLICG
165	MUC16c86 cytoplasmic	DLEDLQ
166	MUC16 3(N to A)c114 ectodomain	AFSPLARRVDRVAIYEEFLRMTRAGTQLQAFTLDRSSVLVDGY SPNRNEPLTGNSDLP
167	LGALS3 sugar binding domain	PYNLPLPGGVVPRMLITILGTVKPNANRIALDFQRGNDVAFHF NPRFNENNRRVIVCNTKLDNNWGREERQSVFPFESGKPFKIQV LVEPDHFKVAVNDAHLLQYNHRVKKLNEISKLGISGDIDLTS
168	MUC16 nonglycosylated peptide 2	CTLDRSSVLVDGYSPNRNE
169	MUC16 unrelated peptide 18mer	GAVPRSATINVSRIATGP
170	18mer (no C)	TRNGTQLQNFTLDRSSV
171	15mer (no C)	GTQLQNFTLDRSSV
172	MUC16c114-N23	NFSPLARRVDRVAIYEEFLRMTRAGTQLQAFTLDRSSVLVDGY SPNRNEPLTGNSDLPFWAVILIGLAGLLGLITCLICGVLVTTRRR KKEGEYNVQQQCPGYYQSHLDLEDLQ
173	N24 mut c344	WELSQLTHGVTQLGFYVLDRDSLFINGYAPQNLSIRGEYQINF HIVNQNLSNPDPTSSEYITLLRDIQDKVTTLYKGSQLHDTFRFC LVTNLTMDSVLVTVKALFSSNLDPSLVEQVFLDKTLNASFHQL GSTYQLVDIHVTEMESSVYQPTSSSSTQHFYLNFTITNLPYSQD KAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQVSTFRS VPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRAGTQLQ NFTLDRSSVLVDGYSPNRNEPLTGNSDLPFWAVILIGLAGLLGL ITCLICGVLVTTRRRKKEGEYNVQQQCPGYYQSHLDLEDLQ
174	N30 mut c344	WELSQLTHGVTQLGFYVLDRDSLFINGYAPQNLSIRGEYQINF HIVNQNLSNPDPTSSEYITLLRDIQDKVTTLYKGSQLHDTFRFC LVTNLTMDSVLVTVKALFSSNLDPSLVEQVFLDKTLNASFHQL GSTYQLVDIHVTEMESSVYQPTSSSSTQHFYLNFTITNLPYSQD KAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQVSTFRS VPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQ AFTLDRSSVLVDGYSPNRNEPLTGNSDLPFWAVILIGLAGLLGL ITCLICGVLVTTRRRKKEGEYNVQQQCPGYYQSHLDLEDLQ
175	N24-N30 mut c344	WELSQLTHGVTQLGFYVLDRDSLFINGYAPQNLSIRGEYQINF HIVNQNLSNPDPTSSEYITLLRDIQDKVTTLYKGSQLHDTFRFC

		LVTNLTMDSVLVTVKALFSSNLDPSLVEQVFLDKTLNASFHQL GSTYQLVDIHVTEMESSVYQPTSSSSTQHFYLNFTITNLPYSQD KAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFSDCQVSTFRS VPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRAGTQLQ AFTLDRSSVLVDGYSPNRNEPLTGNSDLPFWAVILIGLAGLLGL ITCLICGVLVTTRRRKKEGEYNVQQQCPGYYQSHLDLEDLQ

8. EQUIVALENTS

[00695] All publications, patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

2016233309 22 Oct 2021

What is claimed:

1. An antibody or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof

(a) immunospecifically binds to a cell recombinantly expressing a first form of MUC16, which first form is glycosylated, and wherein the amino acid sequence of the first form is SEQ ID NO:133;

(b) lacks immunospecific binding to a cell recombinantly expressing a second form of MUC16, which second form is unglycosylated, and wherein the amino acid sequence of the second form is SEQ ID NO:139; and

(c) inhibits matrigel invasion in vitro of cells recombinantly expressing said first form of MUC16.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein (i) the cell recombinantly expressing the first form of MUC16 is a SKOV3 cell; (ii) the cell recombinantly expressing the second form of MUC16 is a SKOV3 cell; and (iii) the cells in step (c) are SKOV3 cells.

3. The antibody or antigen-binding fragment thereof of any one of claims 1 to 2, wherein the antibody or antigen-binding fragment thereof immunospecifically binds to the amino acid sequence CTRNGTQLQNFTLDRSSV (SEQ ID NO:130), wherein amino acid residue number 4 (N4) and amino acid residue number 10 (N10) of CTRNGTQLQNFTLDRSSV (SEQ ID NO:130) are glycosylated.

4. The antibody or antigen-binding fragment thereof of any one claims 1 to 3 , wherein the antibody or antigen-binding fragment thereof immunospecifically binds to an epitope comprising N-glycosylated asparagine 1806 of SEQ ID NO: 150.

5. The antibody or antigen-binding fragment thereof of any one of claims 1 to 4, wherein the antibody or antigen-binding fragment thereof immunospecifically binds to the amino acid sequence CGTQLQNFTLDRSSV (SEQ ID NO:131), wherein amino acid residue number 7 (N7) of CGTQLQNFTLDRSSV (SEQ ID NO:131) is glycosylated.

2016233309 22 Oct 2021

6. The antibody or antigen-binding fragment thereof of claim 3, wherein the glycosylation of amino acid residue number 4 (N4) and amino acid residue number 10 (N10) consists of an N-linked chitobiose.

7. The antibody or antigen-binding fragment thereof of claim 4, wherein the glycosylation of amino acid residue Asn1806 of SEQ ID NO: 150 consists of an N-linked chitobiose.

8. The antibody or antigen-binding fragment thereof of claim 5, wherein the glycosylation of amino acid residue number 7 (N7) consists of an N-linked chitobiose.

9. The antibody or antigen-binding fragment thereof of any one of claims 1 to 8, wherein the antibody or antigen-binding fragment thereof inhibits growth of a tumor that expresses a glycosylated form of MUC16.

10. The antibody or antigen-binding fragment thereof of any one of claims 1 to 9, wherein the antibody or antigen-binding fragment thereof lacks immunospecific binding to a cell recombinantly expressing a third form of MUC16, which third form is glycosylated, and wherein the amino acid sequence of the third form is SEQ ID NO: 139.

11. The antibody or antigen-binding fragment thereof of any one of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:

(a) (i) a VH comprising a VH CDR1 comprising the amino acid sequence TX1GMGVG (SEQ ID NO:103), wherein X1 is L or V; a VH CDR2 comprising the amino acid sequence HIWWDDX2DKYYX3PALKS (SEQ ID NO:104), wherein X2 is E or absent, and X3 is Y or N; and a VH CDR3 comprising the amino acid sequence IGTAQATDALDY (SEQ ID NO:105); and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence RSSKSLX4X5SNGNTYLY (SEQ ID NO:106), wherein X4 is R or L, and X5 is K or H; a VL CDR2 comprising the amino acid sequence YMSNLAS (SEQ ID NO:107); and a VL CDR3 comprising the amino acid sequence MQX6LEX7PLT (SEQ ID NO:108), wherein X6 is G or S, and X7 is H or Y; or

2016233309 22 Oct 2021

(b) (i) a VH comprising a VH CDR1 comprising the amino acid sequence GFSLX8TX9GM (SEQ ID NO:109), wherein X8 is N or S, and wherein X9 is L or V; a VH CDR2 comprising the amino acid sequence WDDX10 (SEQ ID NO:110), wherein X10 is E or absent; and a VH CDR3 comprising the amino acid sequence GTAQATDALD (SEQ ID NO:111); and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence SKSLX11X12SNGNTY (SEQ ID NO:112), wherein X11 is L or R, and X12 is H or K; a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:113); and a VL CDR3 comprising the amino acid sequence X13LEX14PL (SEQ ID NO:114), wherein X13 is G or S, and X14 is H or Y; or

(c) (i) a VH CDR1 comprising the amino acid sequence GFSLX15TX16GMG (SEQ ID NO:115), wherein X15 is N or S, and X16 is V or L; a VH CDR2 comprising the amino acid sequence IWWDDX17DK (SEQ ID NO:116), wherein X17 is E or absent; and a VH CDR3 comprising the amino acid sequence X18RIGTAQATDALDY (SEQ ID NO:117), wherein X18 is T, A, or S; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence KSLX19X20SNGNTY (SEQ ID NO:118), wherein X19 is V or L, and X20 is H or K; a VL CDR2 comprising the amino acid sequence YMS (SEQ ID NO:119); and a VL CDR3 comprising the amino acid sequence MQSLEYPLT (SEQ ID NO:120); or

(d) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88; or

(e) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94; or

(f) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3

2016233309 22 Oct 2021

comprising the amino acid sequence of SEQ ID NO:97 and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100; or

(g) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:23, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:24, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:25; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:26, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:27, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:28; or

(h) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:29, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:30, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:31; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:32, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:33, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:34; or

(i) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:35, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:36, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:37; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:38, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:39, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:40; or

(j) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:44, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:45; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:46, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:47, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:48; or

(k) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:50, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:51; and (ii) a VL comprising a VL CDR1

2016233309 22 Oct 2021

comprising the amino acid sequence of SEQ ID NO:52, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:53, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:54; or

(l) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:56, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:57; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:58, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:59, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:60; or

(m) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:3, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:4, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:5; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:6, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:7, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:8; or

(n) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:9, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:10, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:11; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:12, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:13, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:14; or

(o) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:16, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:17; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:18, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:19, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:20; or

(p) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:63, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:64, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:65; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:66, a VL CDR2 comprising the amino acid

2016233309 22 Oct 2021

sequence of SEQ ID NO:67, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:68; or

(q) (i) a VH comprising aVH CDR1 comprising the amino acid sequence of SEQ ID NO:69, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:70, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:71; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:72, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:73, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:74; or

(r) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:75, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:76, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:77; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:78, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:79, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:80.

12. The antibody or antigen-binding fragment thereof of any one of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:

(a) (i) a VH comprising the amino acid sequence of QVX21LKESGPGX22LQPSQTLSLTCSFSGFSLX23TX24GMGVGWX25RQX26SGKGLEW LAHIWWDDX27DKYYX28PALKSRLTISX29X30X31SKNQVFLKIX32NVX33TADX34AT YYCX35RIGTAQATDALDYWGQGTSVTVSS (SEQ ID NO:101), wherein X21 is T or N, X22 is I or K, X23 is N or S, X24 is V or L, X25 is S or I, X26 is P or S, X27 is E or absent, X28 is N or Y, X29 is K or R, X30 is A or D, X31 is T or S, X32 is V or A, X33 is G or D, X34 is T, I, or S, and X35 is T, S, or A; and (ii) a VL comprising the amino acid sequence of DIVMTQAAPSX36X37VTPGESVSISCRSSKSLX38X39SNGNTYLYWFLQRPGQSPQRLIY YMSNLASGVPDRFSGRGSGTDFTLX40ISRVEAX41DVGVYYCMQX42LEX43PLTFGGG TKLEIK (SEQ ID NO:102), wherein X36 is I or V, X37 is P or S, X38 is R or L, X39 is K or H, X40 is R or K, X41 is E or G, X42 is S or G, and X43 is Y or H; or

(b) (i) a VH comprising the amino acid sequence of SEQ ID NO:81; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:82; or

2016233309 22 Oct 2021

(c) (i) a VH comprising the amino acid sequence of SEQ ID NO:1; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:2; or

(d) (i) a VH comprising the amino acid sequence of SEQ ID NO:21; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:22; or

(e) (i) a VH comprising the amino acid sequence of SEQ ID NO:41; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:42; or

(f) (i) a VH comprising the amino acid sequence of SEQ ID NO:61; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:62.

13. The antibody or antigen-binding fragment thereof of any one of claims 1 to 10, wherein the antibody or antigen-binding fragment thereof comprises:

(a) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:83, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:84, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:85; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:86, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:87, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:88; or

(b) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:89, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:90, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:91; and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:92, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:93, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:94; or

(c) (i) a VH comprising a VH CDR1 comprising the amino acid sequence of SEQ ID NO:95, a VH CDR2 comprising the amino acid sequence of SEQ ID NO:96, and a VH CDR3 comprising the amino acid sequence of SEQ ID NO:97 and (ii) a VL comprising a VL CDR1 comprising the amino acid sequence of SEQ ID NO:98, a VL CDR2 comprising the amino acid sequence of SEQ ID NO:99, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO:100.

14. The antibody or antigen-binding fragment thereof of any one of claims 1 to 10,

2016233309 22 Oct 2021

wherein the antibody or antigen-binding fragment thereof comprises: (i) a VH comprising the amino acid sequence of SEQ ID NO:81; and (ii) a VL comprising the amino acid sequence of SEQ ID NO:82.

15. The antibody or antigen-binding fragment thereof of any one of claims 1 to 11, and 13, wherein the antibody or antigen-binding fragment thereof is humanized.

16. The antibody or antigen-binding fragment thereof of any one of claims 1 to 15, wherein the antibody is a monoclonal antibody.

17. An antibody conjugate comprising the antibody or antigen-binding fragment thereof of any one of claims 1 to 16 conjugated to an agent.

18. The antibody or antigen-binding fragment thereof of any one of claims 1 to 16, wherein the antibody or antigen-binding fragment thereof is a bispecific antibody.

19. The bispecific antibody of claim 18, wherein the bispecific antibody comprises an immunoglobulin that immunospecifically binds MUC16, wherein the light chain of the immunoglobulin is conjugated via a peptide linker to a single chain variable fragment (scFv) that immunospecifically binds to CD3.

20. A bispecific antibody conjugate comprising the bispecific antibody of claim 18 or 19 conjugated to an agent.

21. The antibody or antigen-binding fragment thereof of any one of claims 1 to 16, which is an antigen-binding fragment that is a scFv.

22. A scFv conjugate comprising the scFv of claim 21 conjugated to an agent.

23. A chimeric antigen receptor (CAR) comprising: the scFv of claim 21 or the scFv conjugate of claim 22.

2016233309 22 Oct 2021

24. A CAR comprising the antigen-binding fragment of any one of claims 1 to 16.

25. A T cell which recombinantly expresses the CAR of claim 23 or 24.

26. A polynucleotide comprising nucleic acid sequences encoding: (i) the scFv of claim 21, (ii) the scFv conjugate of claim 22, or (iii) the CAR of claim 23 or 24.

27. An *ex vivo* cell comprising one or more polynucleotides encoding the antibody or antigen-binding fragment thereof of any one of claims 1 to 16 operably linked to a promoter.

28. A pharmaceutical composition comprising: a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1 to 16, the antibody conjugate of claim 17, the bispecific antibody of claim 18 or 19, the bispecific antibody conjugate of claim 20, the scFv of claim 21, the scFv conjugate of claim 22, or the CAR of claim 23.

29. A pharmaceutical composition comprising a therapeutically effective amount of the CAR of claim 24 and a pharmaceutically acceptable carrier.

30. A pharmaceutical composition comprising a therapeutically effective amount of the T cell of claim 25 and a pharmaceutically acceptable carrier.

31. A method of treating MUC16-expressing cancer in a patient in need thereof, comprising administering to said patient the pharmaceutical composition of claim 28.

32. A method of treating MUC16-expressing cancer in a patient in need thereof, comprising administering to said patient the pharmaceutical composition of claim 29.

33. A method of treating MUC16-expressing cancer in a patient in need thereof, comprising administering to said patient the pharmaceutical composition of claim 30.

2016233309 22 Oct 2021

34. The method of any one of claims 31 to 33, wherein said cancer is a cancer of the lung, pancreas, breast, uterine, fallopian tube, primary peritoneum, or ovary.

35. The method of any one of claims 31 to 34, wherein said patient is a human patient.

36. The method of any one of claims 31 to 35, wherein the pharmaceutical composition is to be administered to the patient in combination with a therapeutically effective amount of an additional therapeutic agent.

37. Use of the pharmaceutical composition of claim 28 in the preparation of a medicament for treating MUC16-expressing cancer in a patient in need thereof.

38. Use of the pharmaceutical composition of claim 29 in the preparation of a medicament for treating MUC16-expressing cancer in a patient in need thereof.

39. Use of the pharmaceutical composition of claim 30 in the preparation of a medicament for treating MUC16-expressing cancer in a patient in need thereof.

Fig. 1A

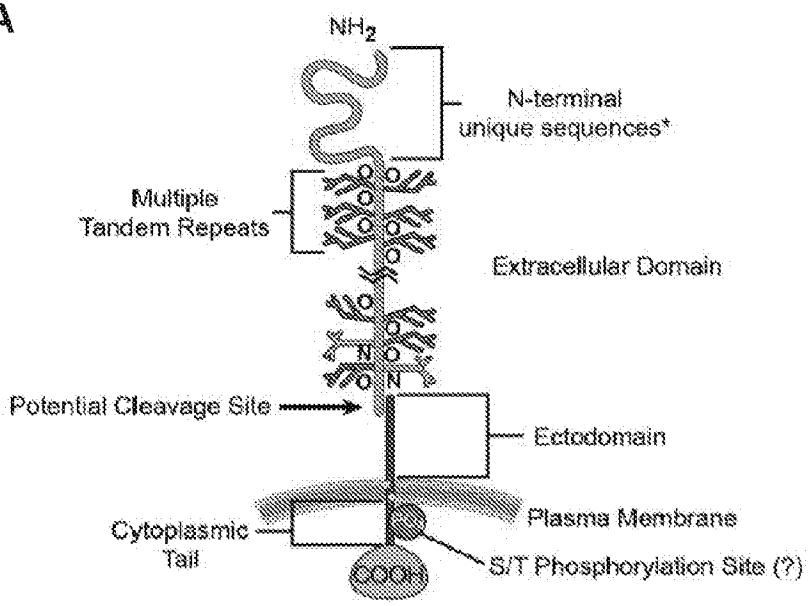
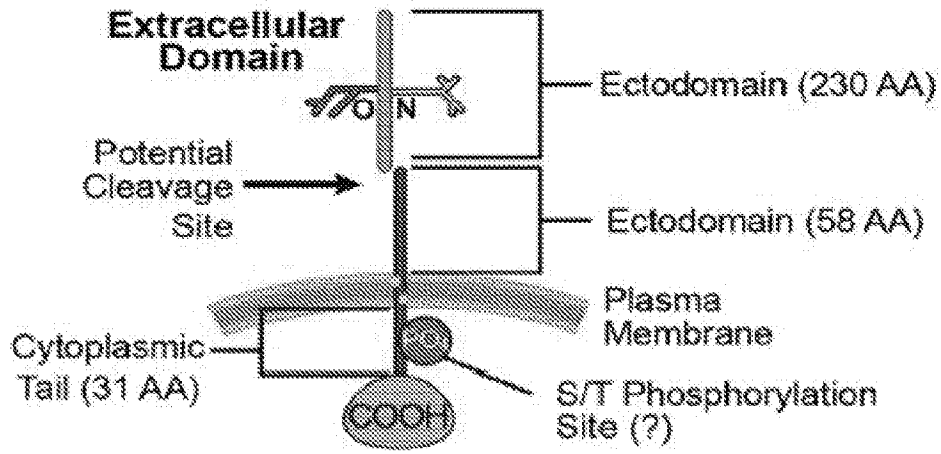


Fig. 1B



MUC16^{c344}

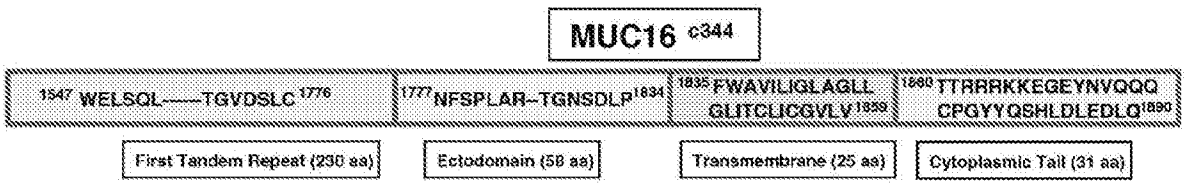


Fig. 1C

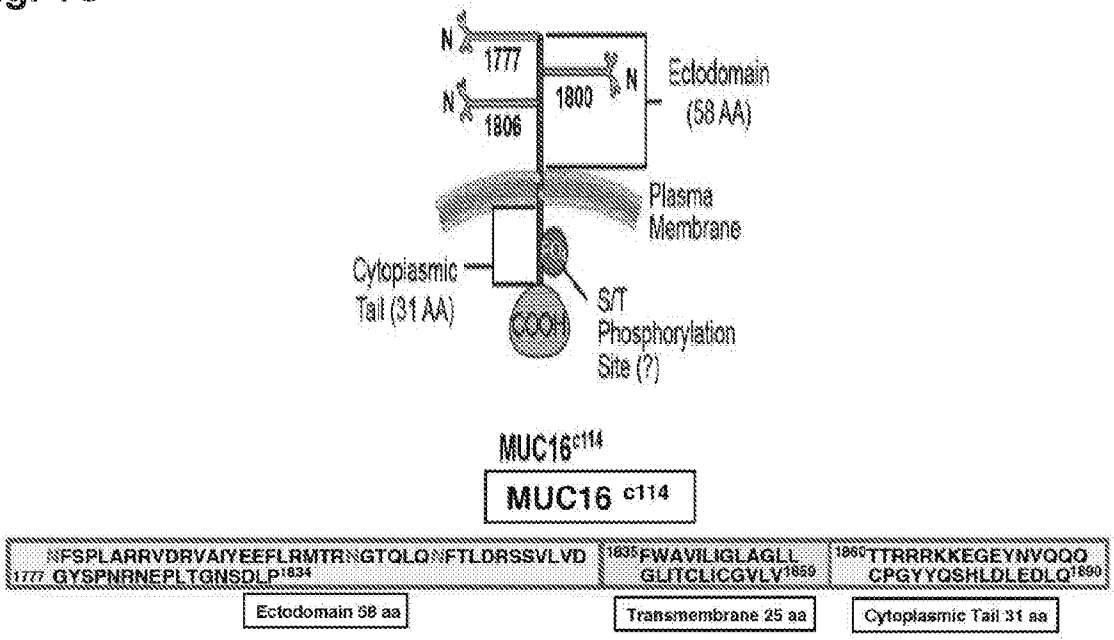

N
1777
N
1806
1800
N
Ectodomain
(58 AA)
Plasma
Membrane
Cytoplasmic
Tail (31 AA)
COOH
S/T
Phosphorylation
Site (?)
MUC16c114
MUC16 c114
NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVD
1777 GYSPNRNEPLTQNSDLP1834
1835FWAVILIGLAGLL
GLITCLICGVLV1859
1860TTRRRKKEGEYNVQQQ
CPGYYQSHLDLEDLQ1890
Ectodomain 58 aa
Transmembrane 25 aa
Cytoplasmic Tail 31 aa

Fig. 1D

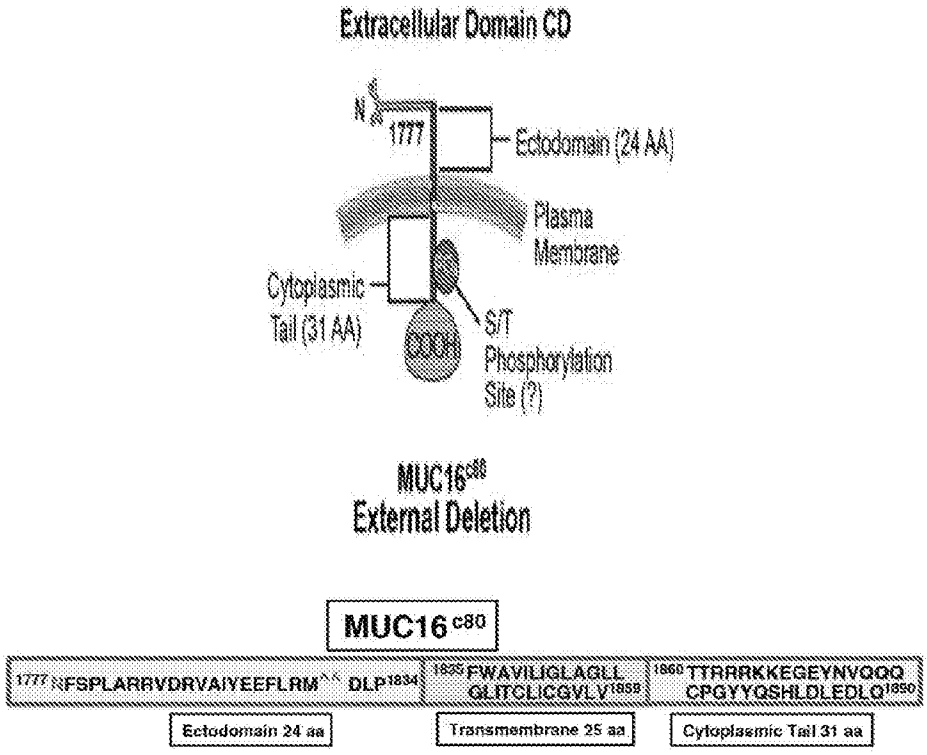
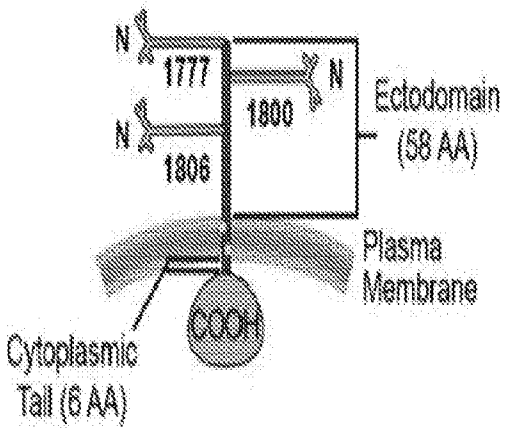

Extracellular Domain CD
N
1777
Ectodomain (24 AA)
Plasma
Membrane
Cytoplasmic
Tail (31 AA)
COOH
S/T
Phosphorylation
Site (?)
MUC16c80
External Deletion
MUC16 c80
1777NFSPLARRVDRVAIYEEFLRM^^ DLP1834
1835FWAVILIGLAGLL
GLITCLICGVLV1859
1860TTRRRKKEGEYNVQQQ
CPGYYQSHLDLEDLQ1890
Ectodomain 24 aa
Transmembrane 25 aa
Cytoplasmic Tail 31 aa

Fig. 1E



MUC16^{c86}
Internal Deletion

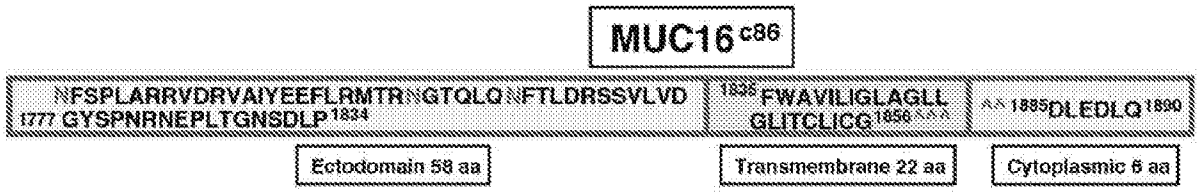


Fig. 1F

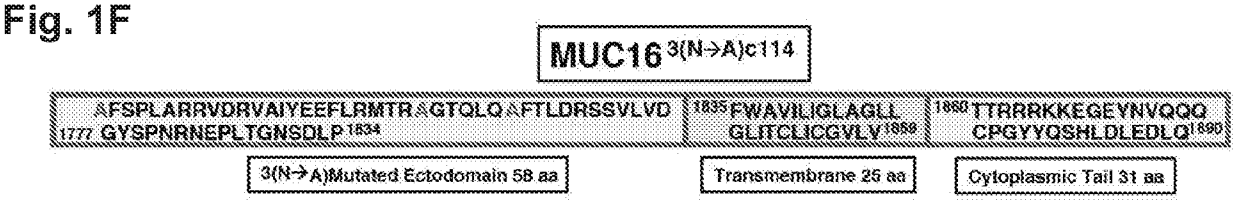


Fig. 1G

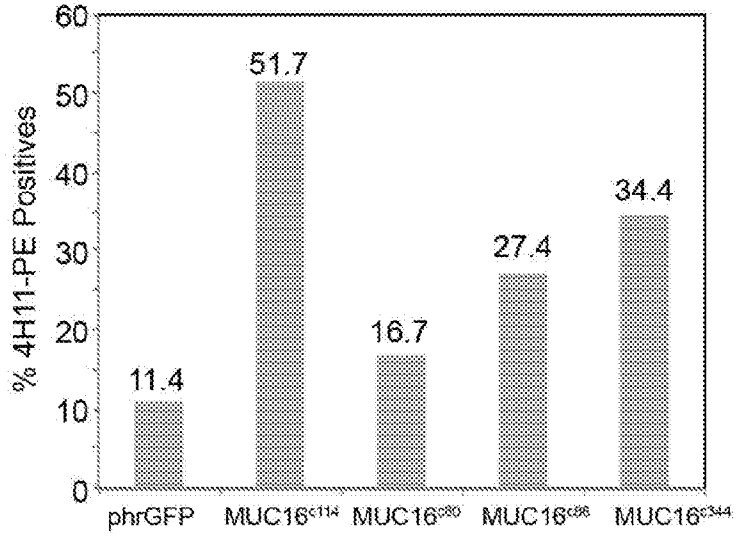


Fig. 1H

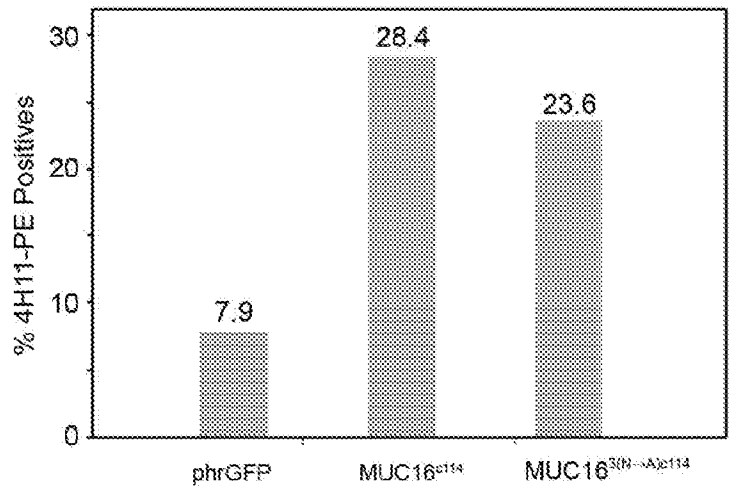


Fig. 1I

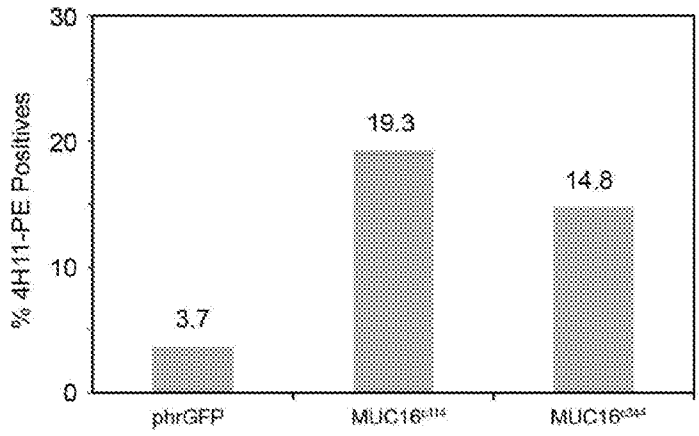


Fig. 2A 3T3 Transfectant *in vitro* Growth

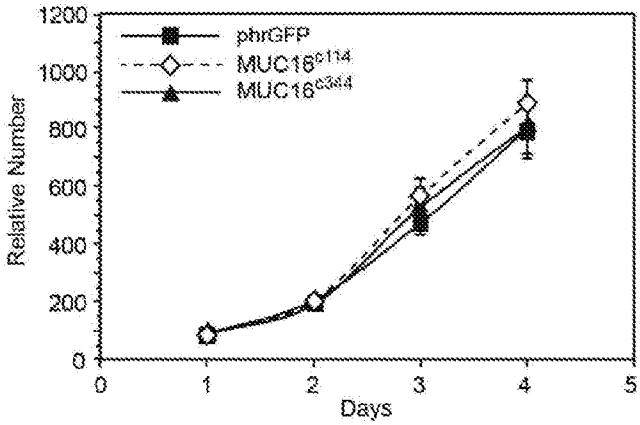


Fig. 2B A2780 Transfectant *in vitro* Growth

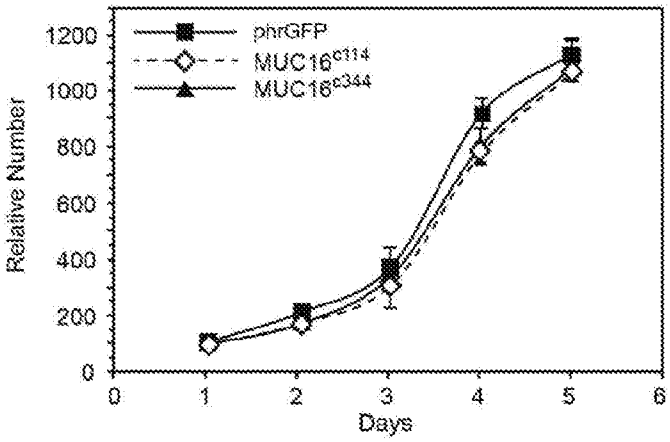


Fig. 2C 3T3 Transfectant *in vitro* Growth

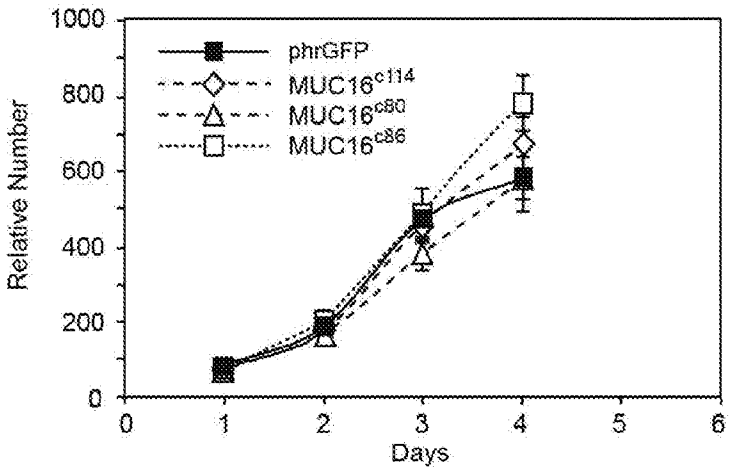


Fig. 3A

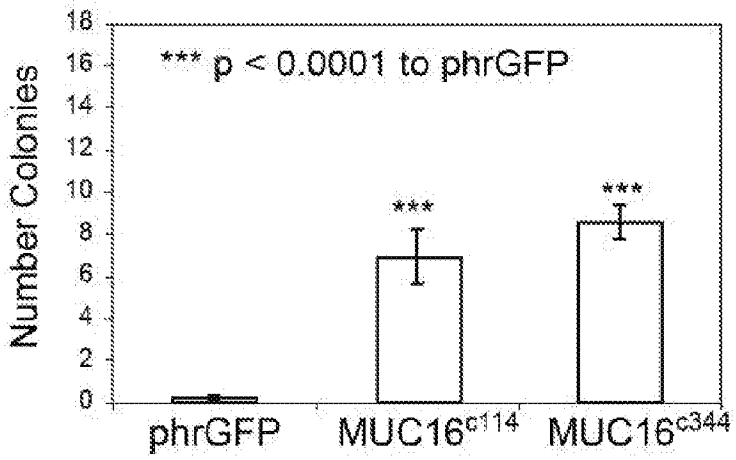


Fig. 3B 3T3 Transfectant Matrigel Invasion

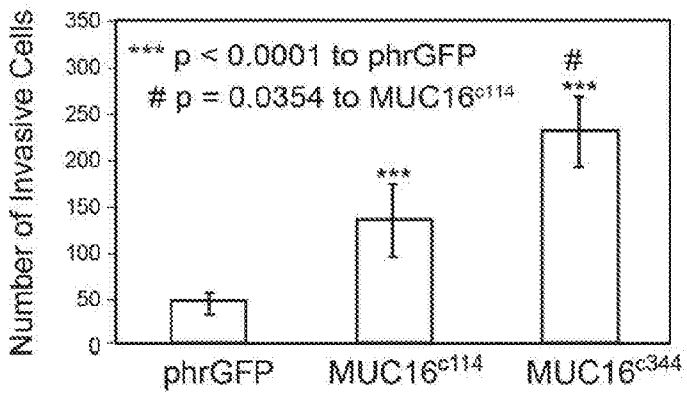


Fig. 3C

Symbol	3T3 phr vs MUC16^{c114}		3T3 phr vs MUC16^{c344}	
	p value	Fold Change	p value	Fold Change
CXCL12	0.0008	10.74	0.0071	3.48
NF2	0.0075	-1.31	0.0317	-1.28
FN1	0.0166	-3.06	0.0377	-2.20
CTBP1	0.0283	-1.76	0.2043	-1.36
SMAD4	0.0324	-2.42	0.1759	-1.34
CDH11	0.0790	2.73	0.0057	9.25
MMP2	0.1634	1.43	0.0445	1.86
MMP9	0.7675	1.03	0.0315	1.12

Fig. 3D

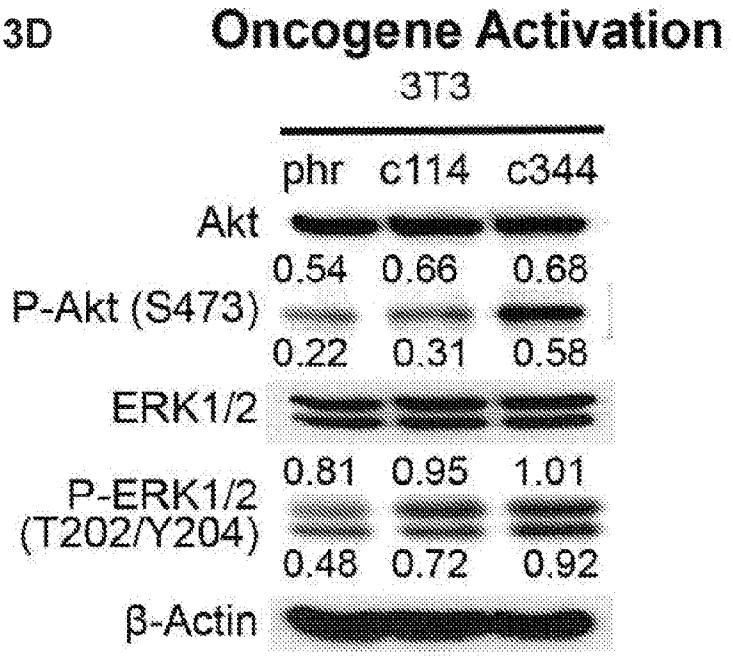
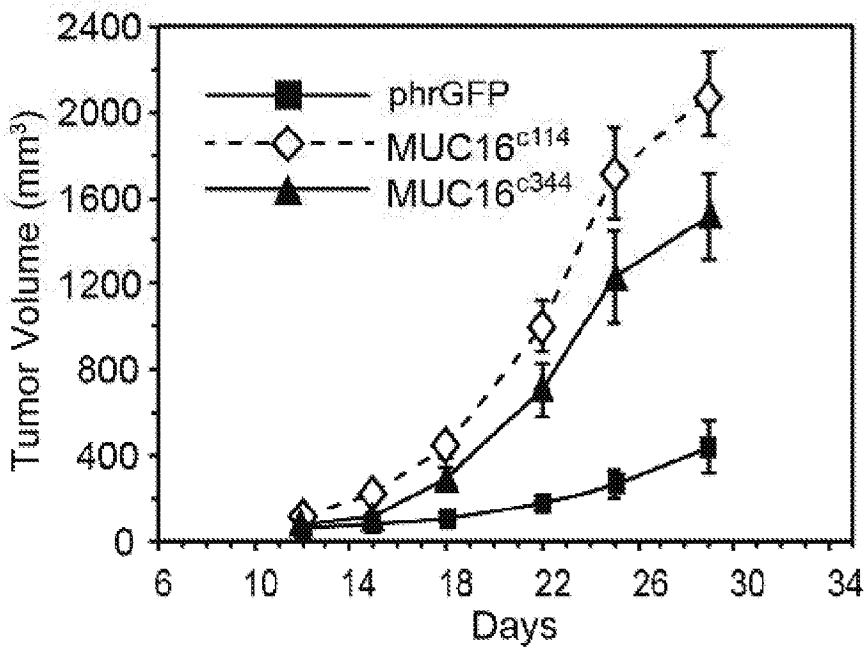

Oncogene Activation
3T3
phr
c114
c344
Akt
0.54
0.66
0.68
P-Akt (S473)
0.22
0.31
0.58
ERK1/2
0.81
0.95
1.01
P-ERK1/2
(T202/Y204)
0.48
0.72
0.92
β-Actin

Fig. 3E


2400
2000
1600
1200
800
400
0
Tumor Volume (mm3)
phrGFP
MUC16c114
MUC16c344
6
10
14
18
22
26
30
34
Days

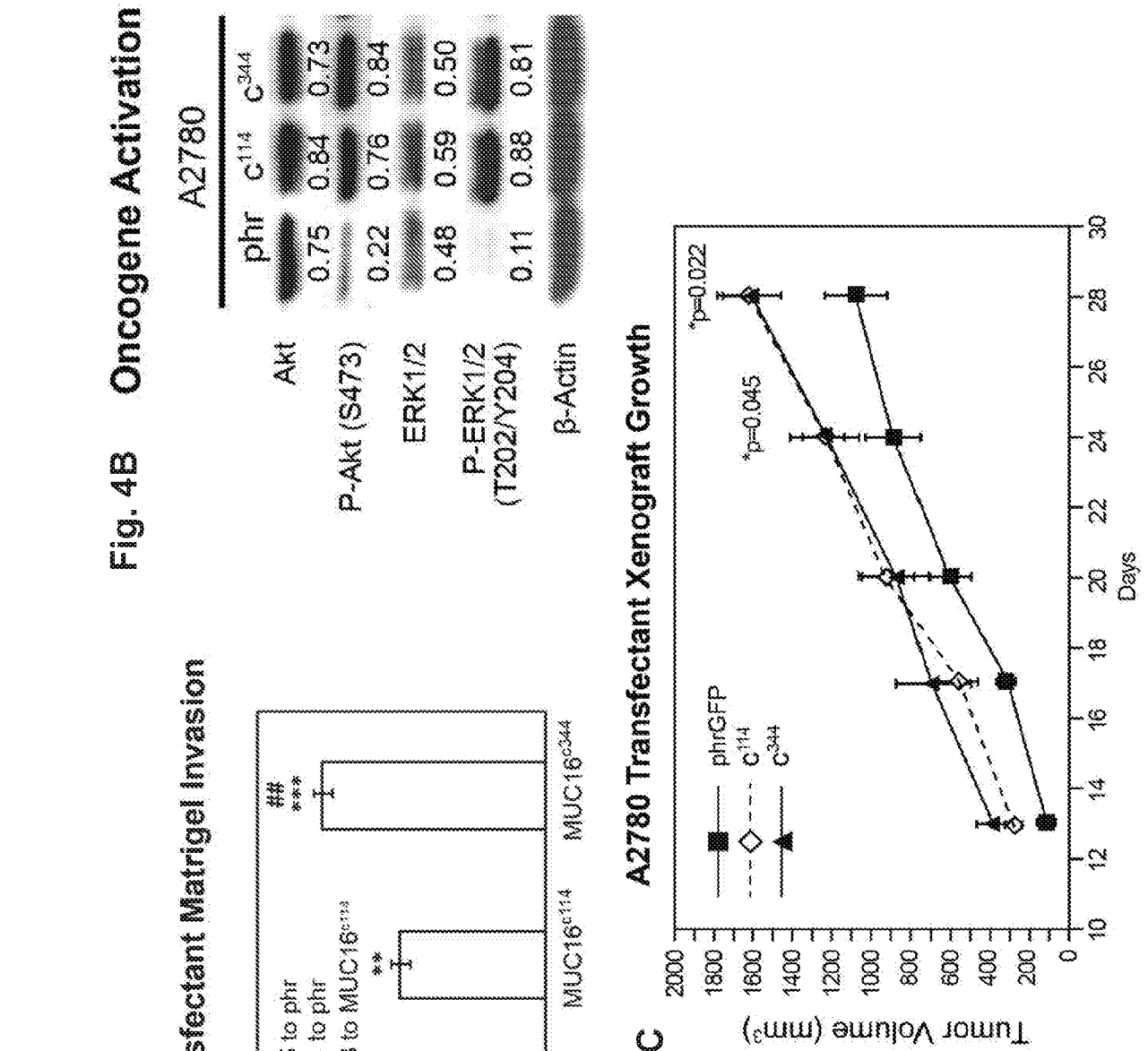

Fig. 4A
A2780 Transfectant Matrigel Invasion
Number of Invasive Cells
** p=0.0025 to phr
*** p<0.0001 to phr
p=0.0018 to MUC16c114
**
##
***
phrGFP
MUC16c114
MUC16c344
Fig. 4B
Oncogene Activation
A2780
phr
c114
c344
Akt
0.75
0.84
0.73
P-Akt (S473)
0.22
0.76
0.84
ERK1/2
0.48
0.59
0.50
P-ERK1/2 (T202/Y204)
0.11
0.88
0.81
β-Actin
Fig. 4C
A2780 Transfectant Xenograft Growth
Tumor Volume (mm3)
Days
phrGFP
c114
c344
*p=0.022
*p=0.045

Fig. 5A

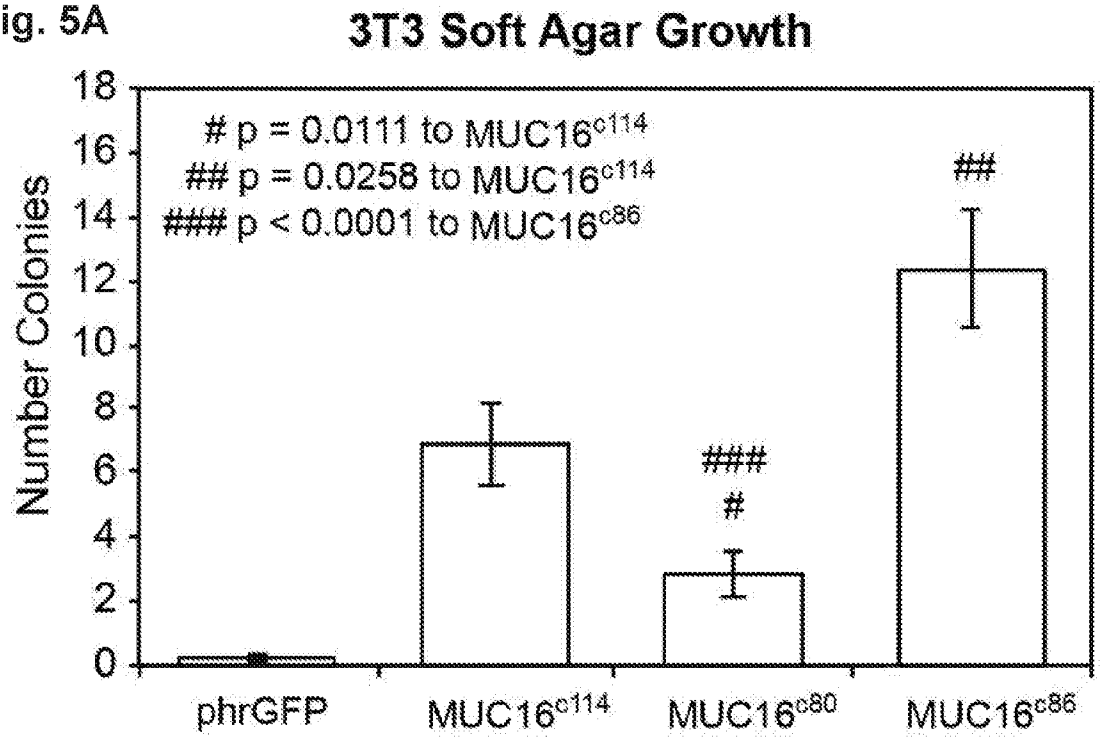

3T3 Soft Agar Growth
p = 0.0111 to MUC16c114
p = 0.0258 to MUC16c114
p < 0.0001 to MUC16c86
Number Colonies
0
2
4
6
8
10
12
14
16
18
###
#
##
phrGFP
MUC16c114
MUC16c80
MUC16c86

Fig. 5B

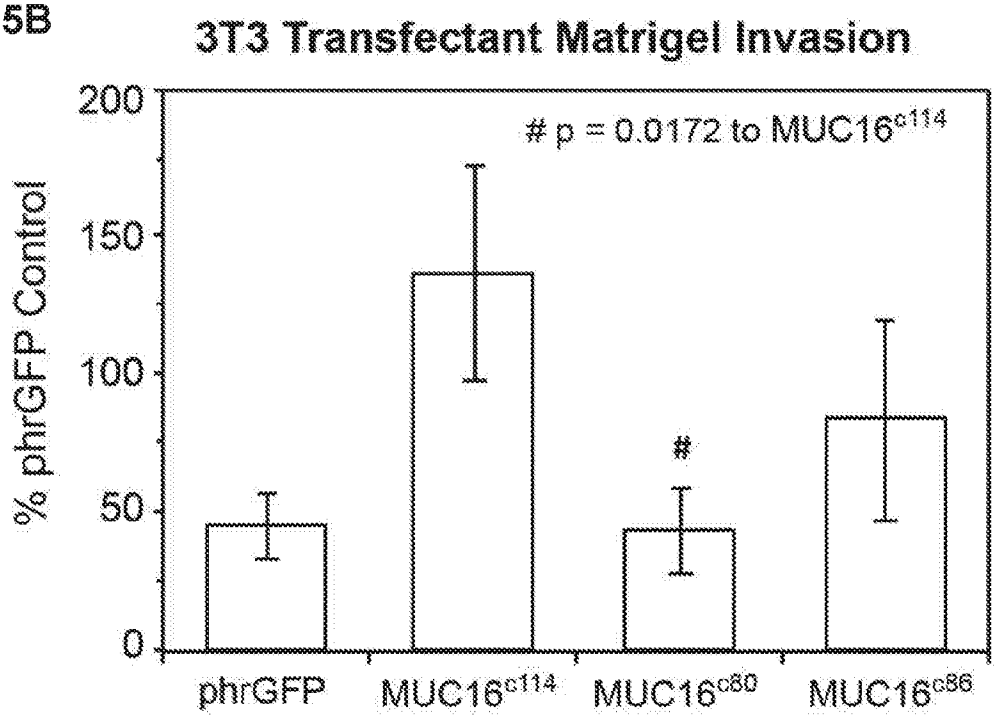

3T3 Transfectant Matrigel Invasion
p = 0.0172 to MUC16c114
% phrGFP Control
0
50
100
150
200
#
phrGFP
MUC16c114
MUC16c80
MUC16c86

Fig. 5C

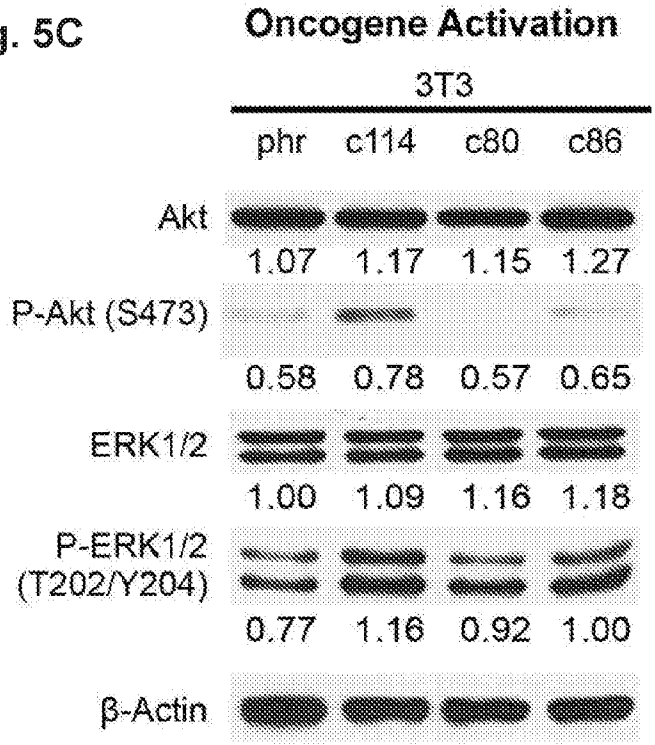

Oncogene Activation
3T3
phr
c114
c80
c86
Akt
1.07 1.17 1.15 1.27
P-Akt (S473)
0.58 0.78 0.57 0.65
ERK1/2
1.00 1.09 1.16 1.18
P-ERK1/2 (T202/Y204)
0.77 1.16 0.92 1.00
β-Actin

Fig. 5D

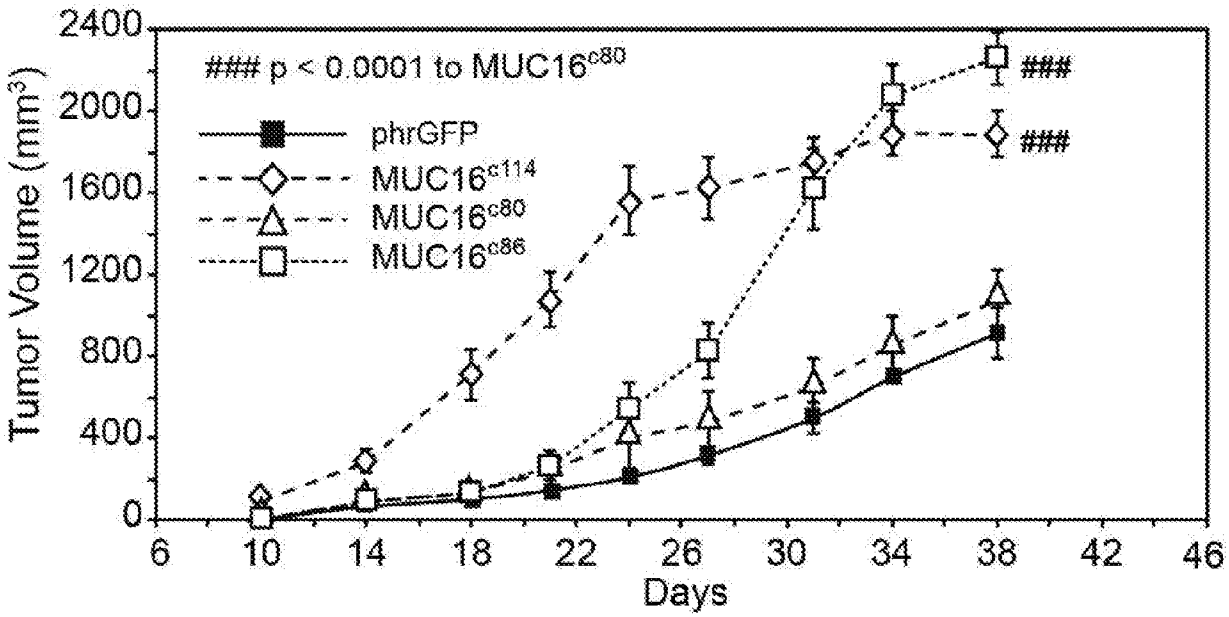

3T3 Transfectant Xenograft Growth
p < 0.0001 to MUC16c80
phrGFP
MUC16c114
MUC16c80
MUC16c86
###
###
Tumor Volume (mm3)
2400
2000
1600
1200
800
400
0
6
10
14
18
22
26
30
34
38
42
46
Days

Fig. 6A MUC16^{c114} Construct

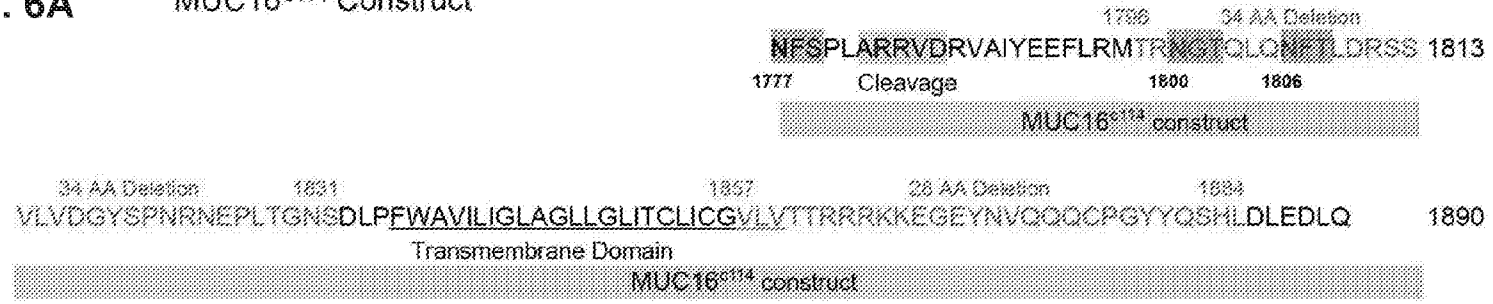


Fig. 6B MUC16^{c344} Construct

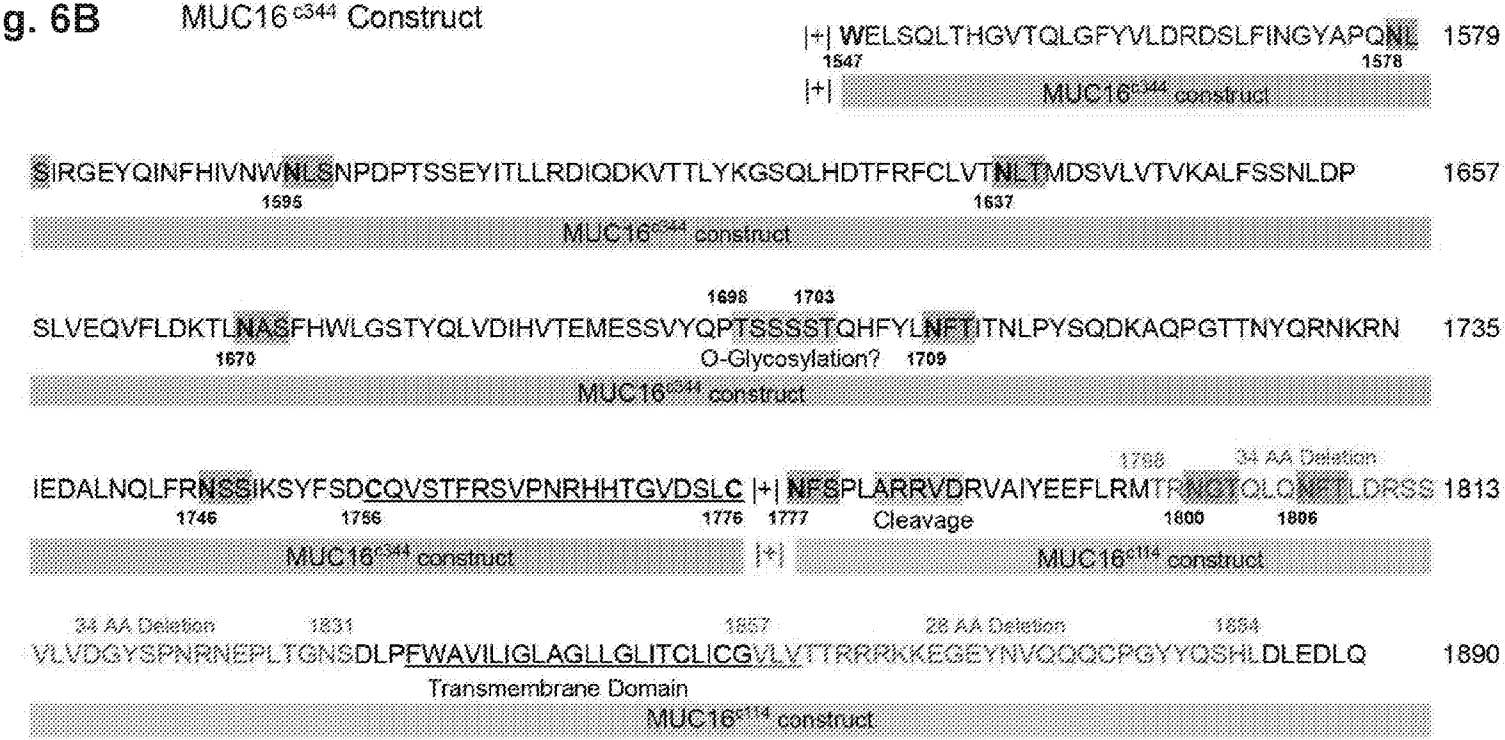


Fig. 7A

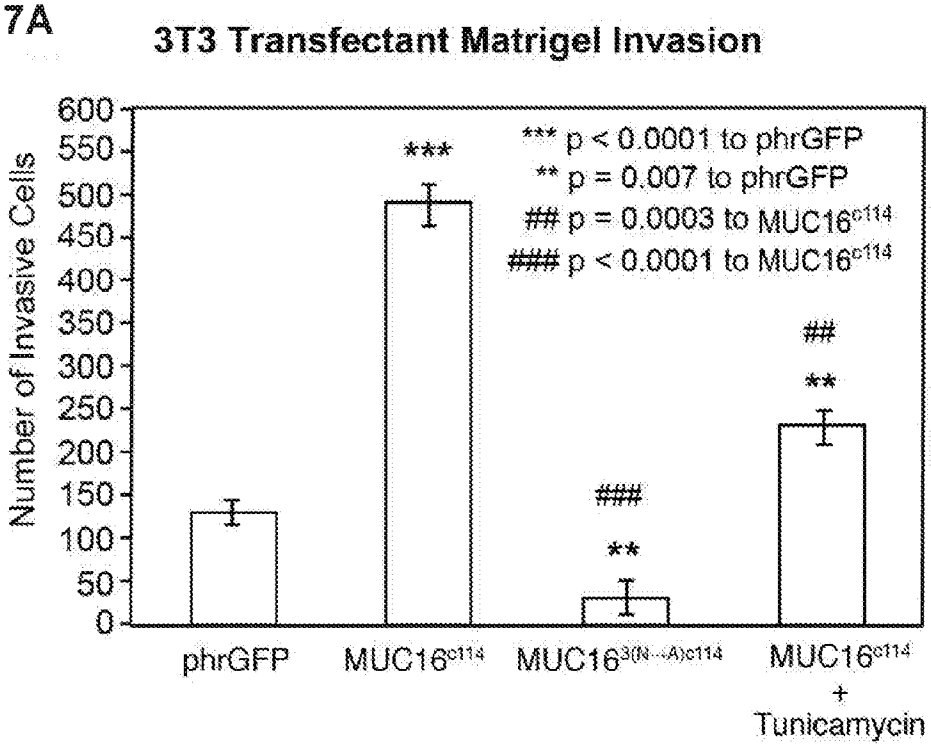

3T3 Transfectant Matrigel Invasion
Number of Invasive Cells
600
550
500
450
400
350
300
250
200
150
100
50
0
*** p < 0.0001 to phrGFP
** p = 0.007 to phrGFP
p = 0.0003 to MUC16c114
p < 0.0001 to MUC16c114
***
###
**
##
**
phrGFP
MUC16c114
MUC16 3(N→A)c114
MUC16c114 + Tunicamycin

Fig. 7B

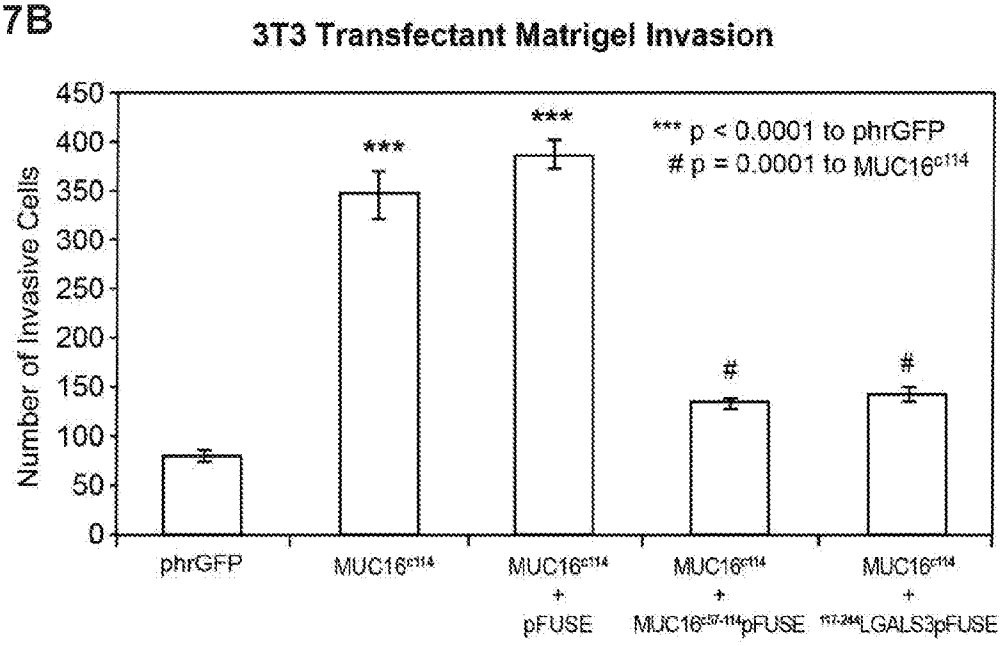

3T3 Transfectant Matrigel Invasion
Number of Invasive Cells
450
400
350
300
250
200
150
100
50
0
*** p < 0.0001 to phrGFP
# p = 0.0001 to MUC16c114
***
***
#
#
phrGFP
MUC16c114
MUC16c114 + pFUSE
MUC16c114 + MUC16c57-114pFUSE
MUC16c114 + 157-244LGALS3pFUSE

Fig. 7C

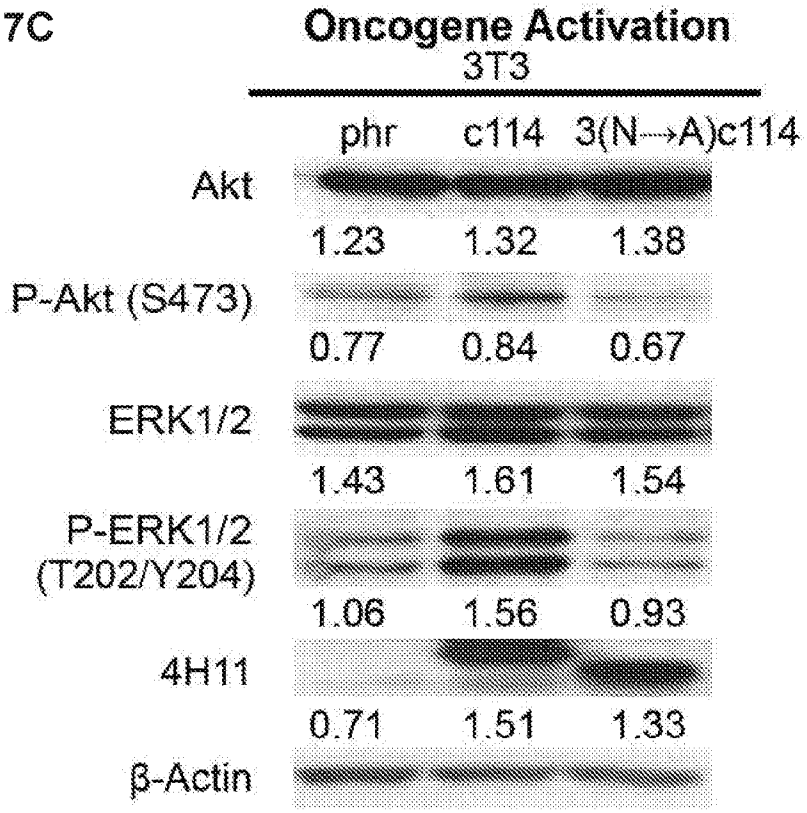

Oncogene Activation
3T3
phr
c114
3(N→A)c114
Akt
1.23
1.32
1.38
P-Akt (S473)
0.77
0.84
0.67
ERK1/2
1.43
1.61
1.54
P-ERK1/2
(T202/Y204)
1.06
1.56
0.93
4H11
0.71
1.51
1.33
β-Actin

Fig. 7D

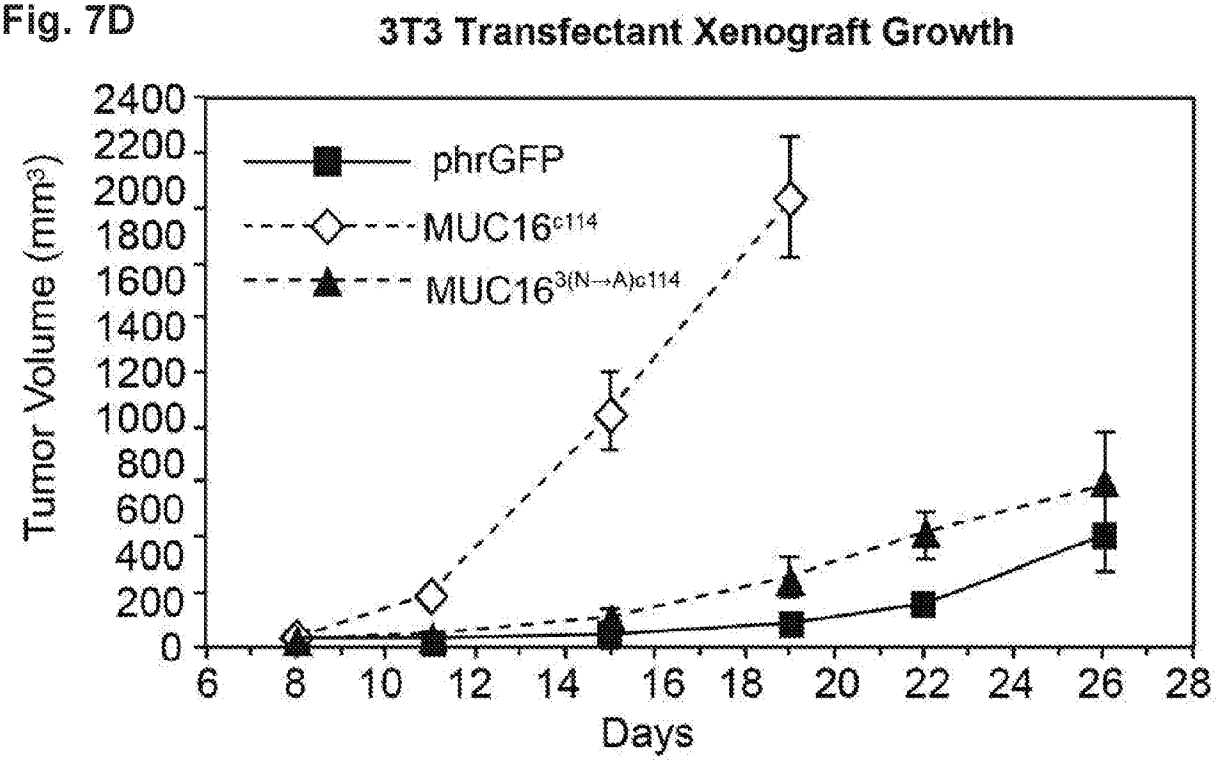

3T3 Transfectant Xenograft Growth
Tumor Volume (mm3)
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
phrGFP
MUC16c114
MUC163(N→A)c114
6
8
10
12
14
16
18
20
22
24
26
28
Days

Fig. 7E

Ectodomain MUC16$^{c57-114}$ -construct (58 aa)-pFUSE-human-IgG1-Fc2

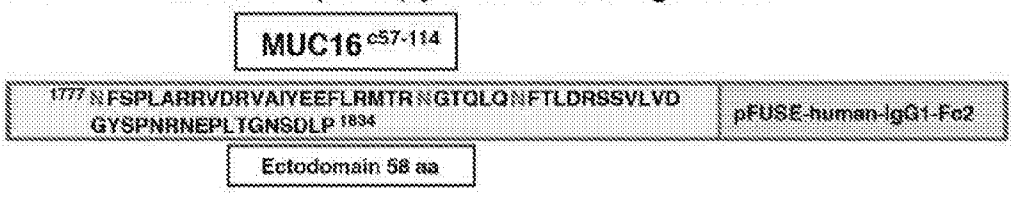


Fig. 7F

293 Expression of MUC16$^{c57-114}$-pFUSE-hIgG1-Fc2

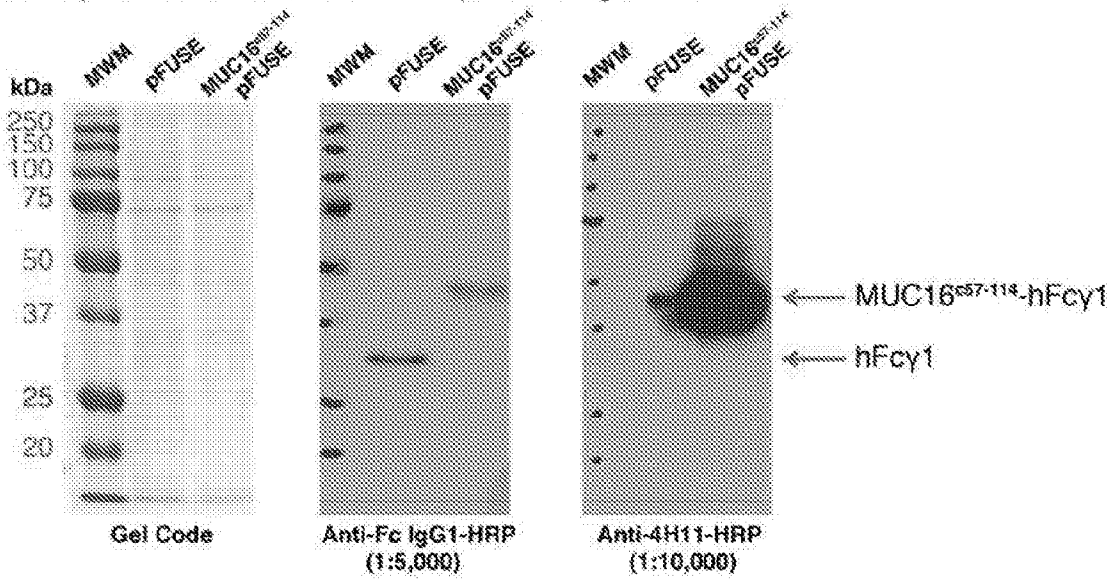


Fig. 7G

$^{117-244}$LGALS3 Sugar binding protein (128 aa)-pFUSE-human-IgG1-Fc2

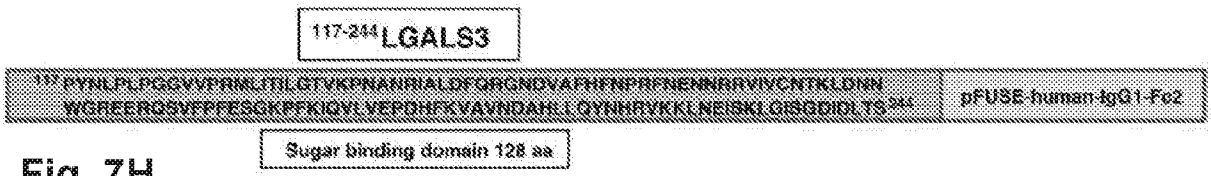
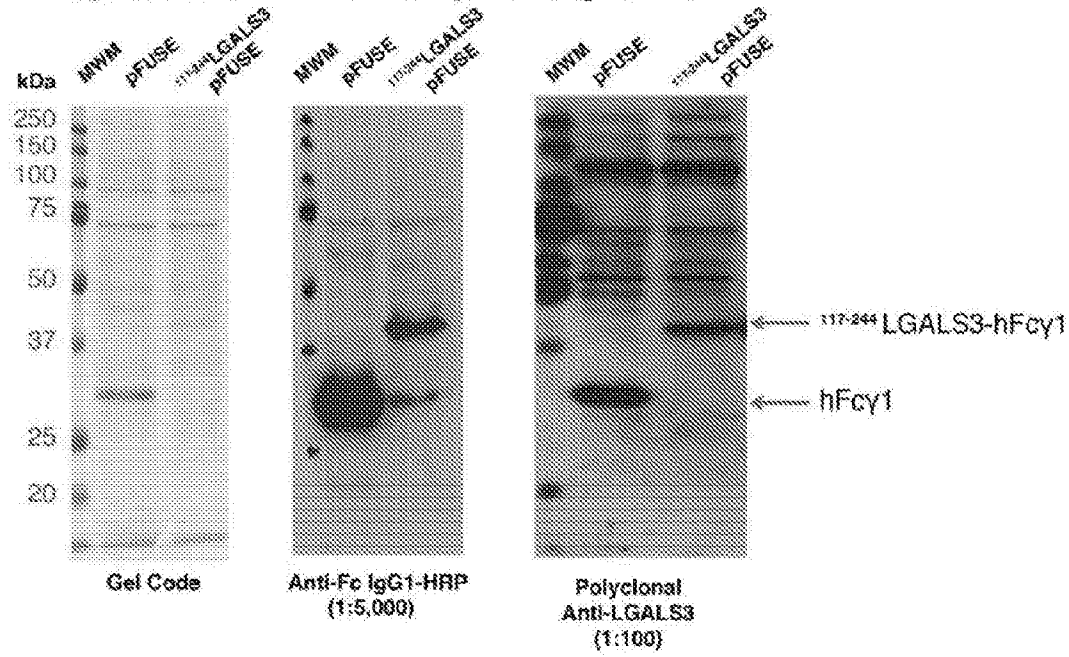


Fig. 7H

293 Expression of $^{117-244}$LGALS3-pFUSE-hIgG1-Fc2



Ectodomain $MUC16^{c57-c114}$ construct (58 aa) pFUSE-hIgG1-Fc2

NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNSDLP - pFUSE-hIgG1-Fc2

$^{117-244}$LGALS3 Sugar binding protein (128 aa)

PYNLPLPGGVVPRMLITILGTVKPNANRIALDFQRGNDVAFHFNPRFNENNRRVIVCNTKLDNNWGRE
ERQSVFPFESGKPFKIQVLVEPDHFKVAVNDAHLLQYNHRVKKLNEISKLGISGDIDLTS - pFUSE-hIgG1-Fc2

Fig. 8

Fig. 9A

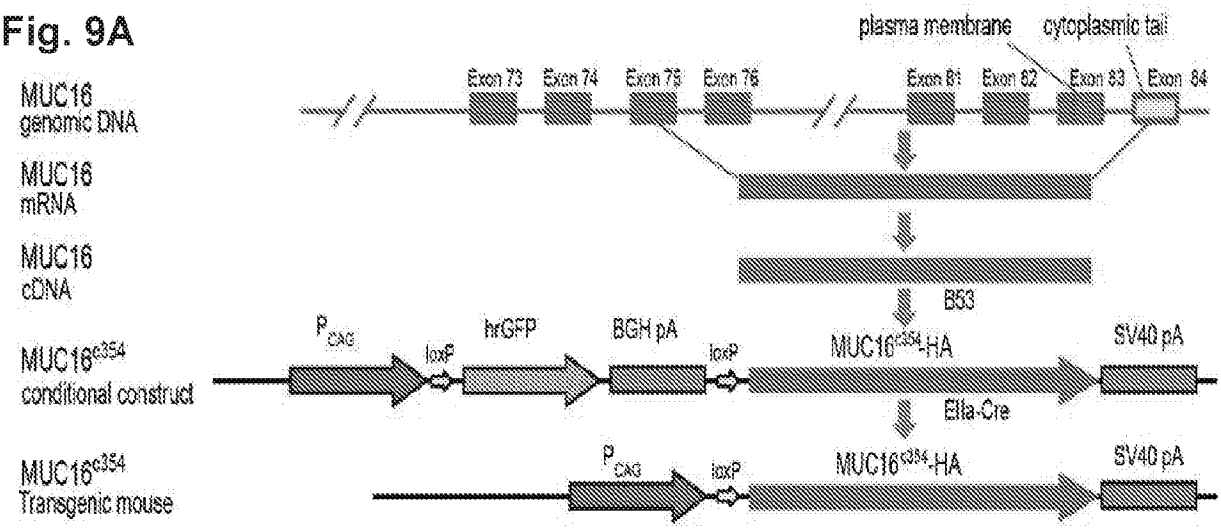

plasma membrane
cytoplasmic tail
MUC16 genomic DNA
Exon 73
Exon 74
Exon 75
Exon 76
Exon 81
Exon 82
Exon 83
Exon 84
MUC16 mRNA
MUC16 cDNA
B53
MUC16c354 conditional construct
P CAG
loxP
hrGFP
BGH pA
loxP
MUC16c354-HA
SV40 pA
Ella-Cre
MUC16c354 Transgenic mouse
P CAG
loxP
MUC16c354-HA
SV40 pA

Fig. 9B

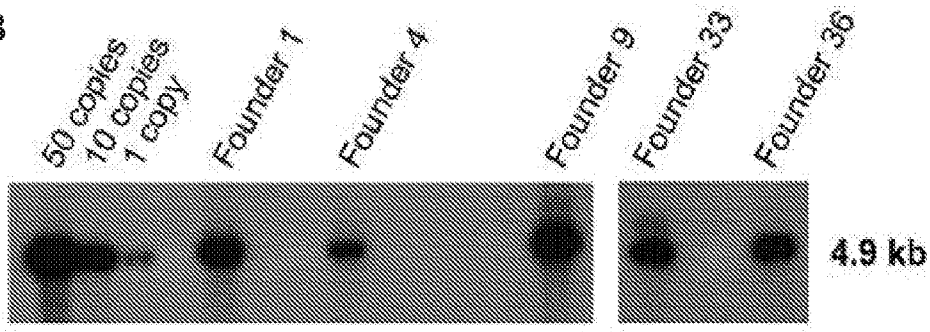

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10 copies
1 copy
Founder 1
Founder 4
Founder 9
Founder 33
Founder 36
4.9 kb

Fig. 9C

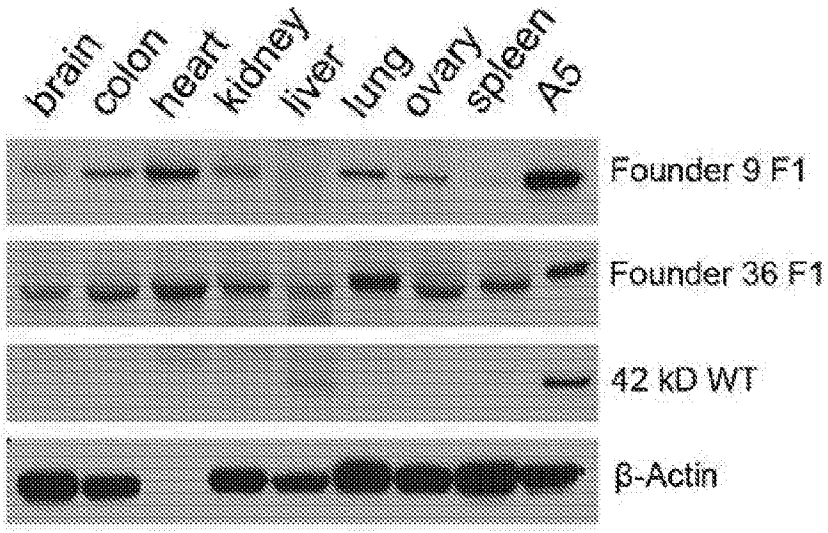

brain
colon
heart
kidney
liver
lung
ovary
spleen
A5
Founder 9 F1
Founder 36 F1
42 kD WT
β-Actin

Fig. 9D

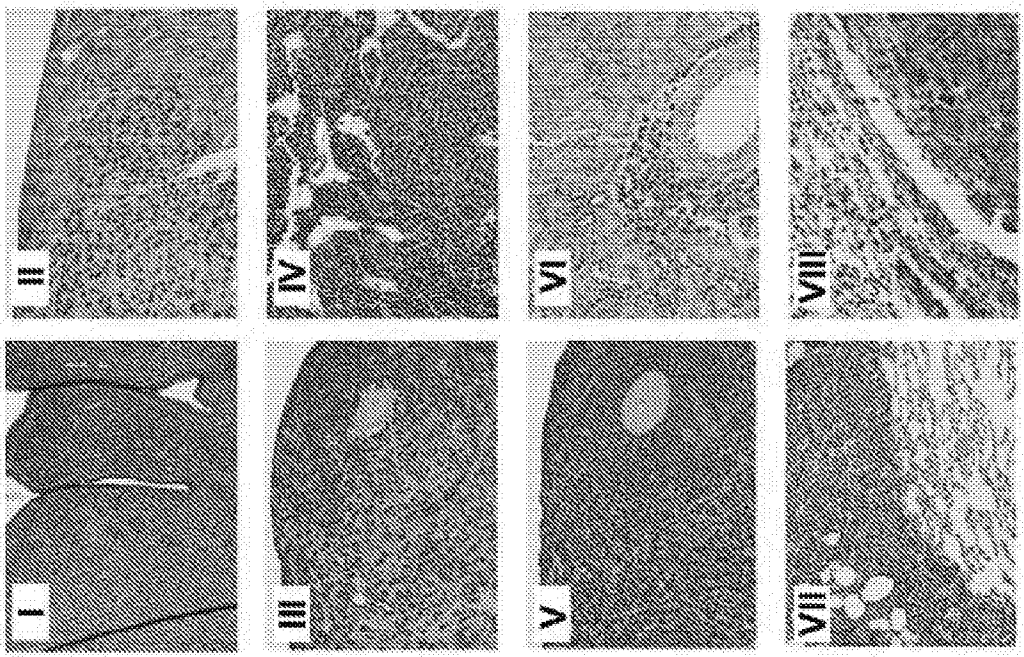
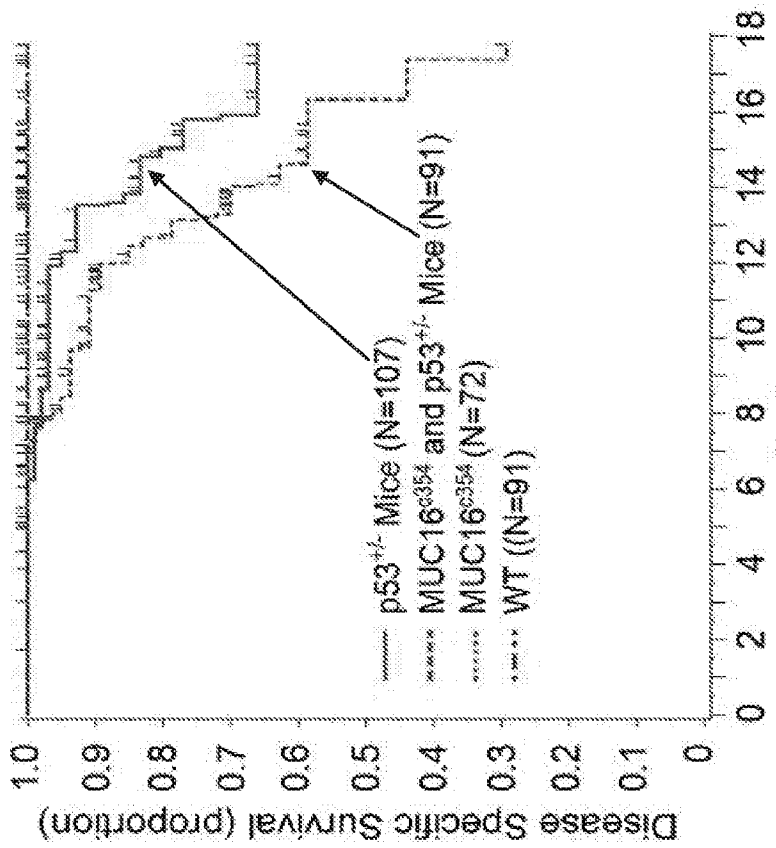

I
II
III
IV
V
VI
VII
VIII

Fig. 9E


DSS by Mouse Type
Disease Specific Survival (proportion)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
12
14
16
18
Months
p53+/- Mice (N=107)
MUC16c354 and p53+/- Mice (N=91)
MUC16c354 (N=72)
WT ((N=91)

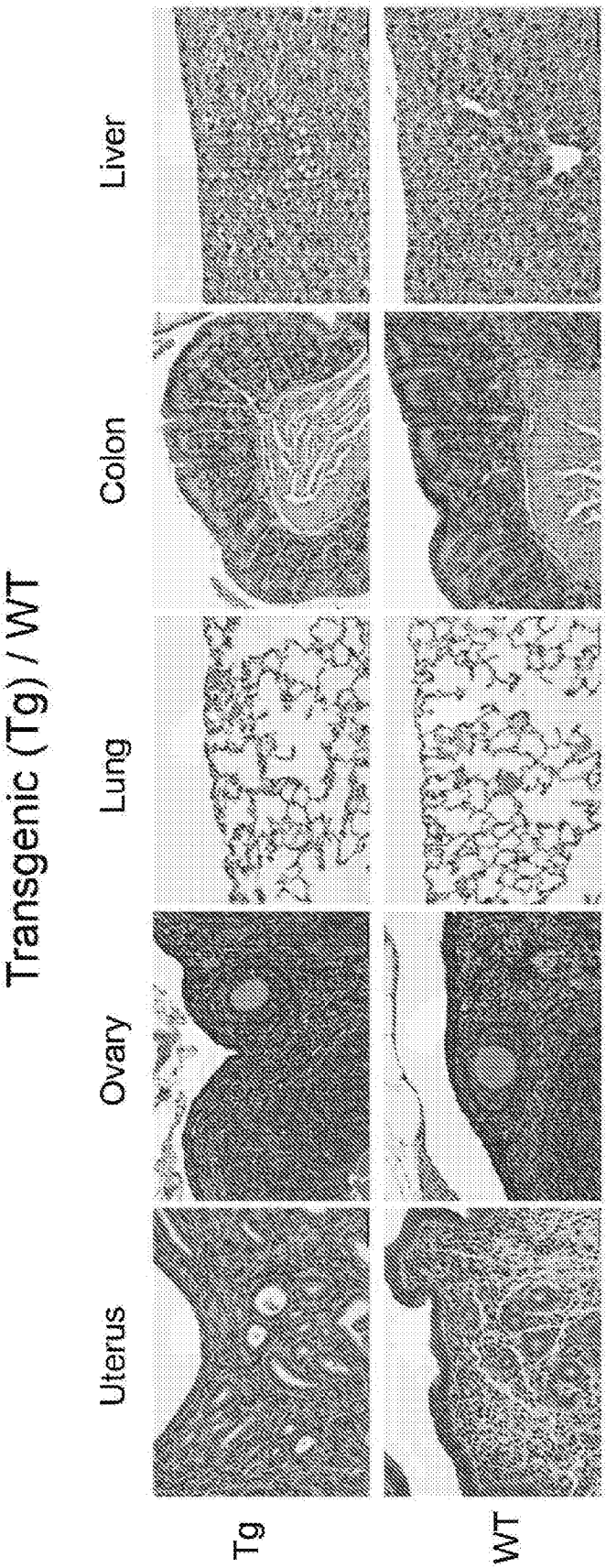
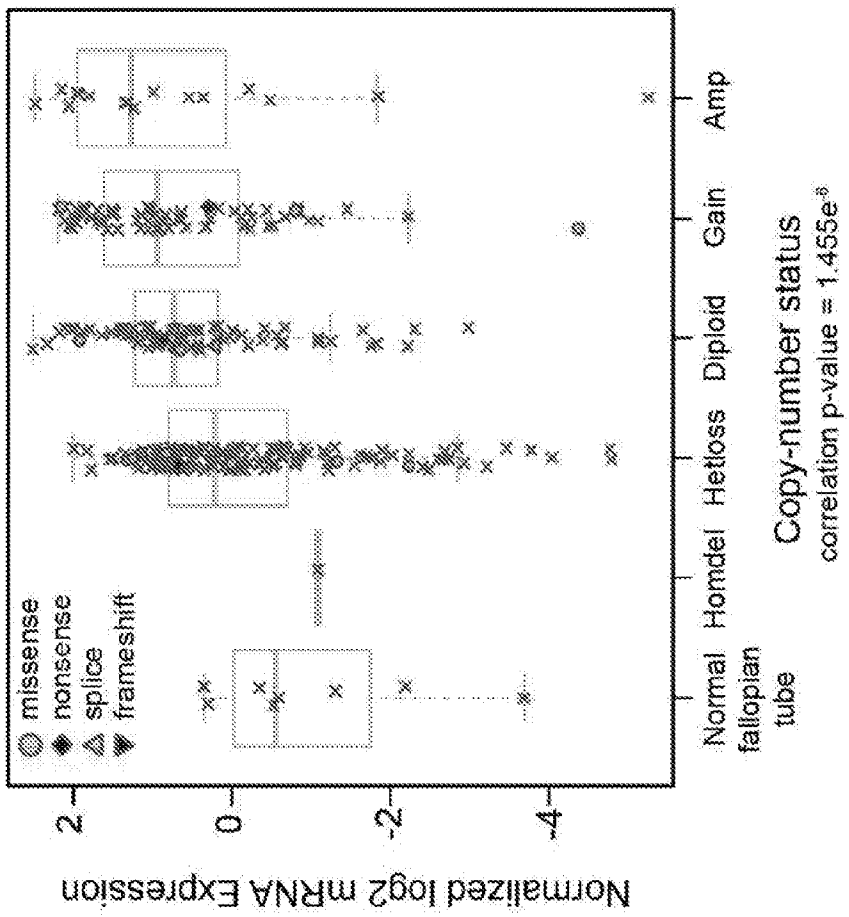


Fig. 10

Fig. 11A


MUC16 Transcript Number
missense
nonsense
splice
frameshift
Normalized log2 mRNA Expression
2
0
-2
-4
Normal fallopian tube
Homdel
Hetloss
Diploid
Gain
Amp
Copy-number status
correlation p-value = 1.455e-8

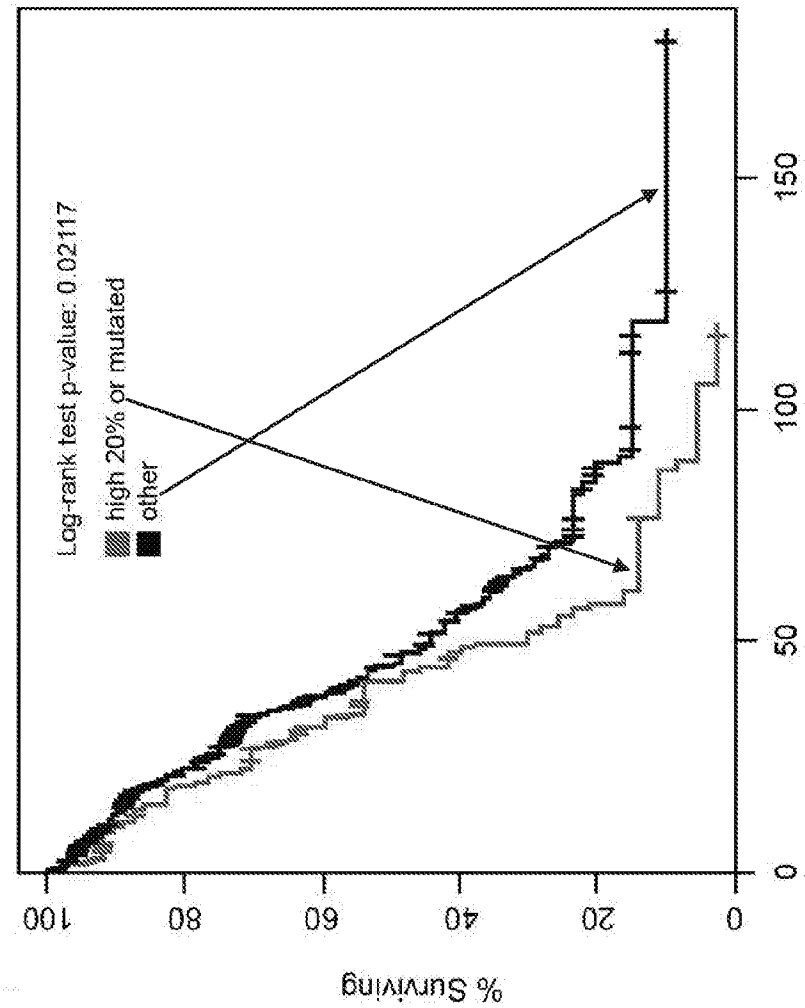


Fig. 11B

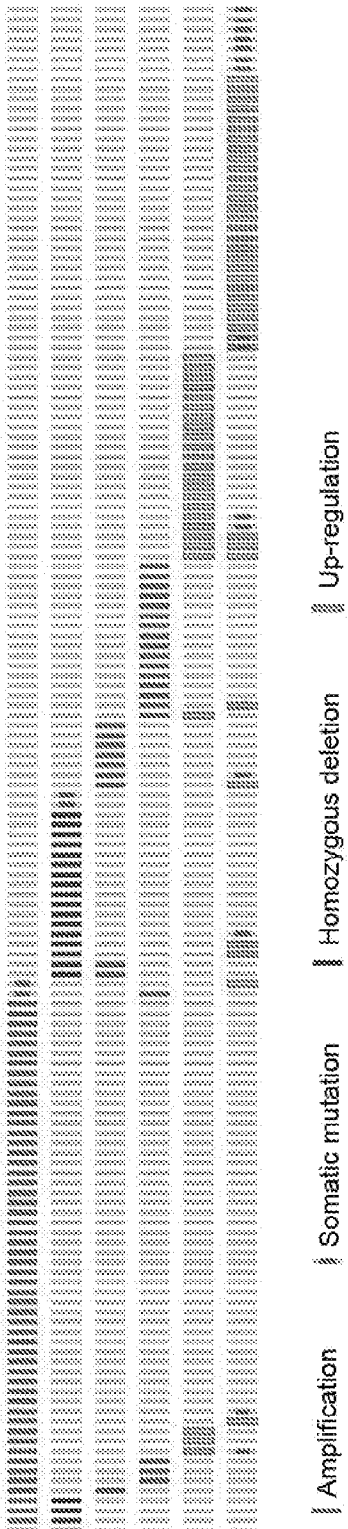


Fig. 11C

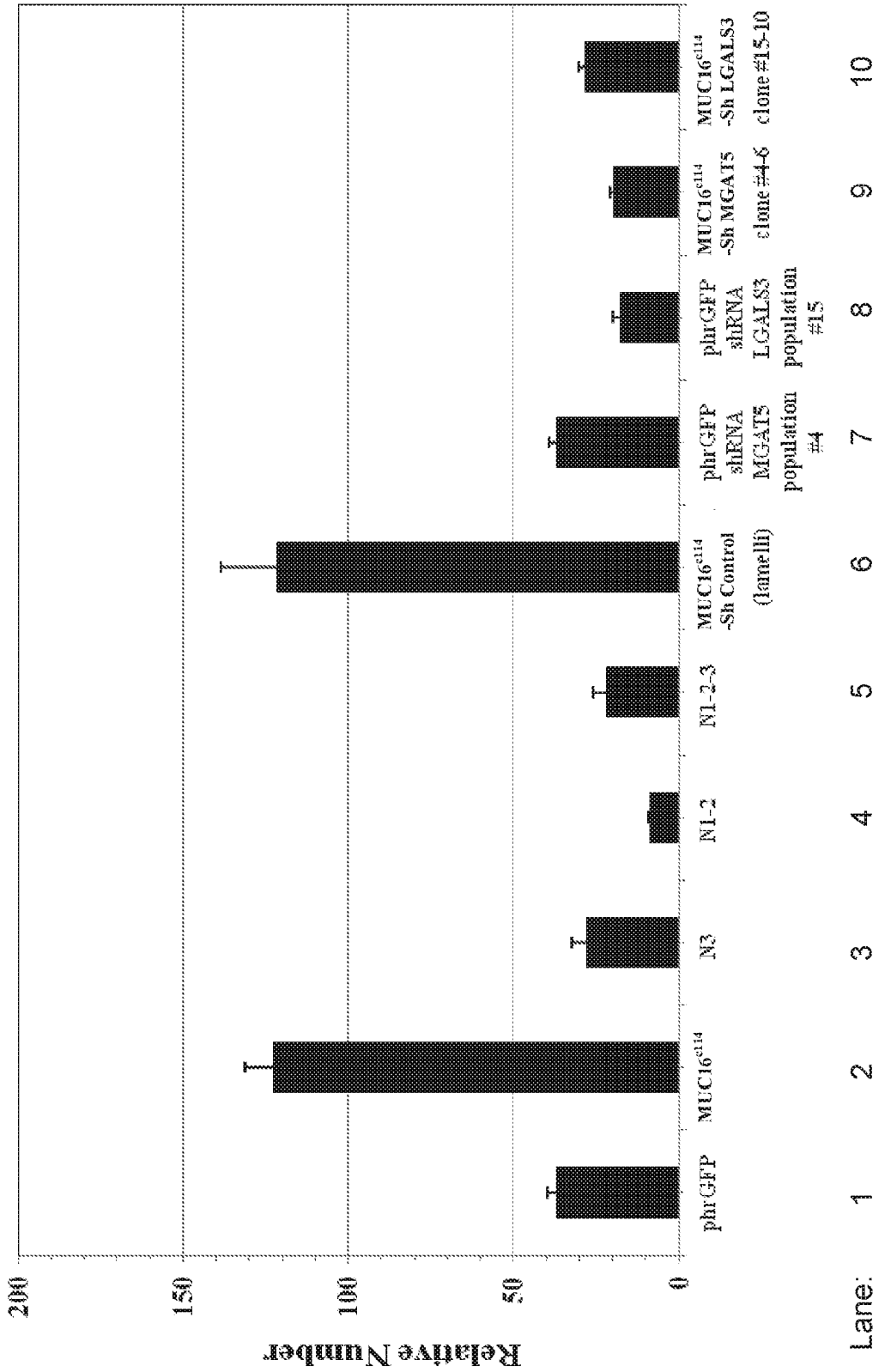

Relative Number
200
150
100
50
0
Lane:
1
2
3
4
5
6
7
8
9
10
phrGFP
MUC16ecto
N3
N1-2
N1-2-3
MUC16ecto -Sh Control (lanelli)
phrGFP shRNA MGAT5 population #4
phrGFP shRNA LGALS3 population #15
MUC16ecto -Sh MGAT5 clone #4-6
MUC16ecto -Sh LGALS3 clone #15-10

Fig. 12A

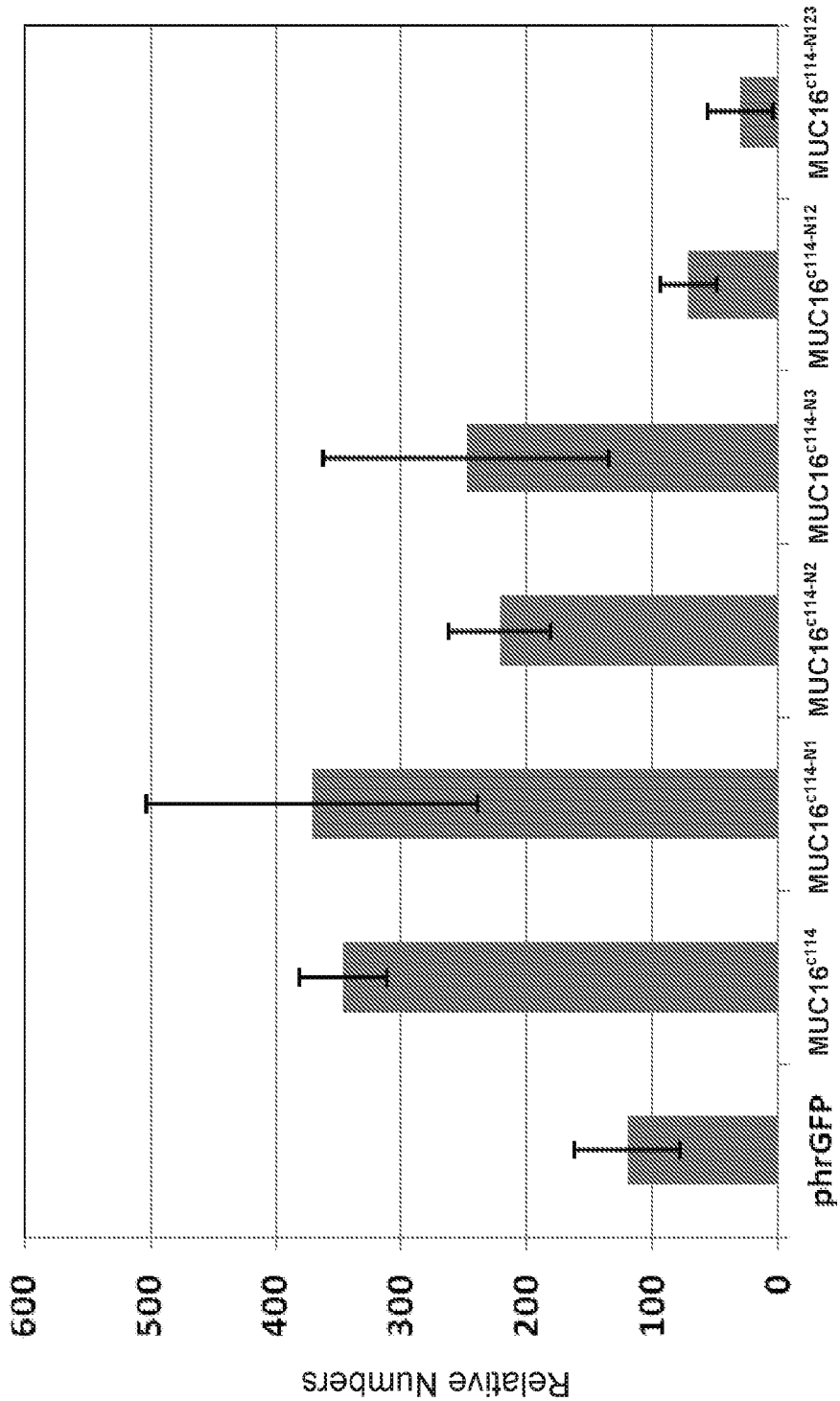

Relative Numbers
600
500
400
300
200
100
0
Lane:
1
2
3
4
5
6
7
phrGFP
MUC16c114
MUC16c114-N1
MUC16c114-N2
MUC16c114-N3
MUC16c114-N12
MUC16c114-N123

Fig. 12B

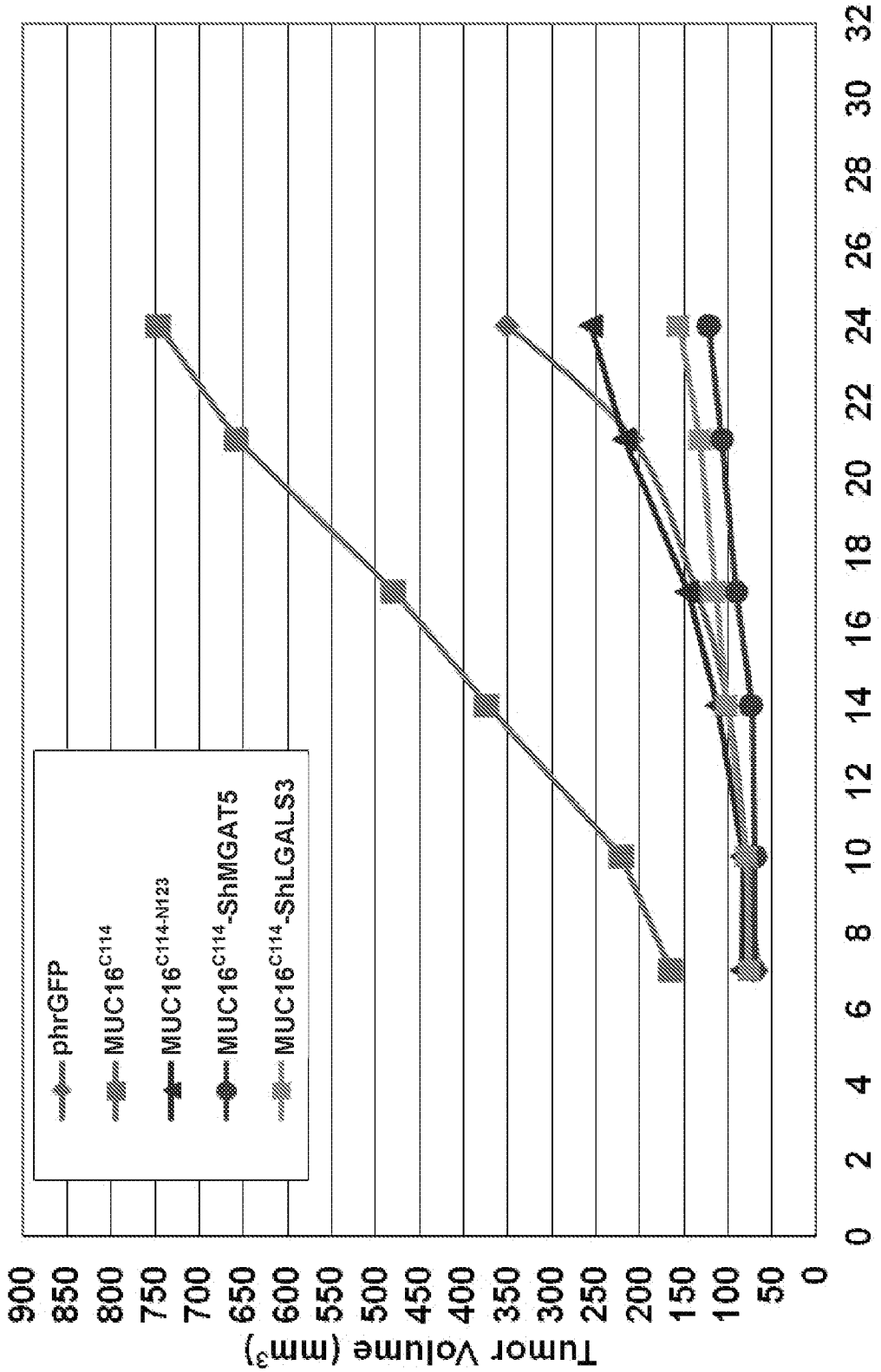

Tumor Volume (mm3)
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32
Days
phrGFP
MUC16C114
MUC16C114-N123
MUC16C114-ShMGAT5
MUC16C114-ShLGALS3

Fig. 12C

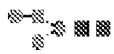
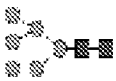
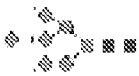
Observed m/z	Charge state	Structural assignment		Mass [M+Na]+	Intensity/Charge state	Glycan %
1142	1	M2N2F		1142	1.02E+03	32.47%
1170	1	M3N2		1171	3.56E+02	11.33%
1346	1	M3N2F		1345	4.18E+02	13.30%
1376	1	M4N2		1376	1.91E+02	6.08%
1580	1	M5N2		1580	3.78E+02	12.03%
1784	1	M6N2		1784	8.68E+01	2.76%
1988	1	M7N2		1988	3.70E+01	1.18%
1134	2	Gal2N2M3N2F		2244	1.91E+02	6.06%
1228	2	NeuAc1Gal2N2M3N2		2431	1.50E+02	4.76%
1316	2	NeuAc1Gal2N2M3N2F		2605	1.65E+02	5.25%
1408	2	NeuAc2Gal2N2M3N2		2792	7.70E+01	2.45%
1496	2	NeuAc1Gal2N2M3N2F		2966	7.30E+01	2.32%
				Total	3.14E+03	100.00%



Fig. 13A

Fig. 13B

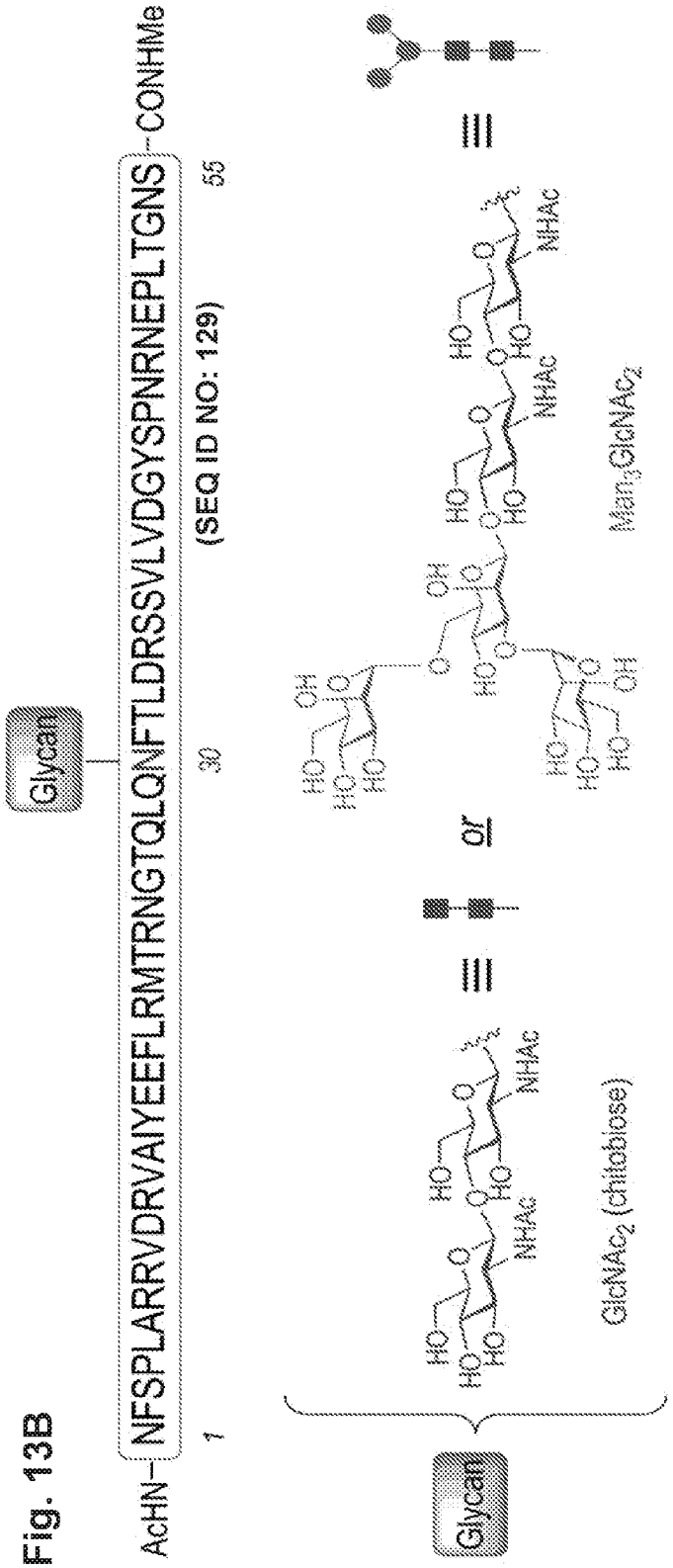
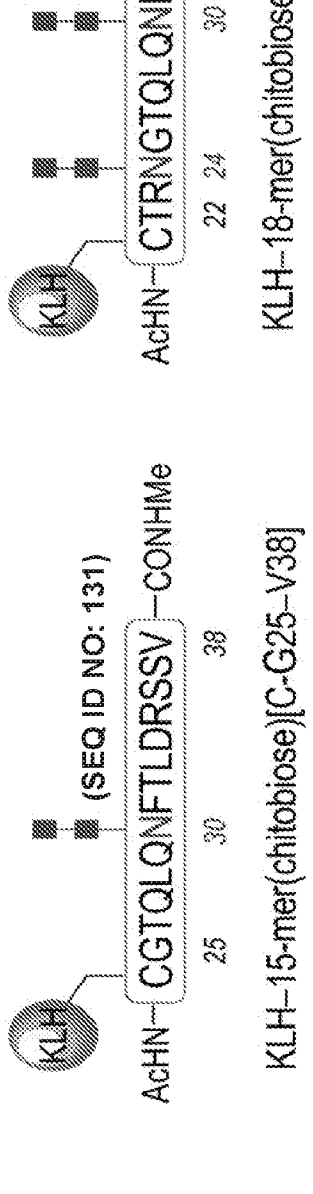


Fig. 13C

Fig. 13D



	15 vs 15s Peptides											18 vs 18s Peptides											Stick ELISAy by
	ELISA on 12/24/13 Sups from time of freezing					ELISA during fusion screen (ELISA performed on Different Days)						ELISA on 12/24/13 Sups from time of freezing					ELISA during fusion screen (ELISA performed on Different Days)						
ID	Dilution	15	15S	15S / 15 Ratio	Fold over TB	Dilution	15	15S	15S / 15 Ratio	Fold over TB	ELISAs Agree	Dilution	18	18S	18S / 18 Ratio	Fold over TB	Dilution	18	18S	18S / 18 Ratio	Fold over TB	ELISAs Agree	
4H11	neat	0.02	0.02	...	...							neat	0.02	0.02	...	...							
9B11	neat	0.02	0.02	...	...							neat	0.02	0.02	...	...							
TB	1:1000	0.72	0.29	0.40	...							1:1000	0.81	0.77	0.95	...							
II01B05	400	0.34	0.47	1.38	1.46	400	0.55	0.52	0.95	1.11	No	400	0.47	0.60	1.28	1.34	400	0.43	0.78	1.81	1.25	Yes	
II02E01	400	0.42	0.37	0.88	2.20	400	0.31	0.22	0.71	0.83	No	400	0.37	0.47	1.27	1.34	400	0.28	0.51	1.82	1.30	Yes	
II04G02	80	0.38	0.05	0.13	0.33	40	0.87	0.51	0.59	0.94	Yes	80	0.34	0.33	0.97	1.02	80	0.37	0.61	1.65	1.24	No	
II07B12	400	0.44	0.25	0.57	1.42	200	0.77	0.80	1.04	1.22	?	400	0.33	0.51	1.55	1.63	400	0.53	0.92	1.74	1.24	?	
II09A06	100	0.96	0.31	0.32	0.81	100	0.61	0.40	0.66	1.18	?	100	1.00	0.92	0.92	0.97	400	0.25	0.37	1.48	1.56	No	Yes / ?
II09G09	400	0.51	0.27	0.53	1.32	200	0.47	0.31	0.66	1.77	?	400	0.50	0.62	1.24	1.31	400	0.24	0.52	2.17	1.37	Yes	
II09H07	200	0.71	0.21	0.30	0.74	200	0.51	0.30	0.59	1.06	?	200	0.62	0.69	1.11	1.17	200	0.40	0.51	1.28	1.34	?	? / Yes
II10C06	400	0.41	0.26	0.63	1.59	100	0.62	0.49	0.79	1.42	Yes	400	0.38	0.56	1.47	1.55	400	0.25	0.37	1.48	1.56	Yes	
II12H08	200	0.68	0.26	0.38	0.96	200	0.37	0.18	0.49	1.31	No	200	0.68	0.76	1.12	1.18	400	0.17	0.36	2.12	1.34	?	Yes / ?
II13A07	400	0.26	0.14	0.54	1.35	200	0.51	0.53	1.04	1.22	Yes	400	0.23	0.34	1.48	1.56	400	0.23	0.53	2.30	1.64	Yes	
II15A08	400	0.59	0.25	0.42	1.06	400	0.33	0.19	0.58	1.55	No	400	0.60	0.67	1.12	1.18	400	0.30	0.59	1.97	1.24	?	Double Yes
II16C05	400	0.62	0.23	0.37	0.93	100	0.58	0.45	0.78	1.40	No	400	0.63	0.68	1.08	1.14	400	0.24	0.36	1.50	1.58	No	
II18C06	400	0.44	0.14	0.32	0.80	200	0.70	0.29	0.41	1.11	?	400	0.45	0.55	1.22	1.29	400	0.39	0.64	1.64	1.17	?	
II19C11	400	0.30	0.10	0.33	0.83	400	0.16	0.19	1.19	1.39	No	400	0.20	0.36	1.80	1.89	400	0.38	0.47	1.24	0.88	No	? / ?
II21C03	200	0.73	0.36	0.49	1.23	200	0.40	0.33	0.83	1.49	Yes	200	0.7	0.78	1.11	1.17	200	0.34	0.48	1.41	1.49	?	
II21G12	50	0.99	0.32	0.32	0.81	50	0.62	0.30	0.48	0.87	Yes	50	0.92	0.88	0.96	1.01	50	0.31	0.46	1.48	1.56	No	
II06H10	50	0.30	0.32	1.07	2.67	50	0.16	0.25	1.56	4.19	Yes	50	0.28	0.33	1.18	1.24	50	0.13	0.26	2.00	1.26	Yes	Double Yes
II16H08	20	0.12	0.16	1.33	3.33	20	0.11	0.26	2.36	3.81	Yes	20	0.06	0.14	2.33	2.46	20	0.13	0.33	2.54	1.92	Yes	Double Yes
II21F08	20	0.20	0.28	1.40	3.50	40	0.14	0.34	2.43	3.81	Yes	20	0.09	0.25	2.78	2.92	20	0.17	0.43	2.53	1.91	Yes	Double Yes

Fig. 14

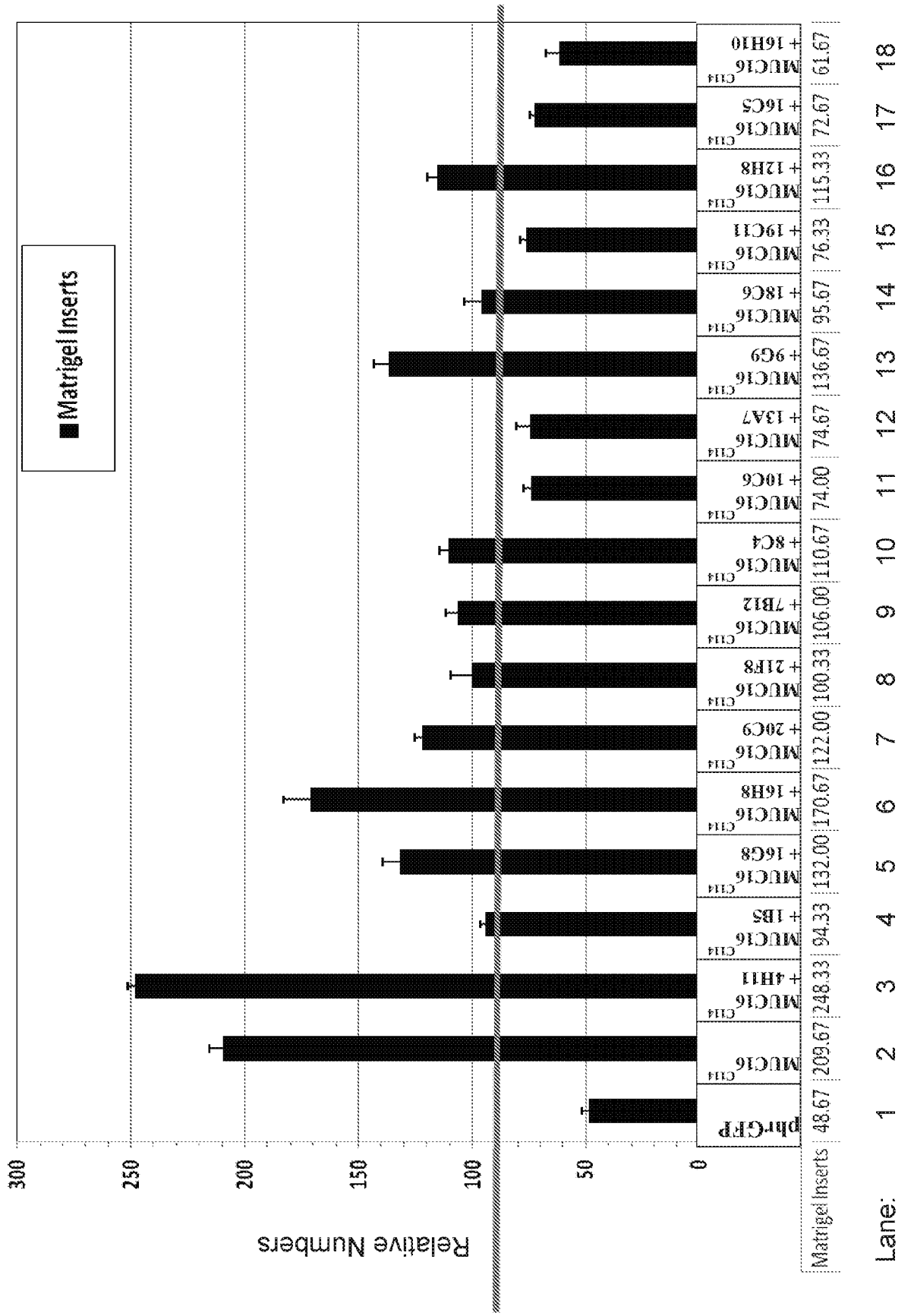

Matrigel Inserts
Relative Numbers
300
250
200
150
100
50
0
Lane:
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Matrigel Inserts 48.67 209.67 248.33 94.33 132.00 170.67 122.00 100.33 106.00 110.67 74.00 74.67 136.67 95.67 76.33 115.33 72.67 61.67
pbr-GFP
MUC16 CD44
MUC16 CD44 + 4H11
MUC16 CD44 + 1B5
MUC16 CD44 + 16G8
MUC16 CD44 + 16H8
MUC16 CD44 + 20C9
MUC16 CD44 + 21F8
MUC16 CD44 + 7B12
MUC16 CD44 + 8C4
MUC16 CD44 + 10C6
MUC16 CD44 + 13A7
MUC16 CD44 + 9G9
MUC16 CD44 + 18C6
MUC16 CD44 + 19C11
MUC16 CD44 + 12H8
MUC16 CD44 + 16C5
MUC16 CD44 + 16H10

Fig. 15A

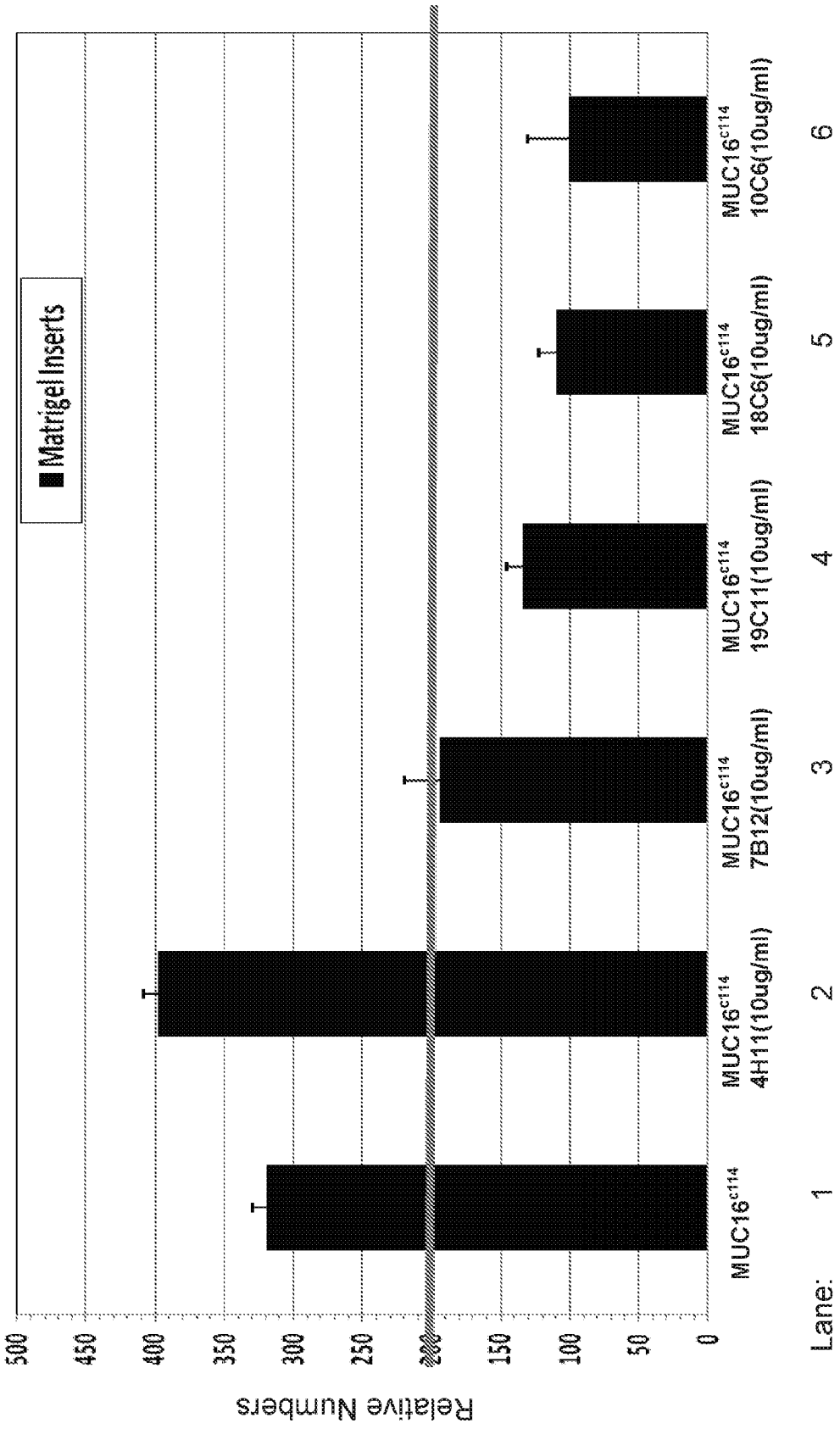

Relative Numbers
500
450
400
350
300
250
200
150
100
50
0
Matrigel Inserts
Lane:
1
2
3
4
5
6
MUC16c114
MUC16c114 4H11(10ug/ml)
MUC16c114 7B12(10ug/ml)
MUC16c114 19C11(10ug/ml)
MUC16c114 18C6(10ug/ml)
MUC16c114 10C6(10ug/ml)

Fig. 15B

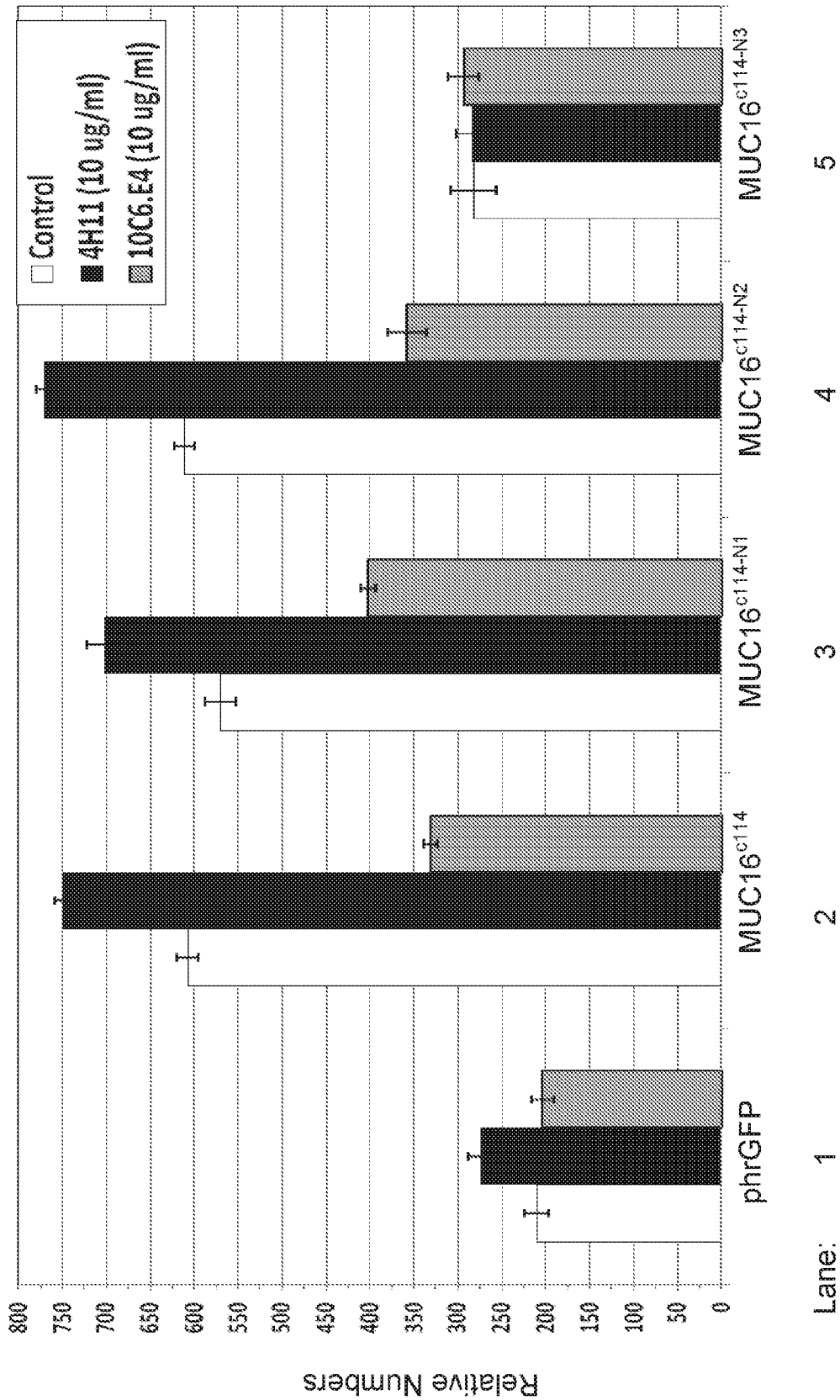

Control
4H11 (10 ug/ml)
10C6.E4 (10 ug/ml)
Relative Numbers
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Lane:
1
2
3
4
5
phrGFP
MUC16c114
MUC16c114-N1
MUC16c114-N2
MUC16c114-N3

Fig. 16A

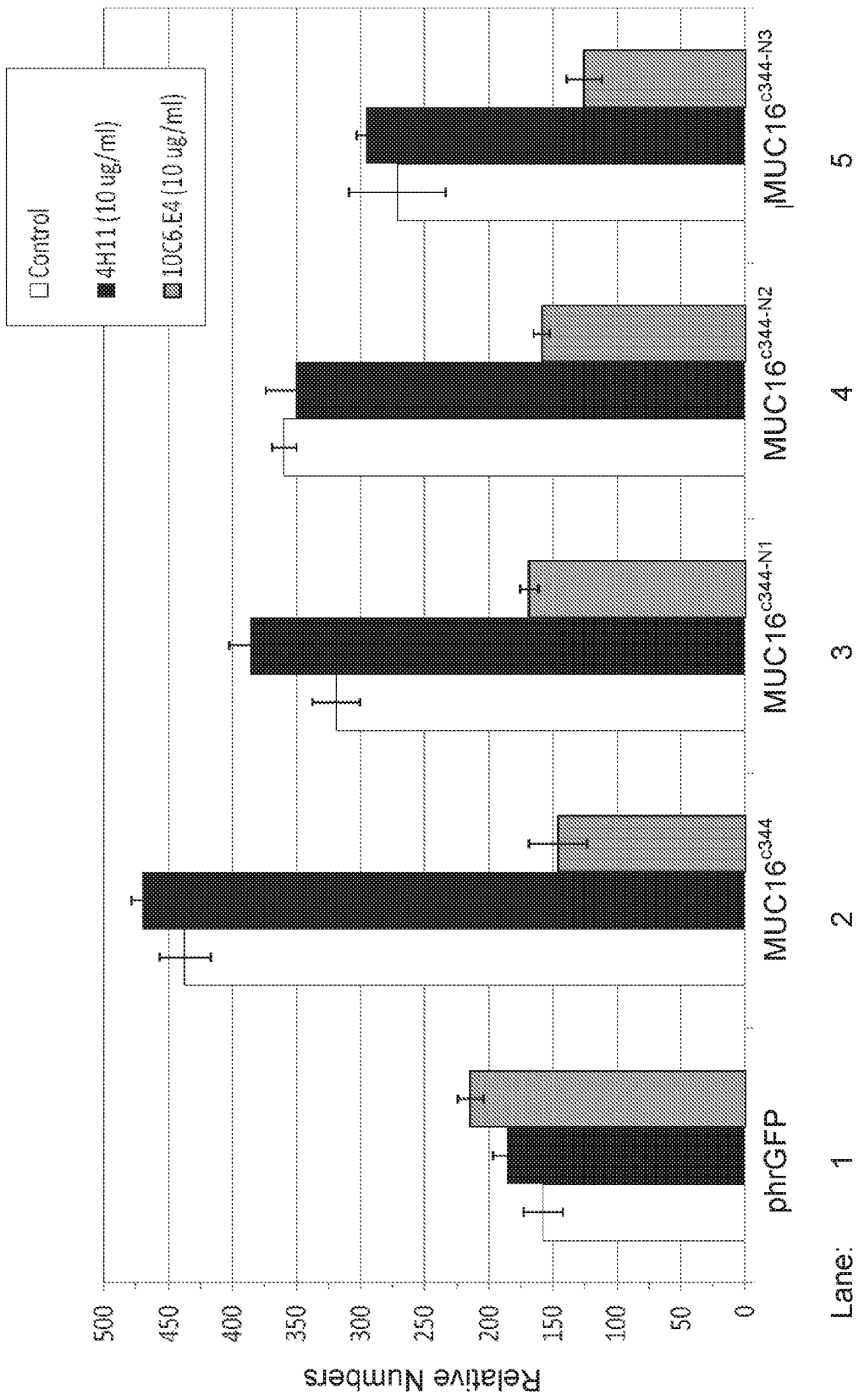

Control
4H11 (10 ug/ml)
10C6.E4 (10 ug/ml)
Relative Numbers
500
450
400
350
300
250
200
150
100
50
0
Lane:
1
2
3
4
5
phrGFP
MUC16c344
MUC16c344-N1
MUC16c344-N2
MUC16c344-N3

Fig. 16B

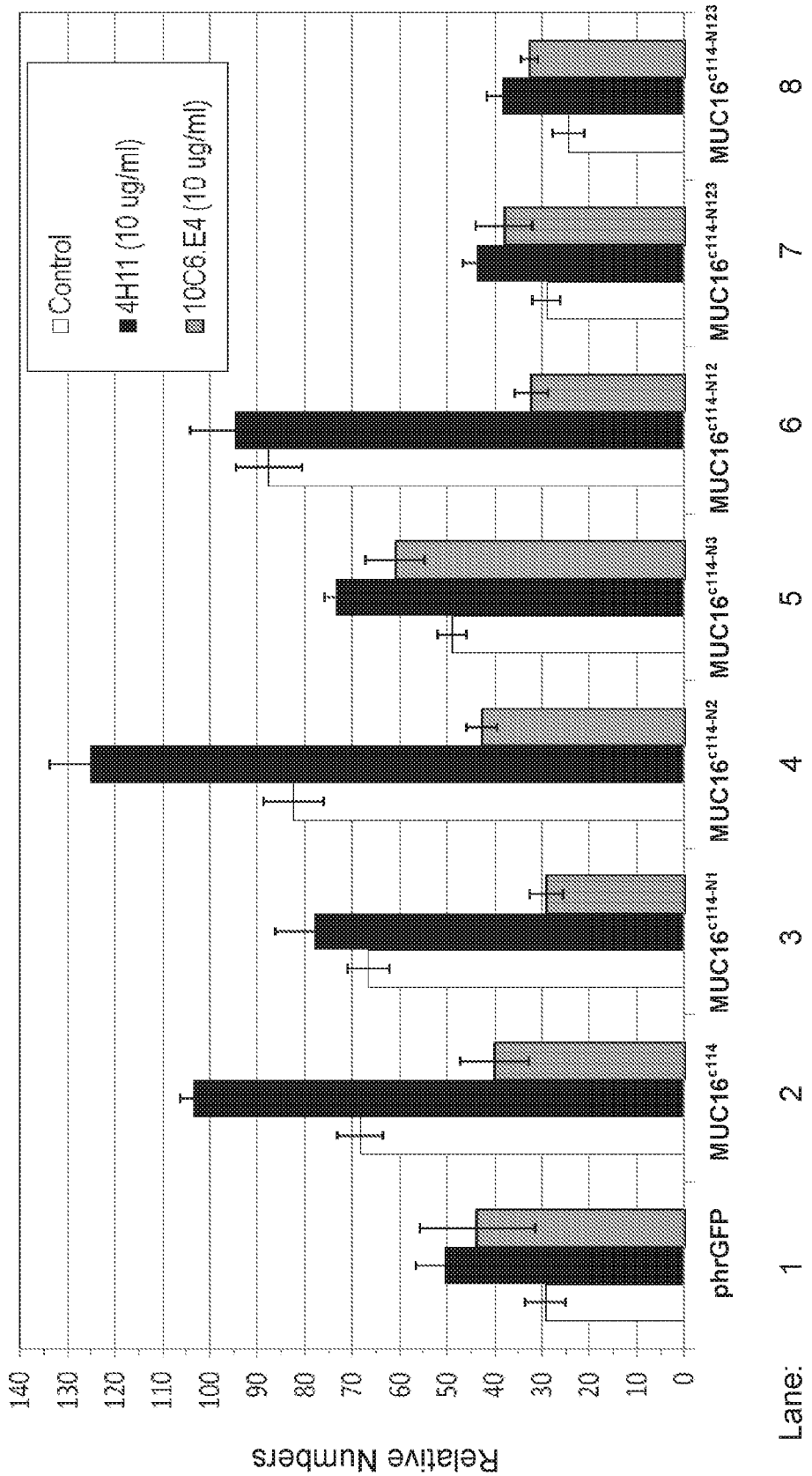

Control
4H11 (10 ug/ml)
10C6.E4 (10 ug/ml)
Relative Numbers
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Lane:
1
2
3
4
5
6
7
8
phrGFP
MUC16c114
MUC16c114-N1
MUC16c114-N2
MUC16c114-N3
MUC16c114-N12
MUC16c114-N123
MUC16c114-N123

Fig. 16C

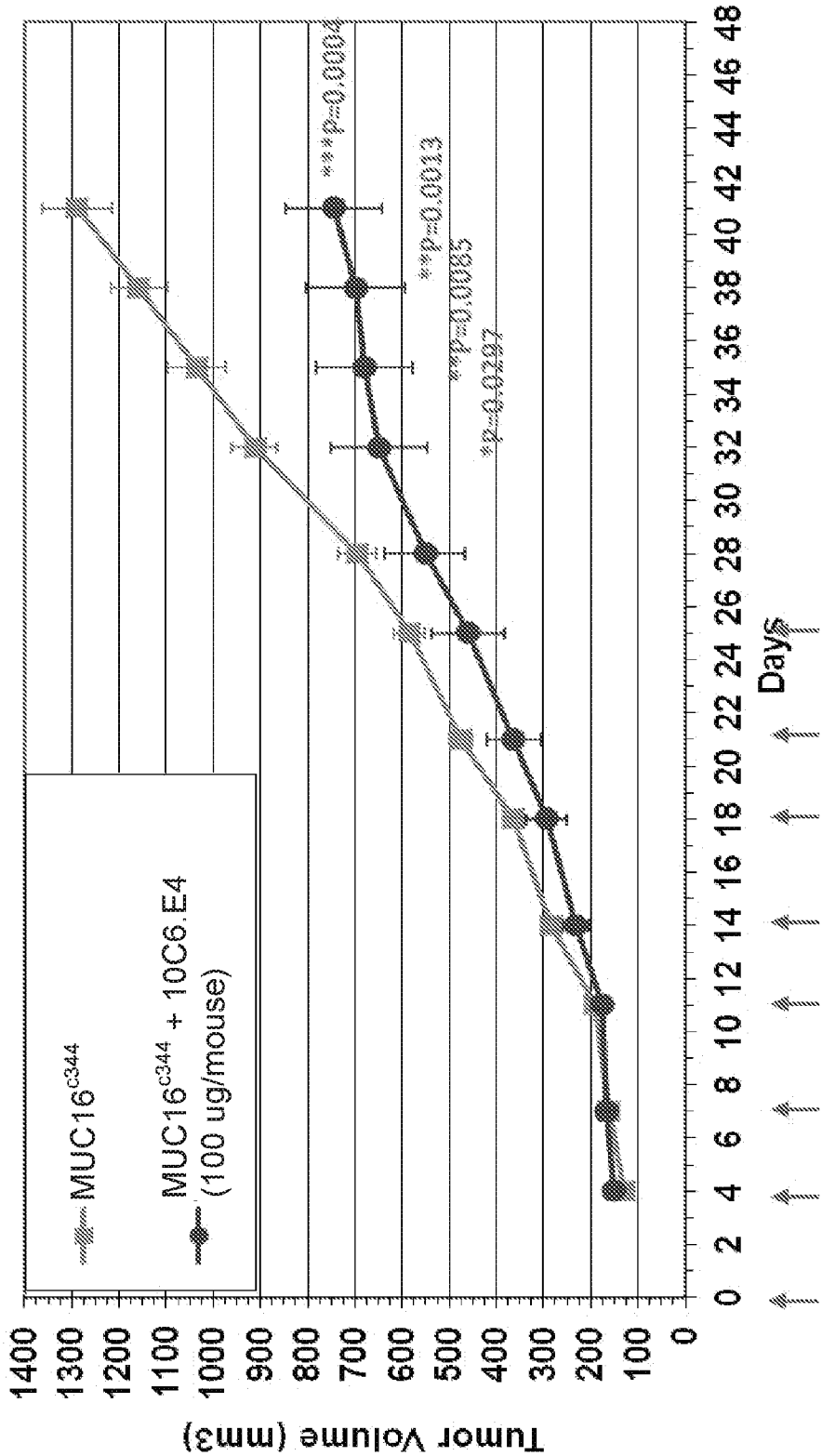

Tumor Volume (mm3)
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40 42 44 46 48
Days
MUC16c344
MUC16c344 + 10C6.E4
(100 ug/mouse)
***p=0.0004
**p=0.0013
**p=0.0085
*p=0.0207

Fig. 16D

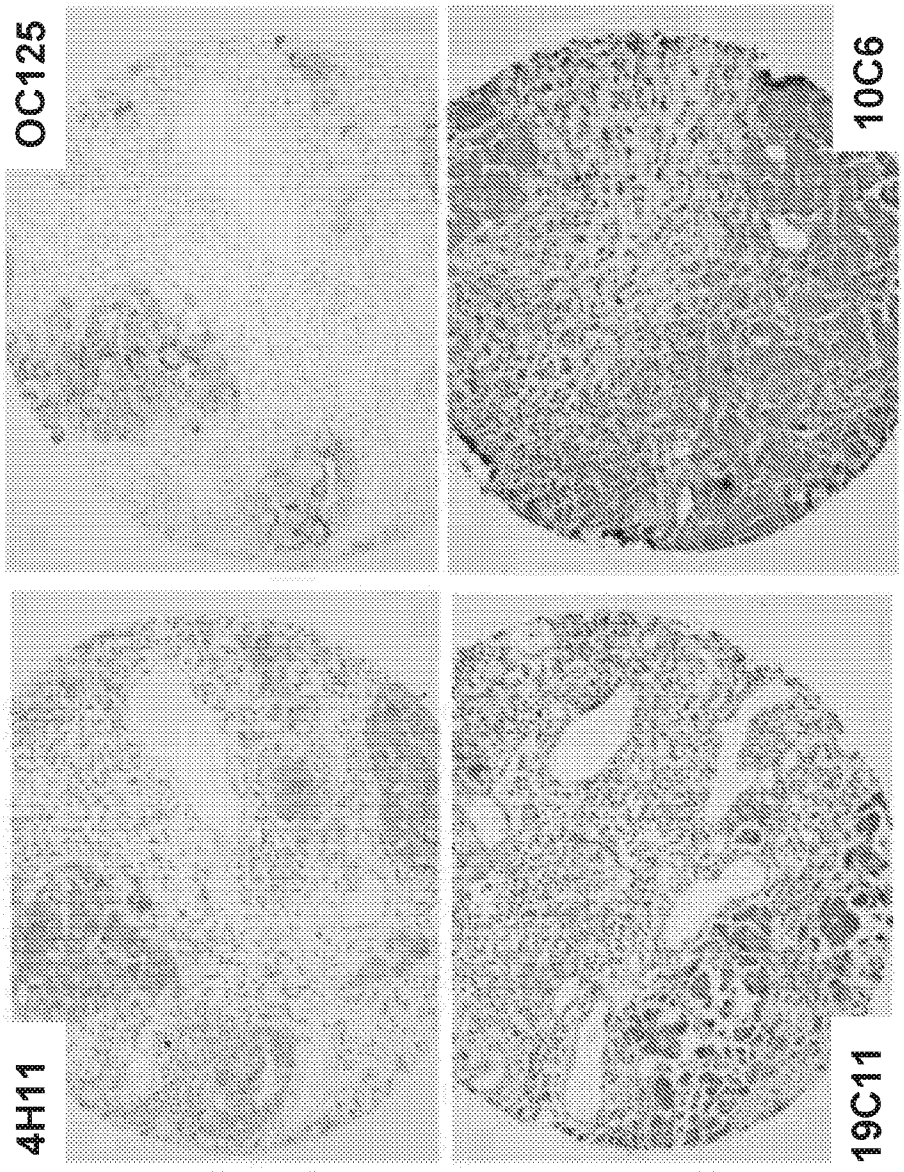


Fig. 16E

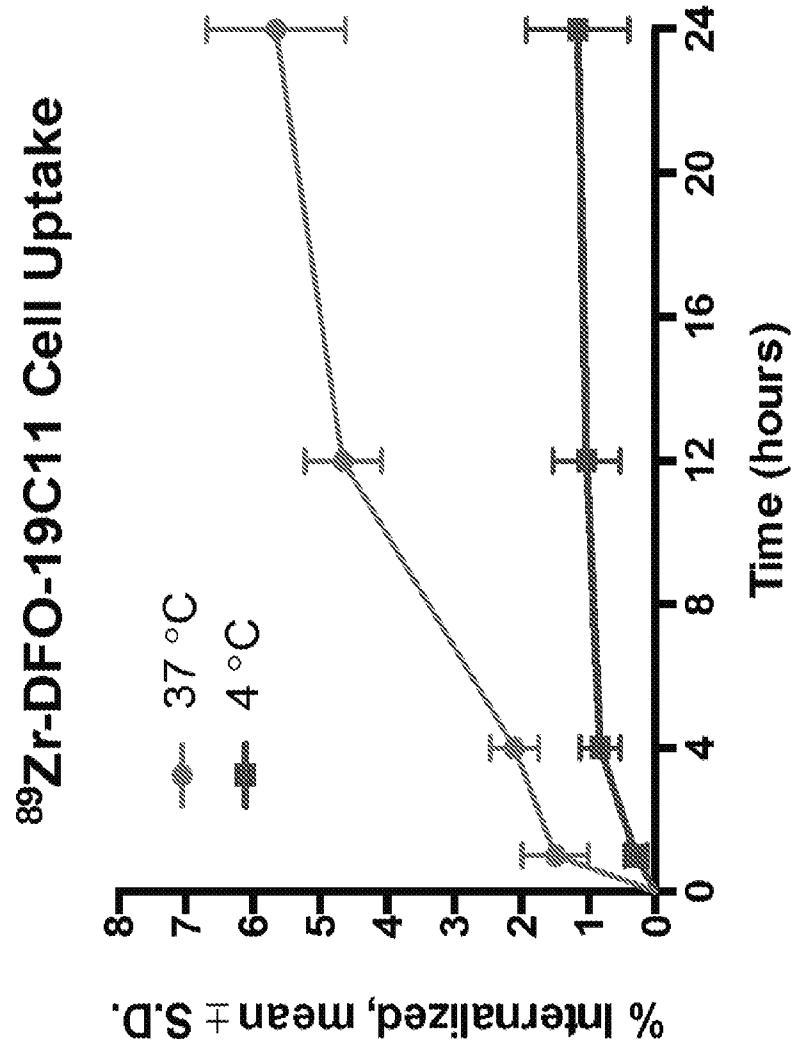

^{89}Zr-DFO-19C11 Cell Uptake
37 °C
4 °C
% Internalized, mean ± S.D.
0
1
2
3
4
5
6
7
8
0
4
8
12
16
20
24
Time (hours)

Fig. 17

Fig. 18A

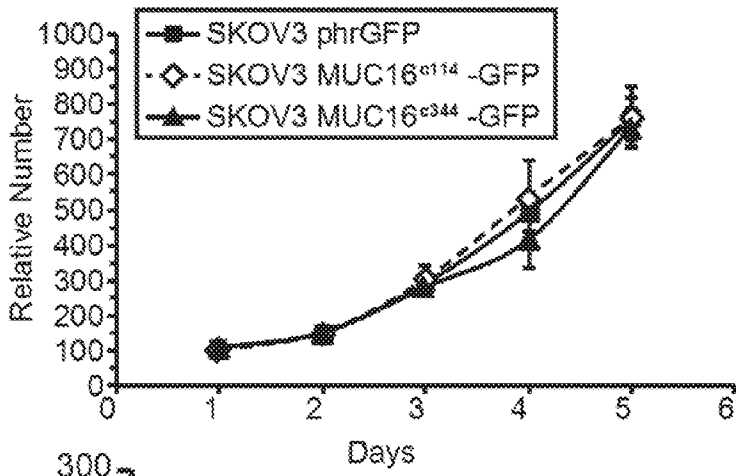


Fig. 18B

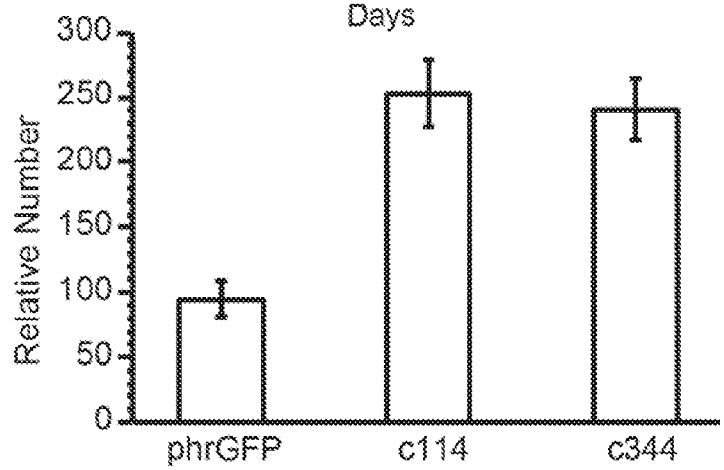
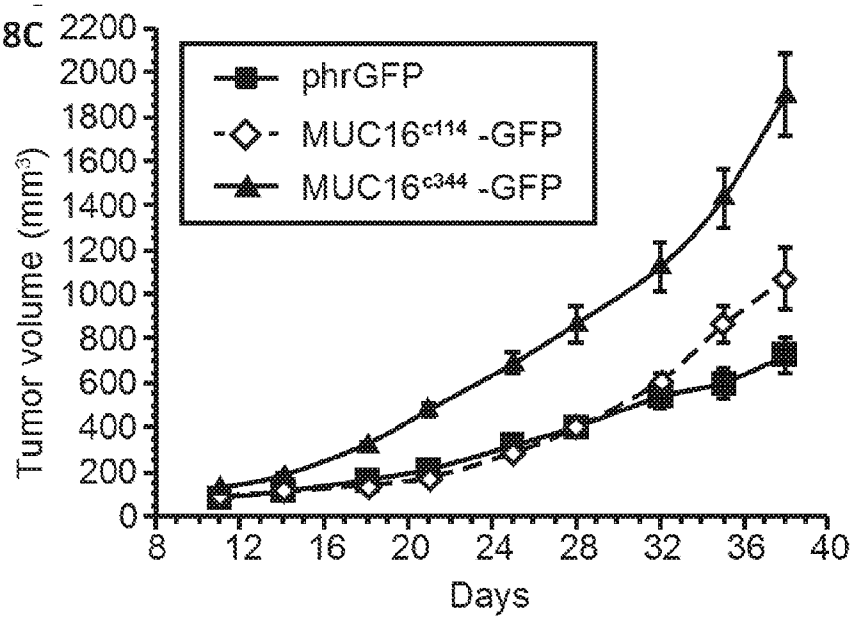


Fig. 18C



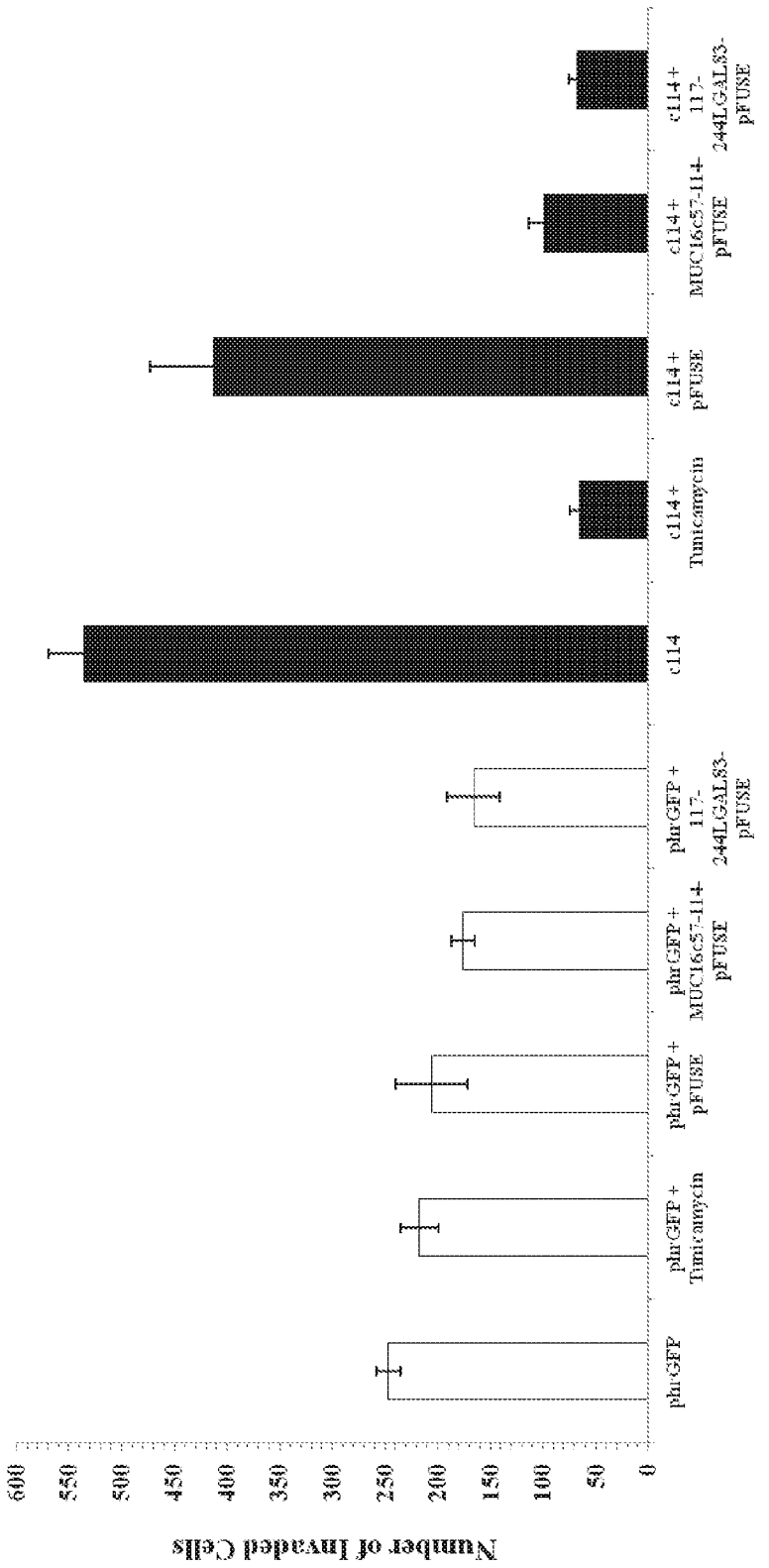

Number of Invaded Cells
600
550
500
450
400
350
300
250
200
150
100
50
0
phrGFP
phrGFP + Tunicamycin
phrGFP + pFUSE
phrGFP + MUC16c57-114-pFUSE
phrGFP + 117-244LGAL83-pFUSE
c114
c114 + Tunicamycin
c114 + pFUSE
c114 + MUC16c57-114-pFUSE
c114 + 117-244LGAL83-pFUSE

Fig. 19A

Fig. 19B

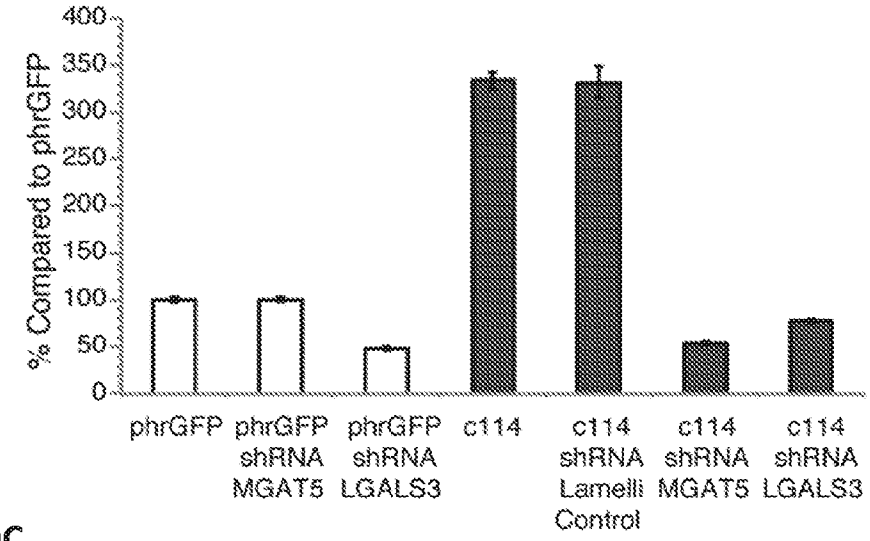


Fig. 19C

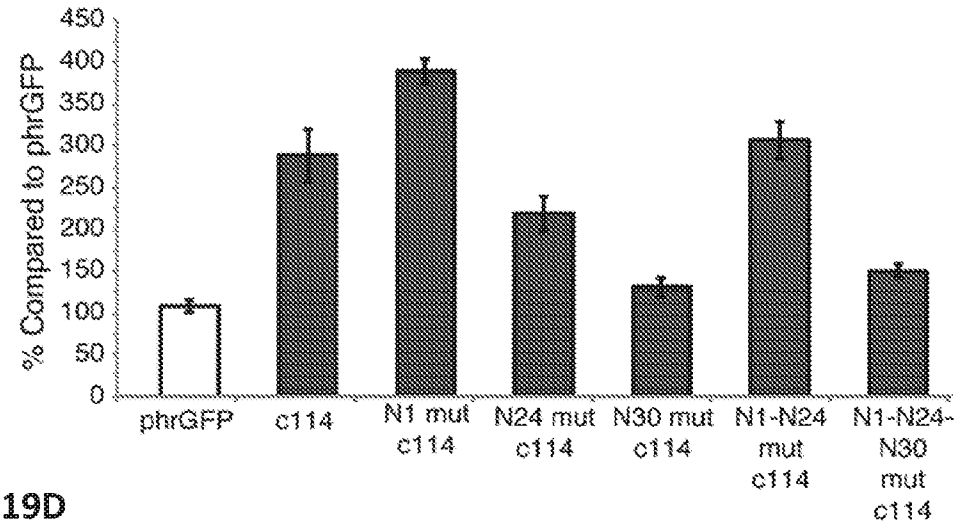


Fig. 19D

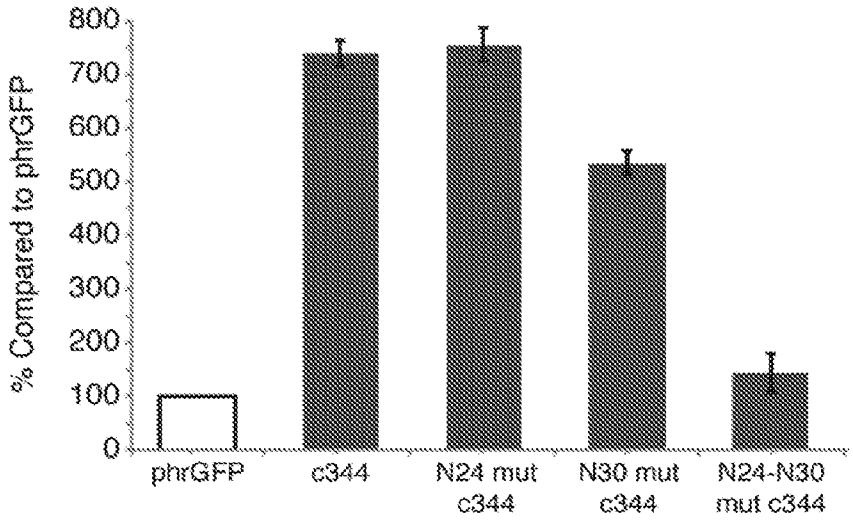


Fig. 19E

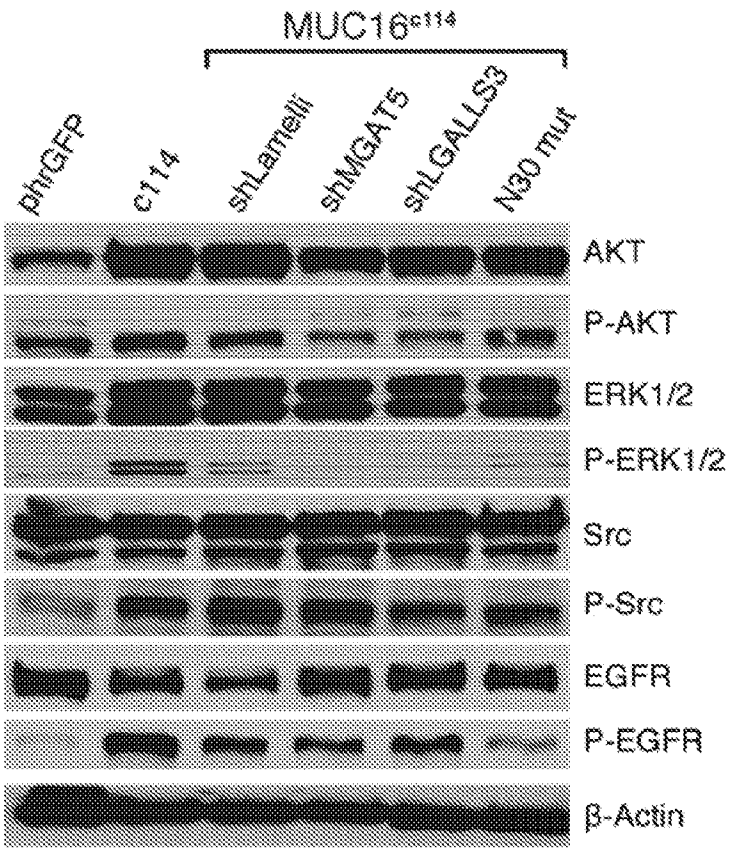


Fig. 19F

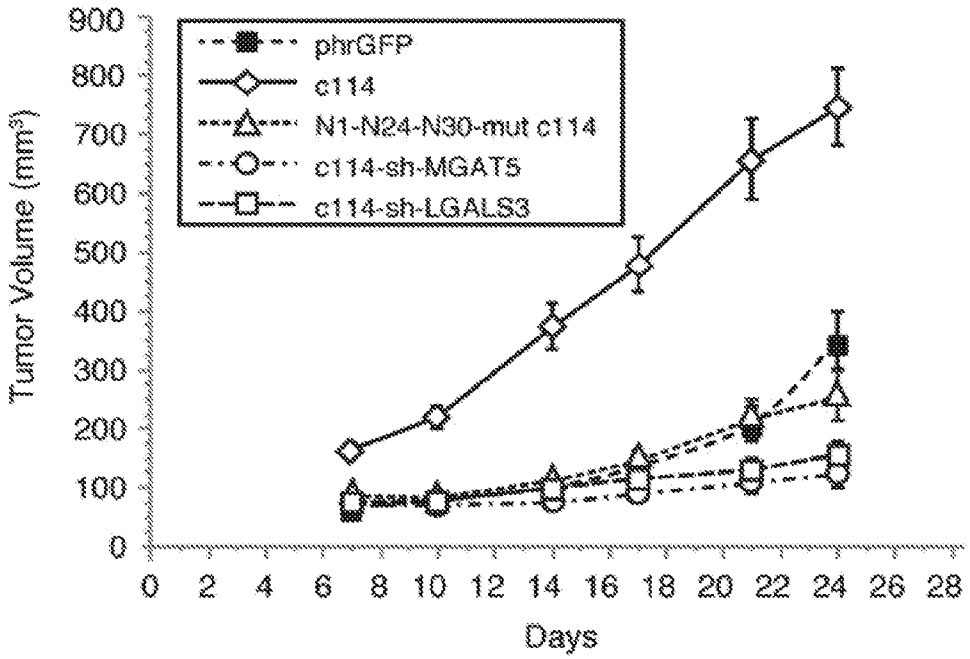


Fig. 20A

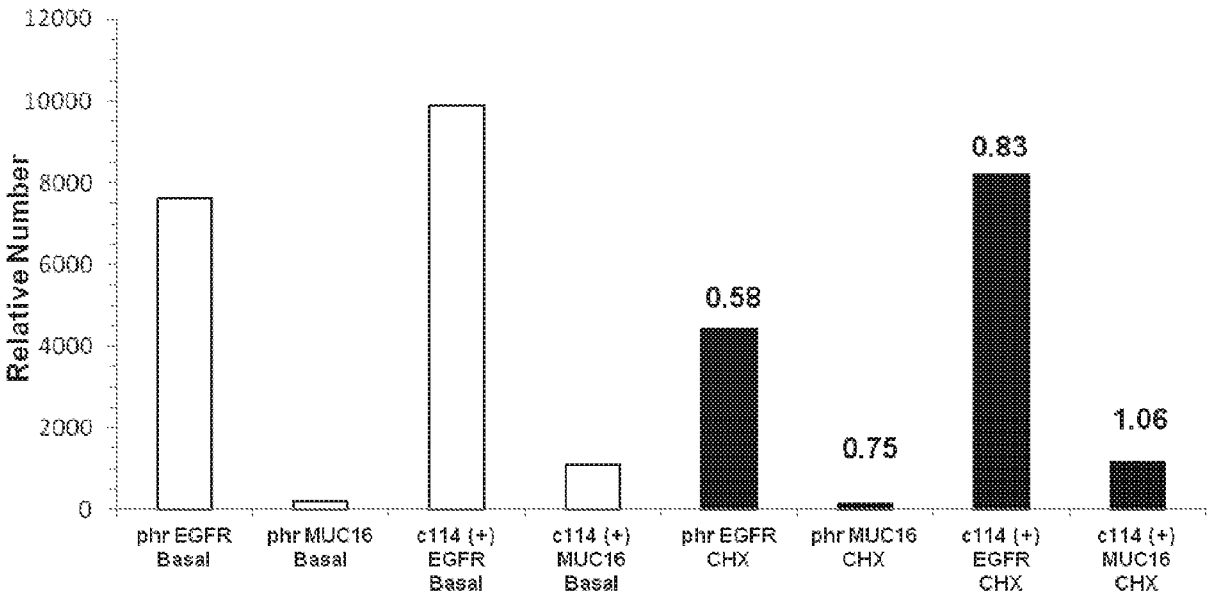
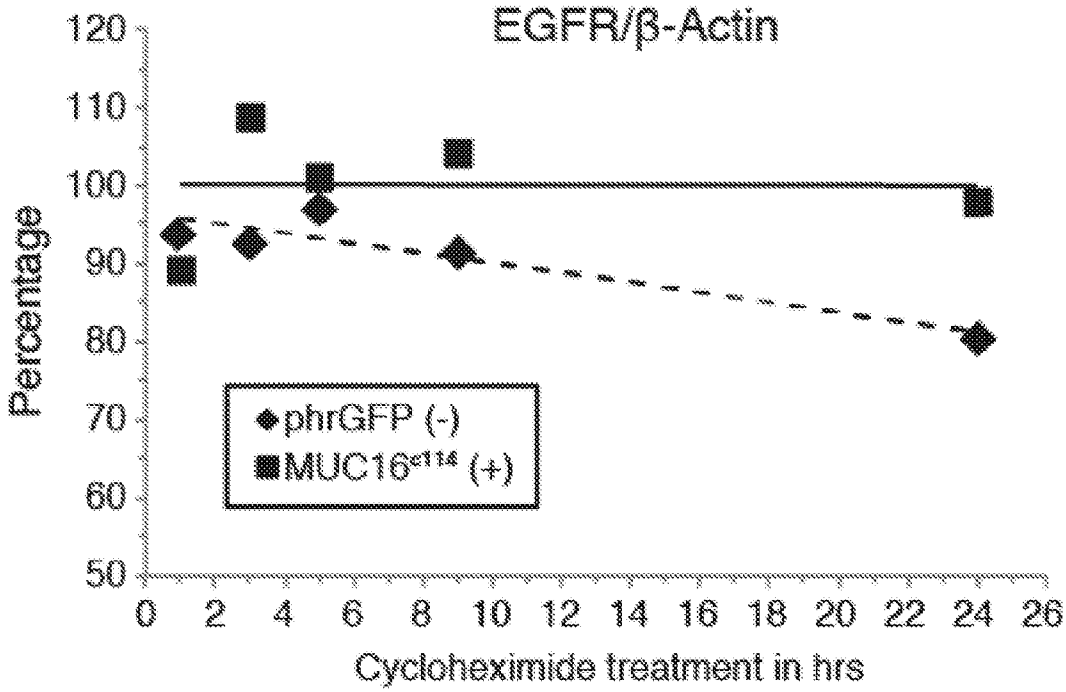


Fig. 20B



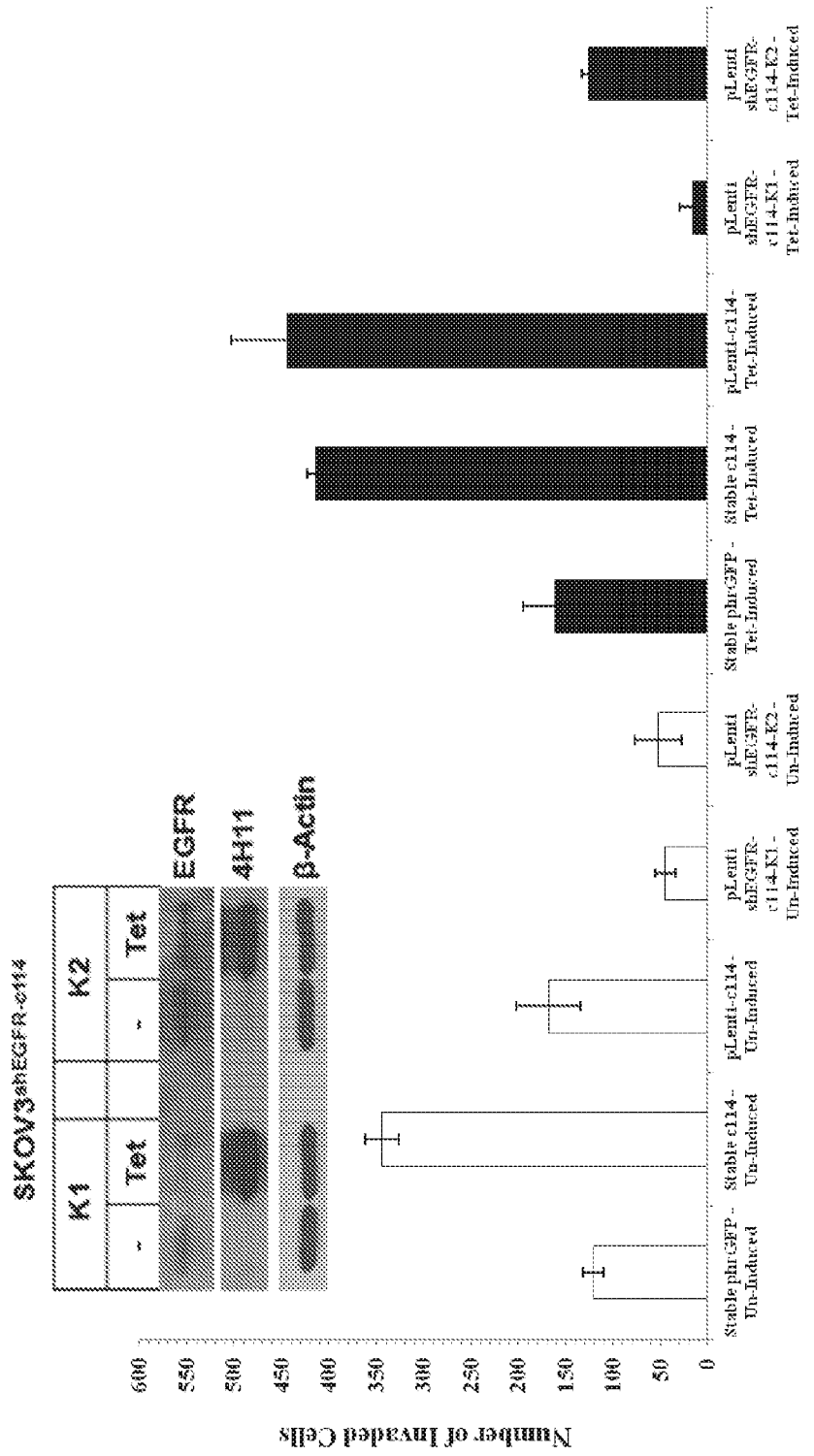

SKOV3shEGFR-c114
K1
K2
-
Tet
-
Tet
EGFR
4H11
β-Actin
Number of Invaded Cells
600
550
500
450
400
350
300
250
200
150
100
50
0
Stable phrGFP-Un-Induced
Stable c114-Un-Induced
pLenti-c114-Un-Induced
pLenti shEGFR-c114-K1-Un-Induced
pLenti shEGFR-c114-K2-Un-Induced
Stable phrGFP-Tet-Induced
Stable c114-Tet-Induced
pLenti-c114-Tet-Induced
pLenti shEGFR-c114-K1-Tet-Induced
pLenti shEGFR-c114-K2-Tet-Induced

Fig. 20C

Fig. 20D

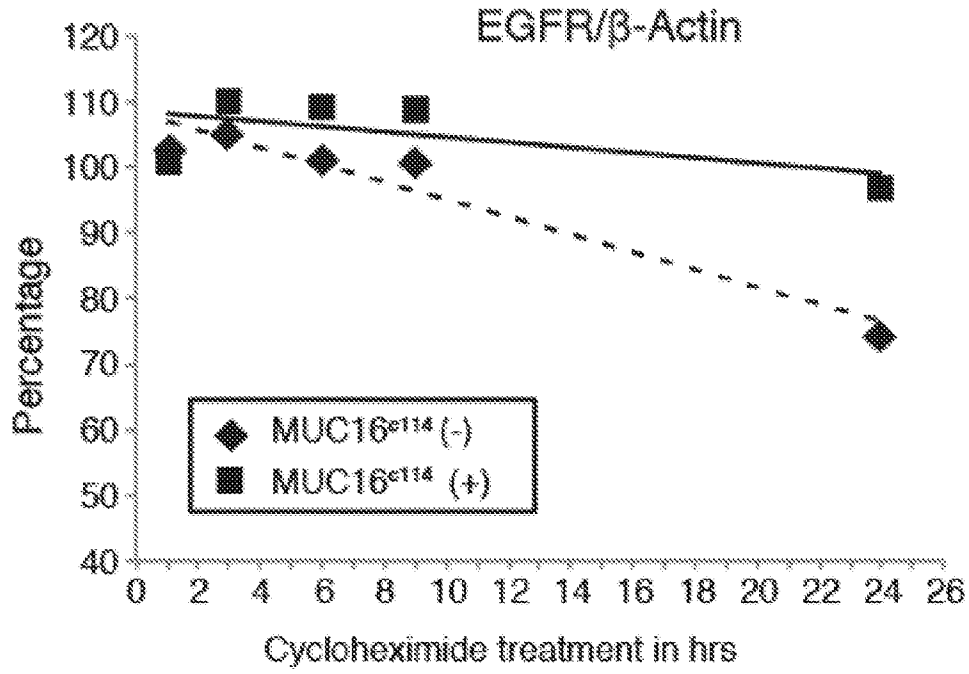


Fig. 21

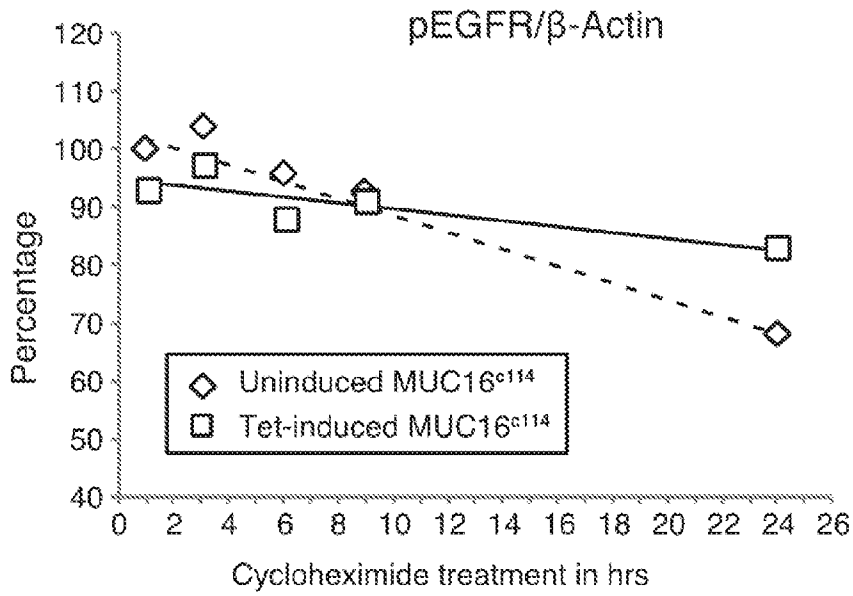
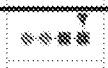
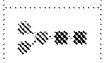
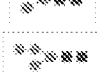
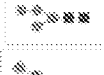
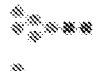
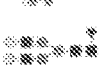
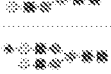
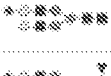
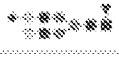


Fig. 22A

N-glycans listed in this table were detected through total ion mapping (M: Mannose, N: N-acethyglucosamine, F: fucose, Gal: Galactose, NeuAc: N-acethylneuraminic acid)

Structural assignment		Mass $[M+Na]^+$	Intensity/Charge state	Glycan %
M2N2F		1142	0.10×10^{-2}	32.47%
M3N2		1171	3.56×10^{-2}	11.33%
M3N2F		1345	4.18×10^{-2}	13.30%
M4N2		1376	1.91×10^{-2}	6.08%
M5N2		1580	3.78×10^{-2}	12.03%
M6N2		1784	0.87×10^{-2}	2.76%
M7N2		1988	0.37×10^{-2}	1.18%
Gal2N2M3N2F		2244	1.91×10^{-2}	6.06%
NeuAc1Gal2N2M3N2		2431	1.50×10^{-2}	4.76%
NeuAc1Gal2N2M3N2F		2605	1.65×10^{-2}	5.25%
NeuAc2Gal2N2M3N2		2792	0.77×10^{-2}	2.45%
NeuAc2Gal2N2M3N2F		2966	0.73×10^{-2}	2.32%
		Total	3.14×10^{-3}	100.00%

▼ Fucose ■ N-acetylglucosamin ● Mannose

○ Galactose ◆ N-acetylneuraminic acid

Fig. 22B

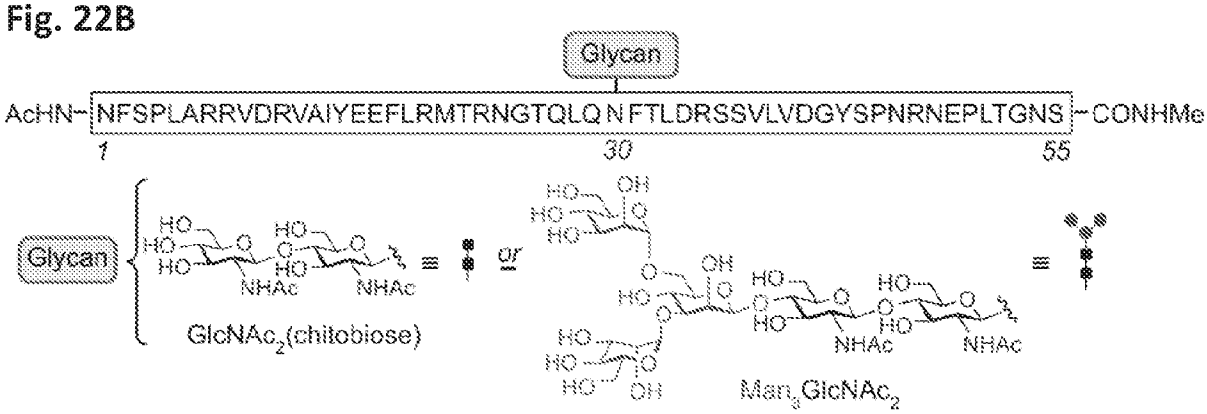


Fig. 22C

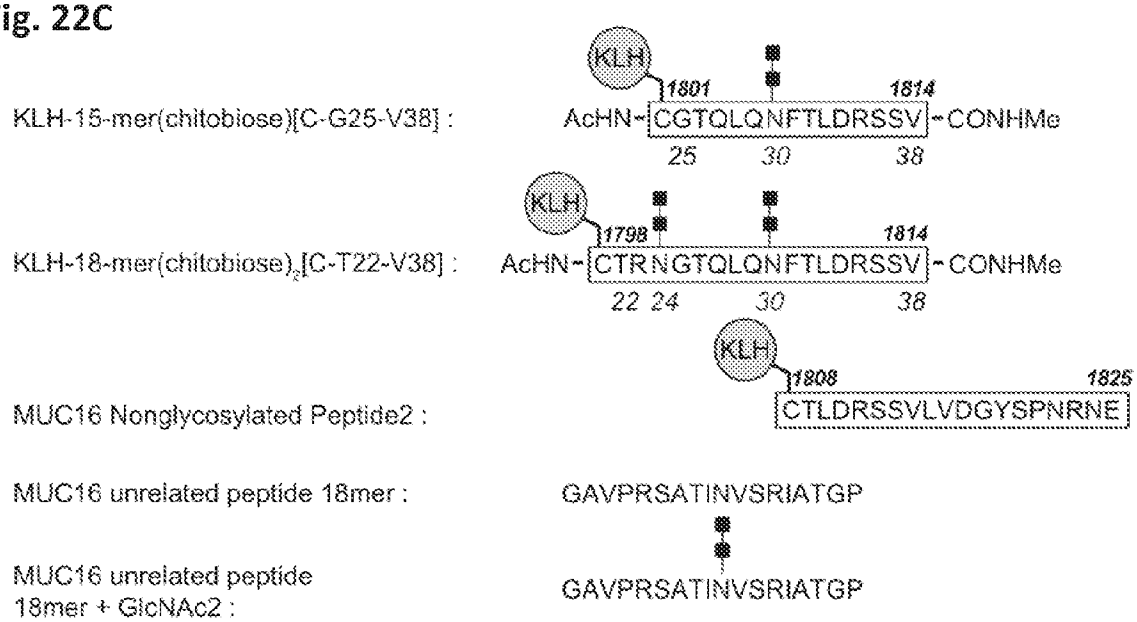


Fig. 23A

Peptides	Structure	Blank	4H11	Anti-glycosylated-MUC16 ectodomain antibodies			
				7B12	10C6	18C6	19C11
MUC16 unrelated peptide 18mer		0.013	0.045	0.04	0.03	0.02	0.03
MUC16 unrelated 18mer + GlcNAc2		0.014	0.038	0.03	0.03	0.02	0.03
MUC16 15mer		0.021	0.049	1.206	0.543	1.061	1.167
MUC16 15mer + GlcNAc2		0.019	0.06	1.323	0.573	1.442	1.514
MUC16 18mer		0.032	0.076	1.09	1.06	1.01	0.98
MUC16 18mer + GlcNAc1		0.042	ND	1.03	1.01	0.95	0.96
MUC16 18mer + GlcNAc2		0.029	0.063	1.06	1.13	1.06	1.10
MUC16 18mer + GlcNAc2-Trimannose		0.035	ND	1.05	0.99	0.89	0.99
MUC16 18mer + GlcNAc2-FUCOSE1		0.044	ND	1.10	1.08	1.03	1.01
MUC16 Nonglycosylated Peptide2		0.029	2.139	0.02	0.02	0.02	0.03

Fig. 23B

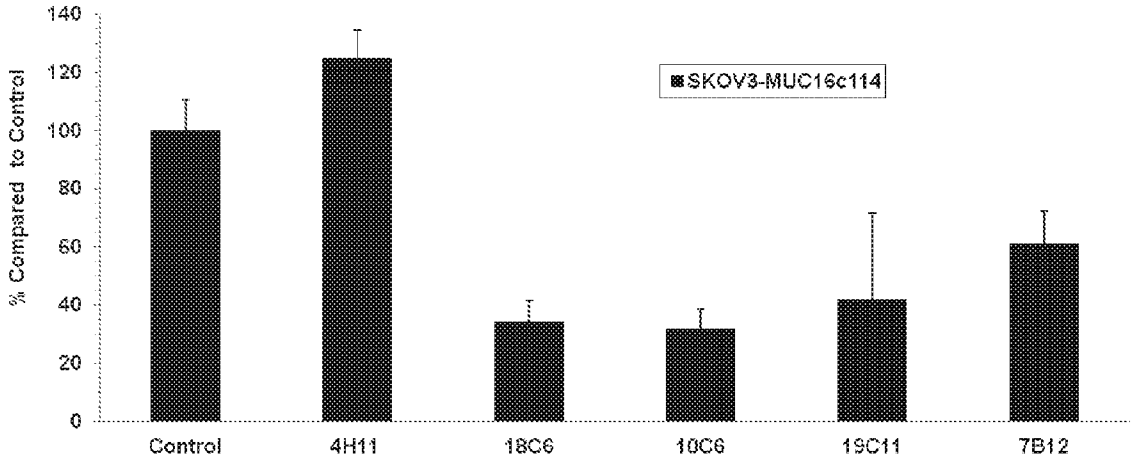


Fig. 23C

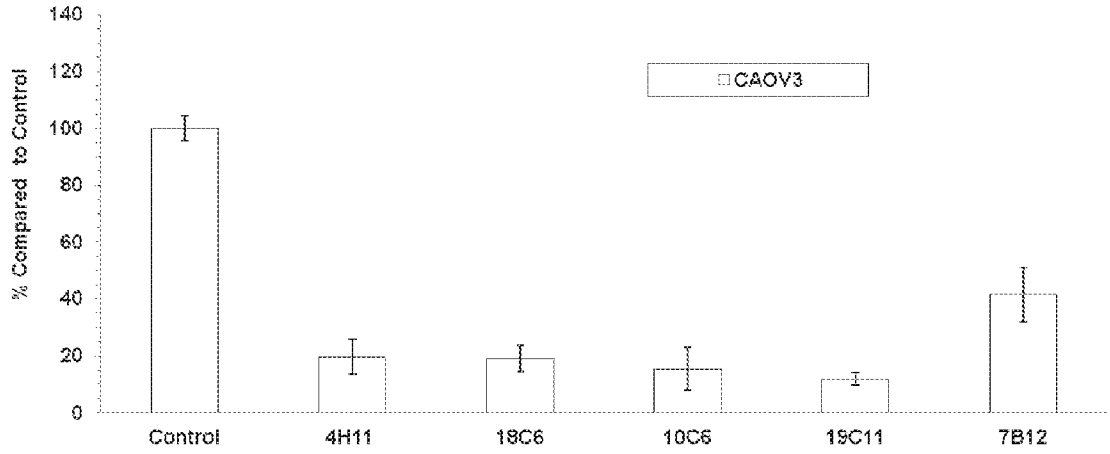


Fig. 23D

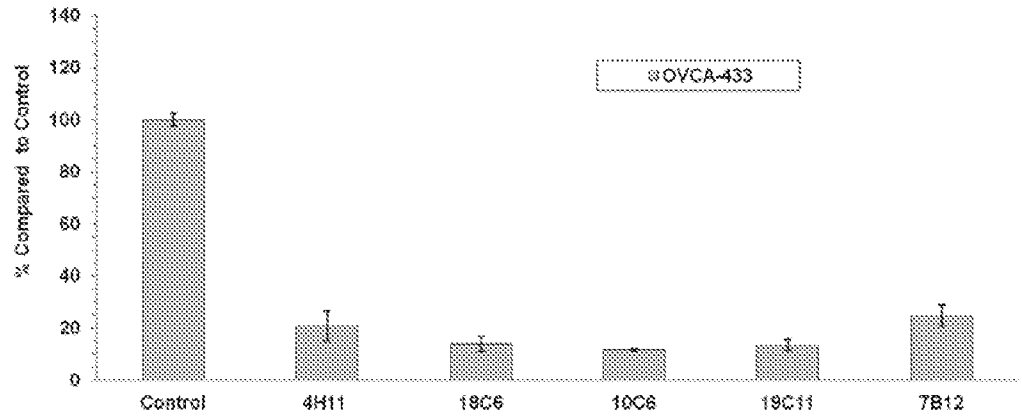


Fig. 23E

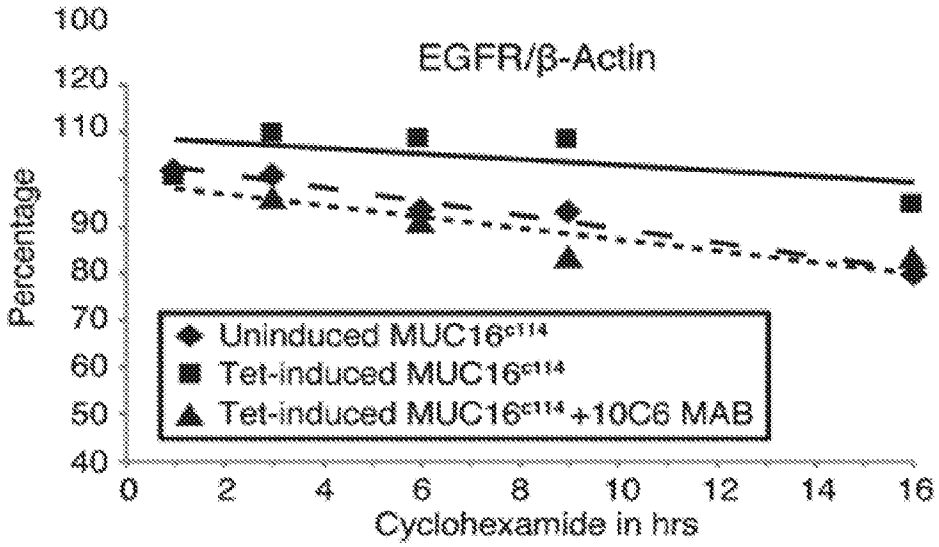


Fig. 23F

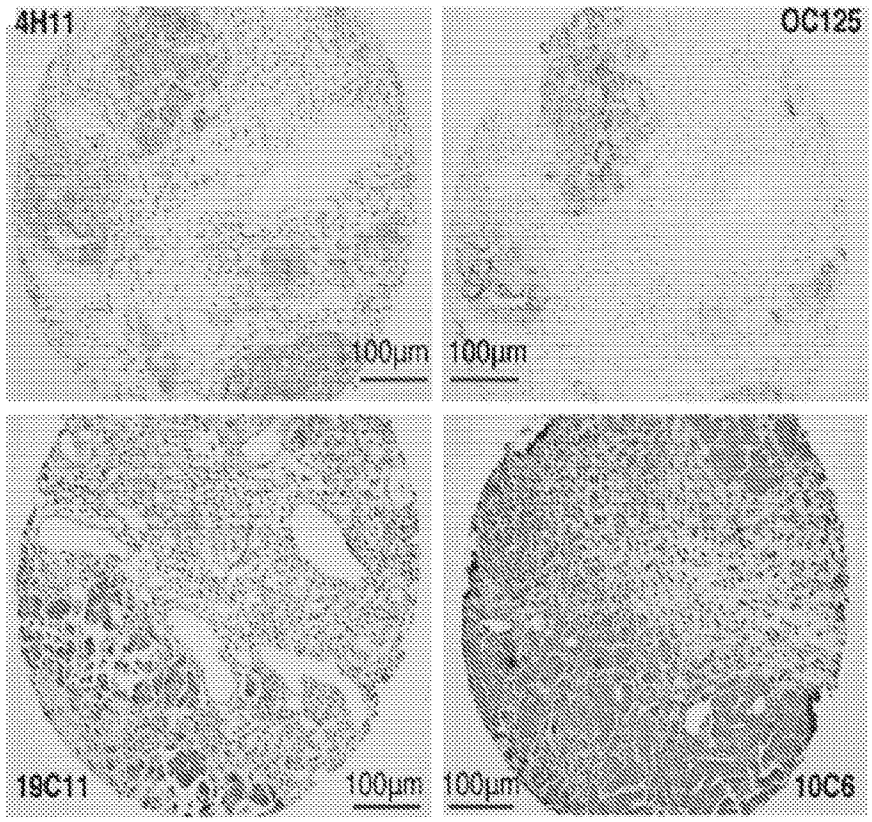


Fig. 23G

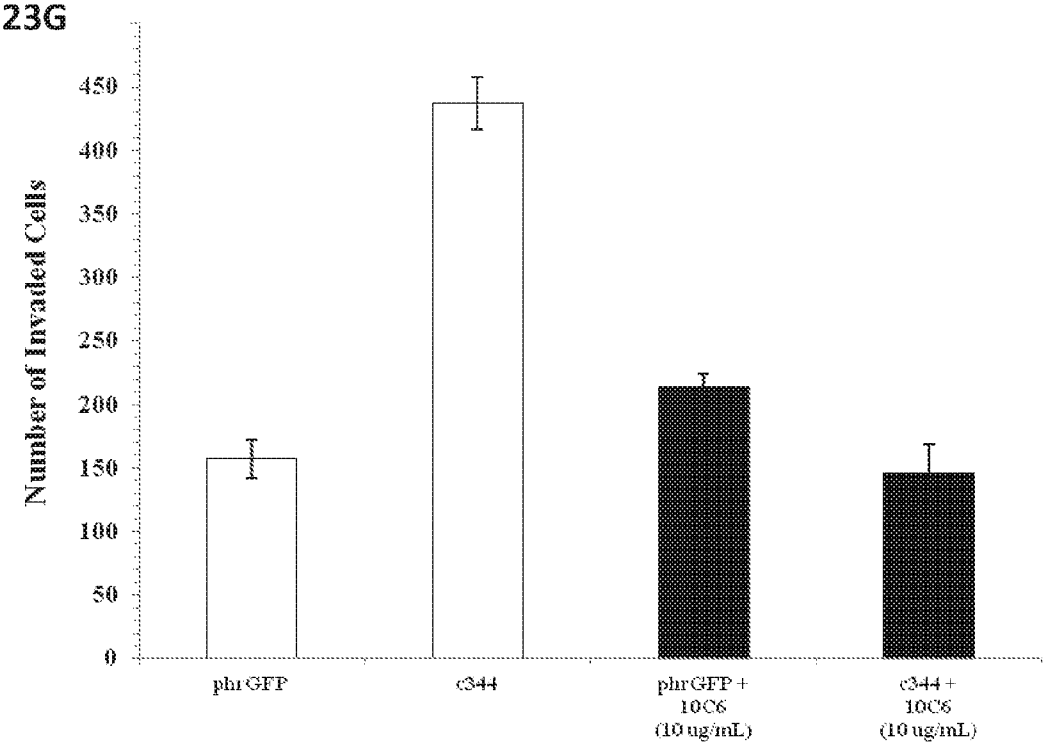


Fig. 23H

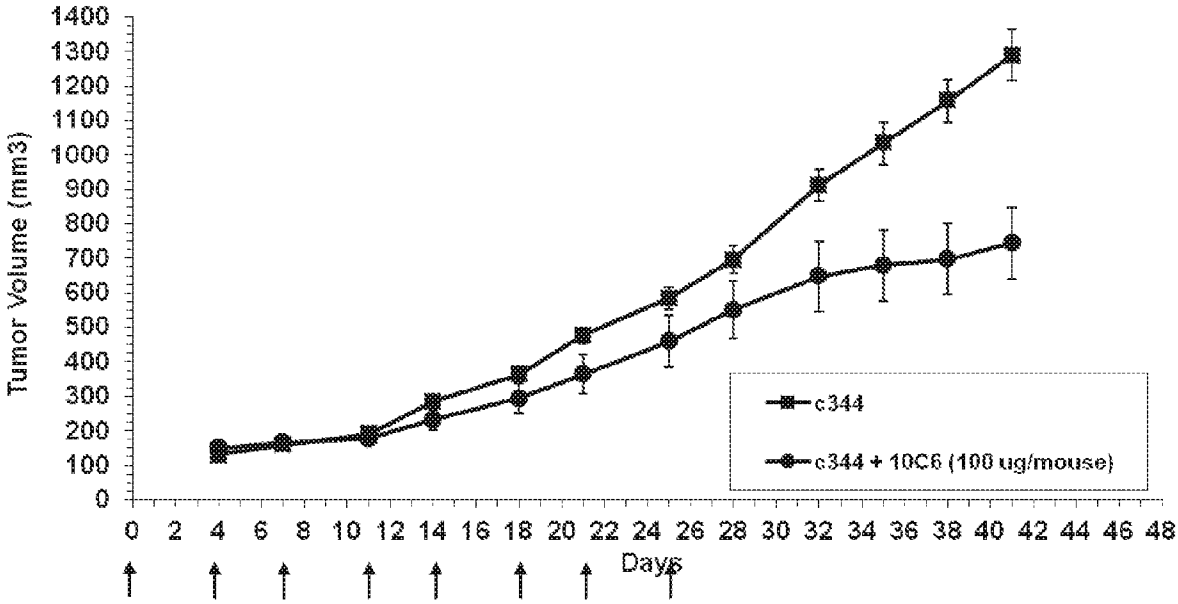


Fig. 24A

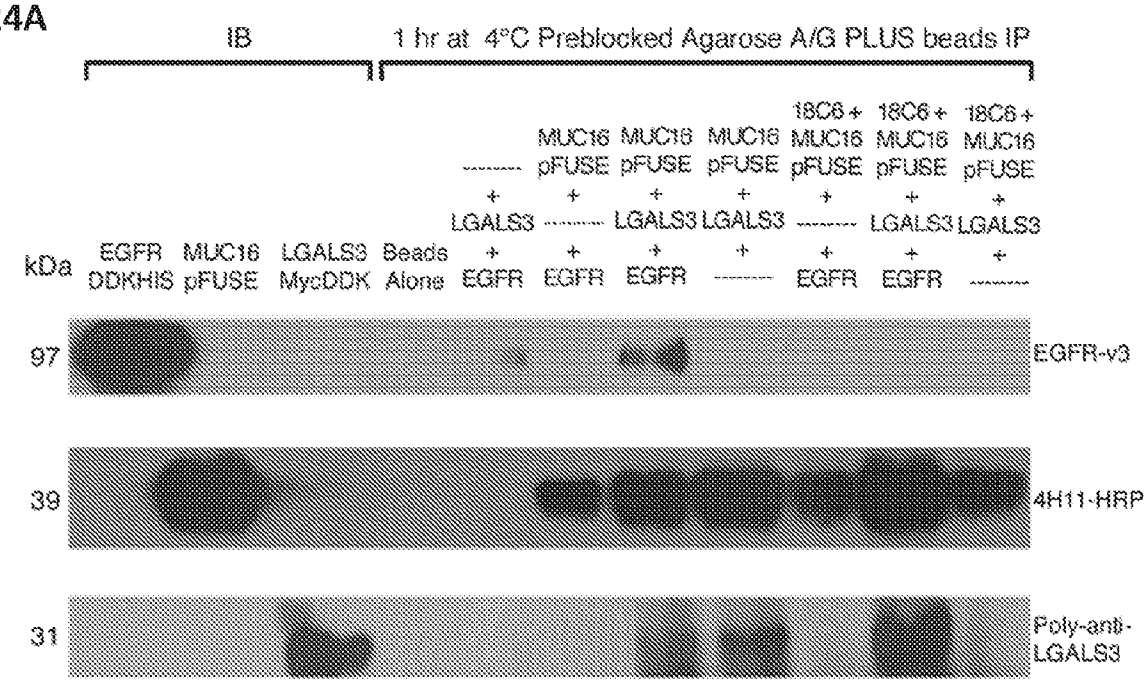


Fig. 24B

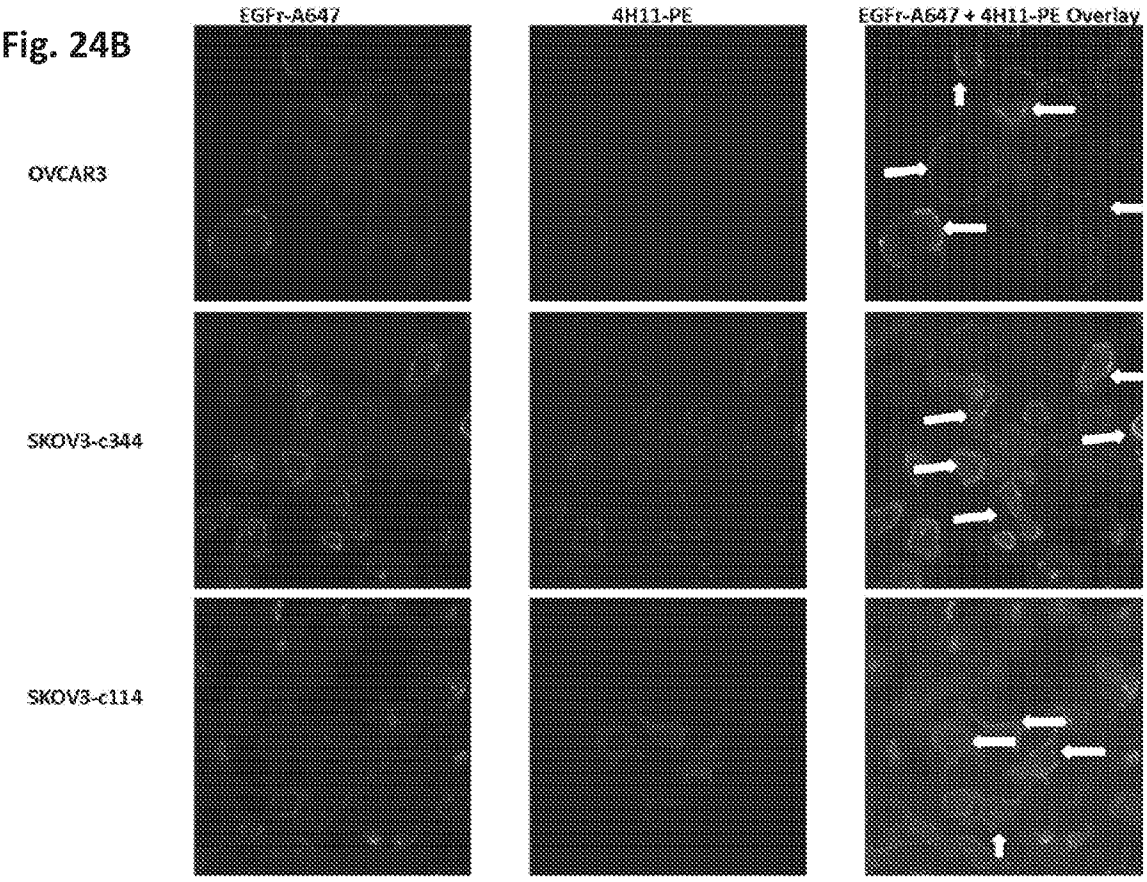


Fig. 24C

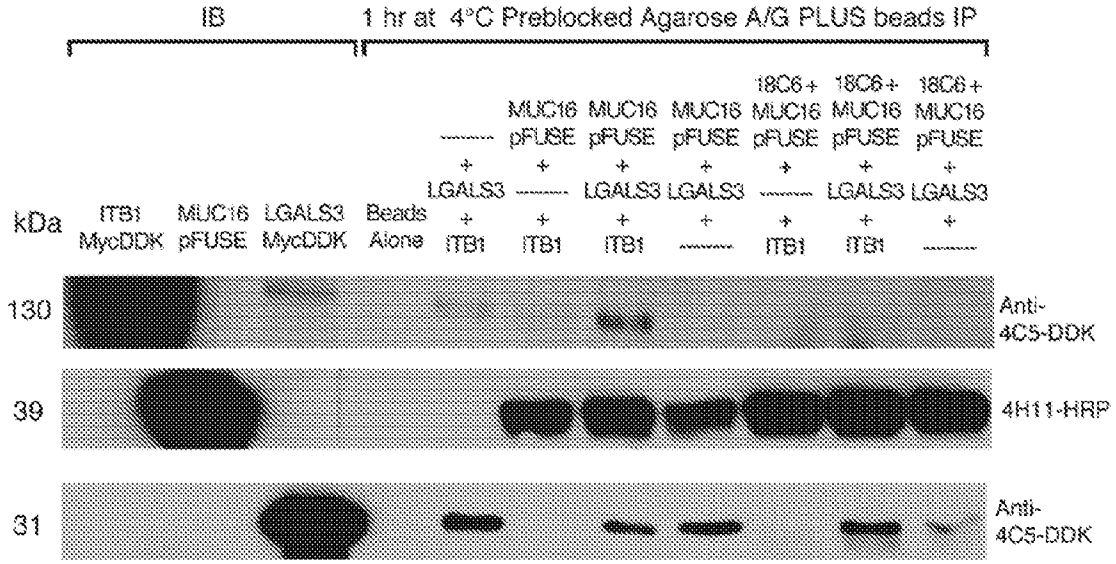


Fig. 24D

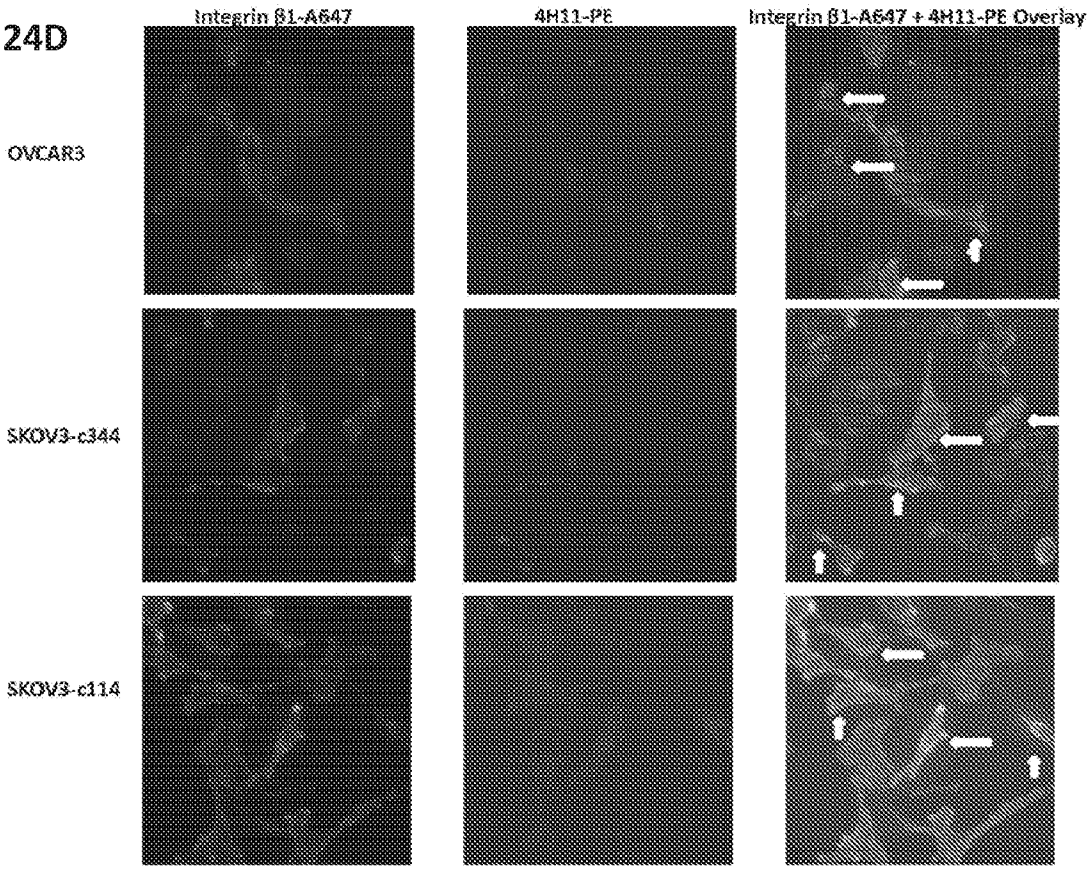


Fig. 25A

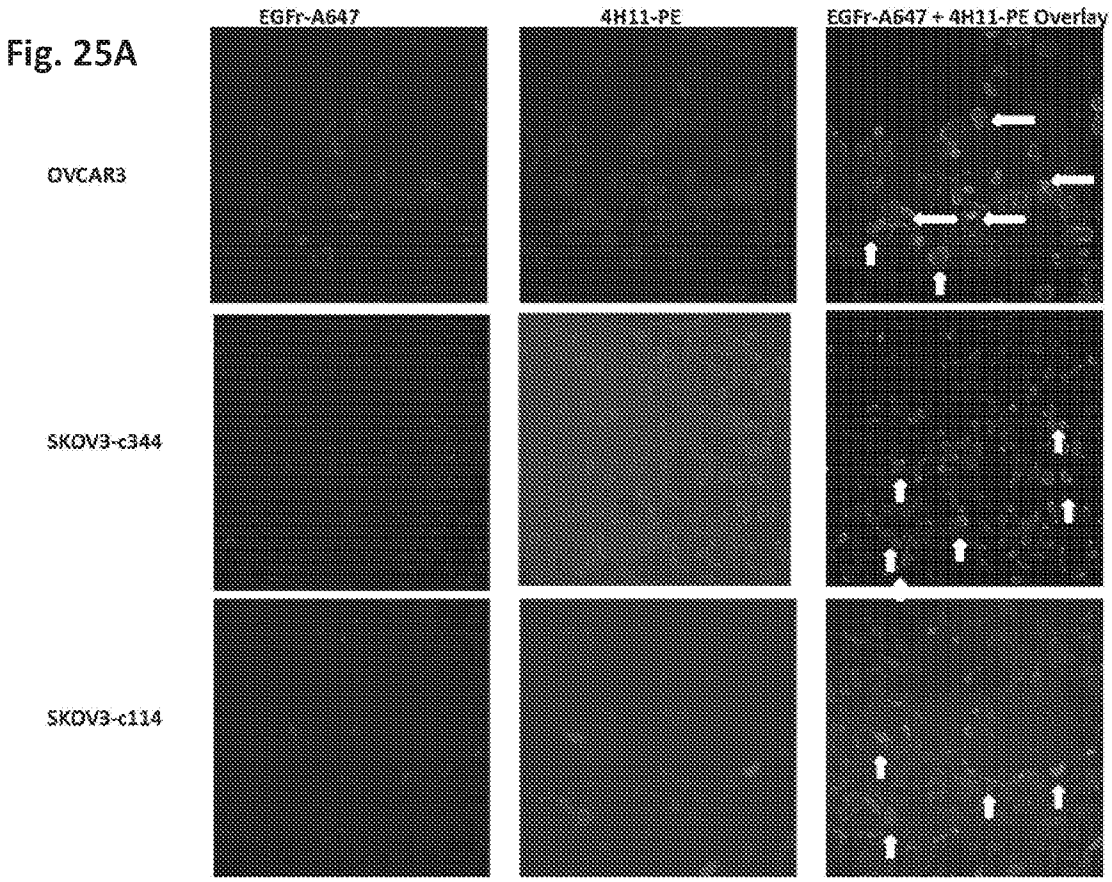
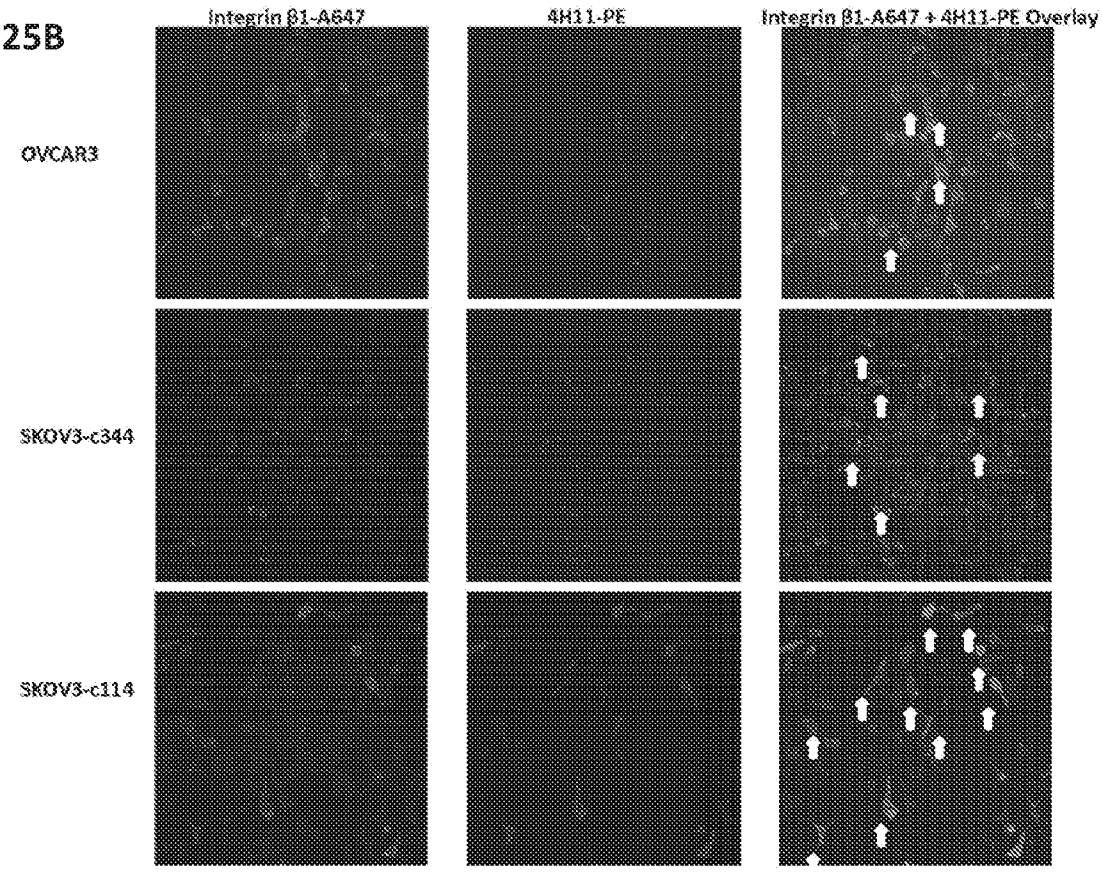
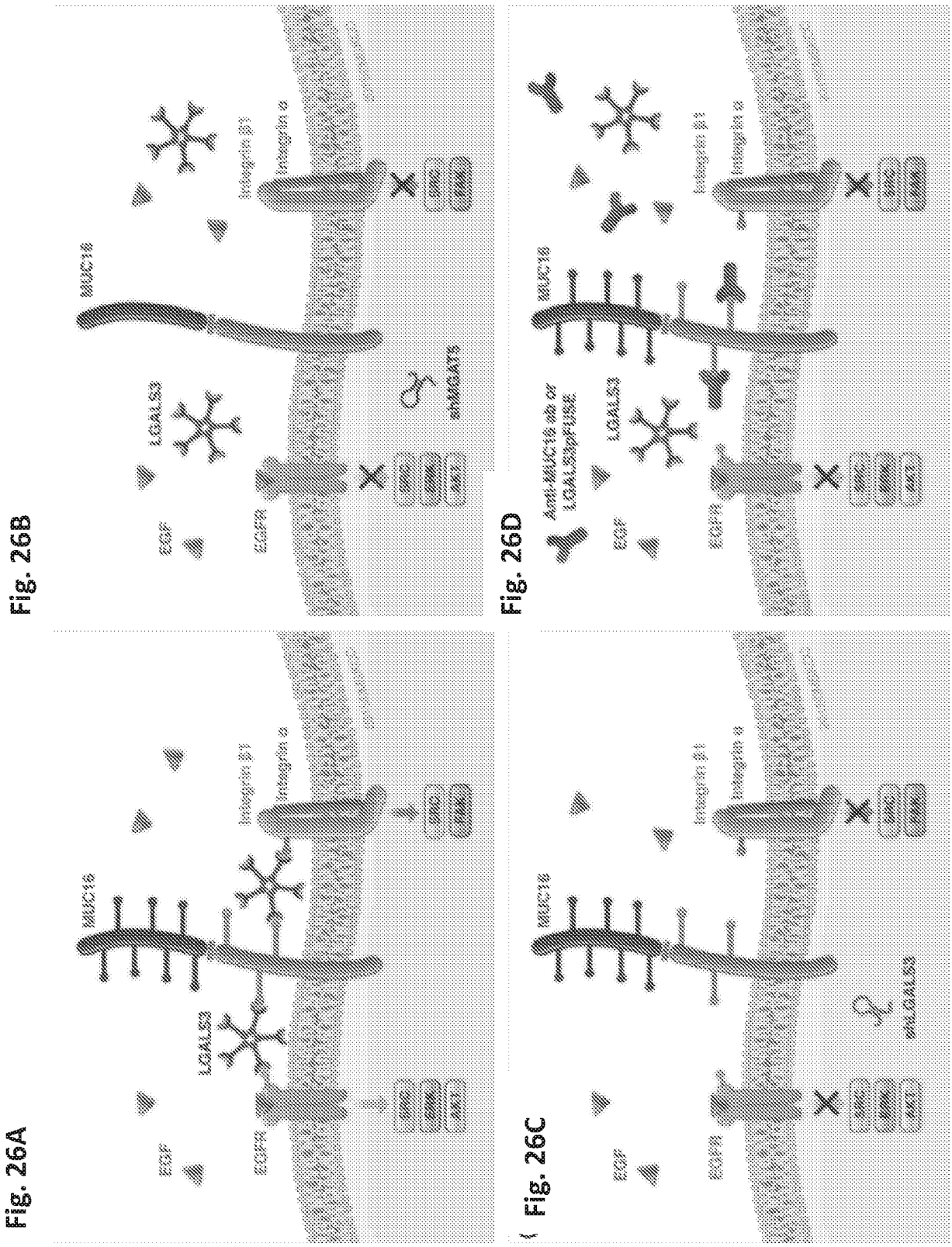

EGFr-A647
4H11-PE
EGFr-A647 + 4H11-PE Overlay
OVCAR3
SKOV3-c344
SKOV3-c114

Fig. 25B


Integrin β1-A647
4H11-PE
Integrin β1-A647 + 4H11-PE Overlay
OVCAR3
SKOV3-c344
SKOV3-c114


Fig. 26A
MUC16
LGALS3
EGF
EGFR
Integrin β1
Integrin α
PI3K
MEK
AKT
Fig. 26B
MUC16
LGALS3
EGF
EGFR
Integrin β1
Integrin α
PI3K
MEK
AKT
anti-MGAT5
Fig. 26C
MUC16
EGF
EGFR
Integrin β1
Integrin α
PI3K
MEK
AKT
anti-GALS3
Fig. 26D
Anti-MUC16 ab or LGALS3bpFUSE
MUC16
LGALS3
EGF
EGFR
Integrin β1
Integrin α
PI3K
MEK
AKT

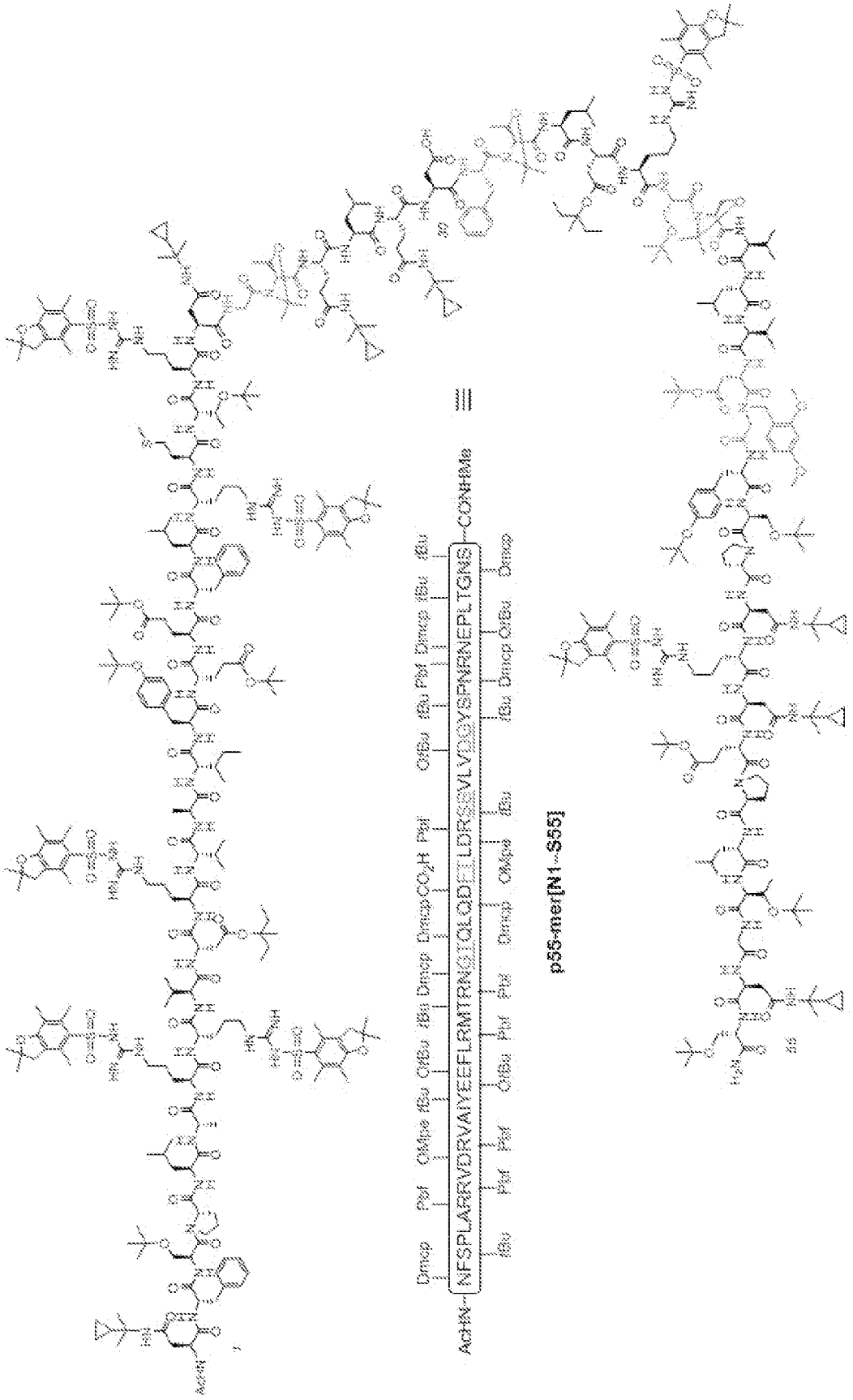


Fig. 27A

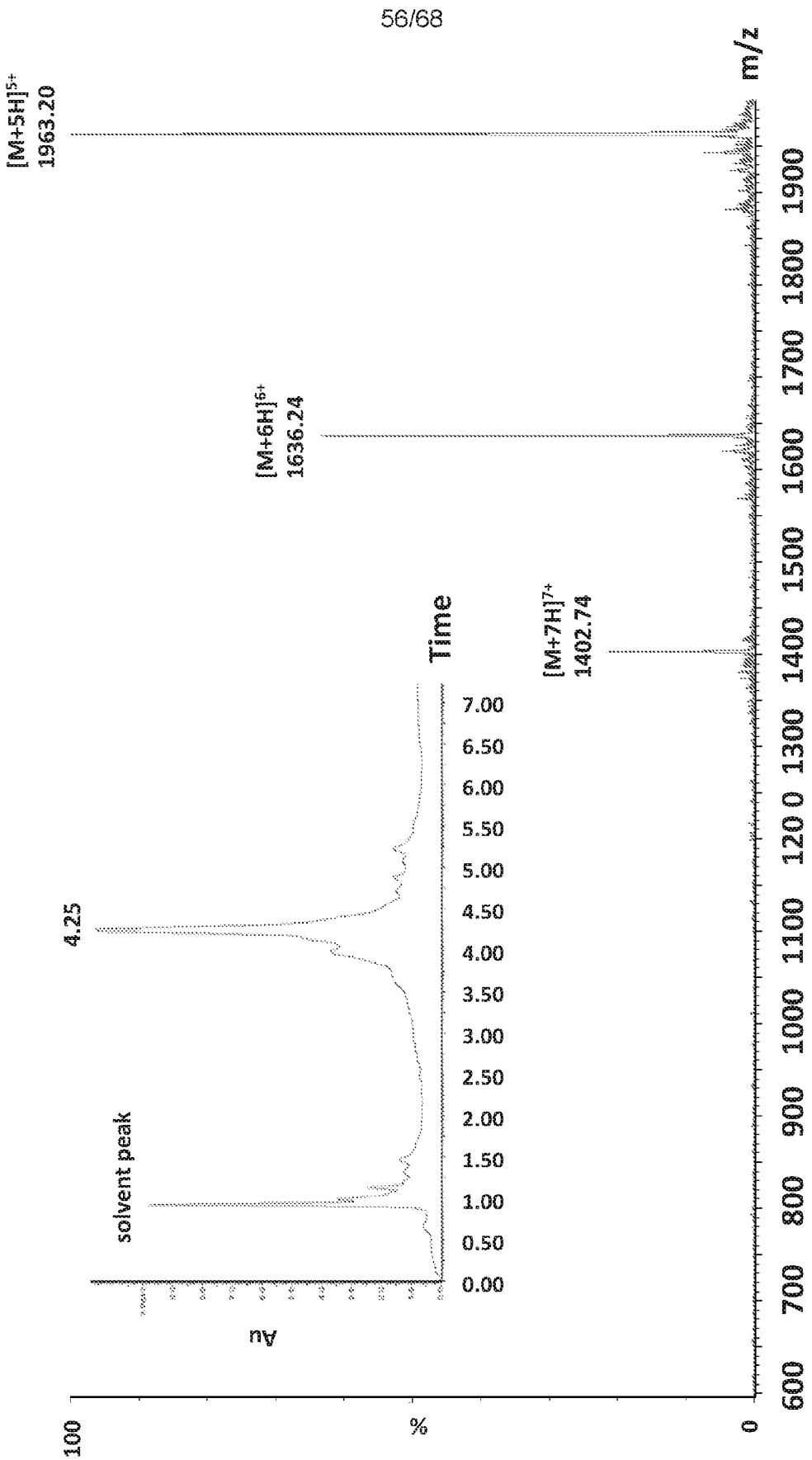

[M+5H]5+
1963.20
[M+6H]6+
1636.24
[M+7H]7+
1402.74
m/z
600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900
100
%
0
Au
Time
4.25
solvent peak
7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00

Fig. 27B

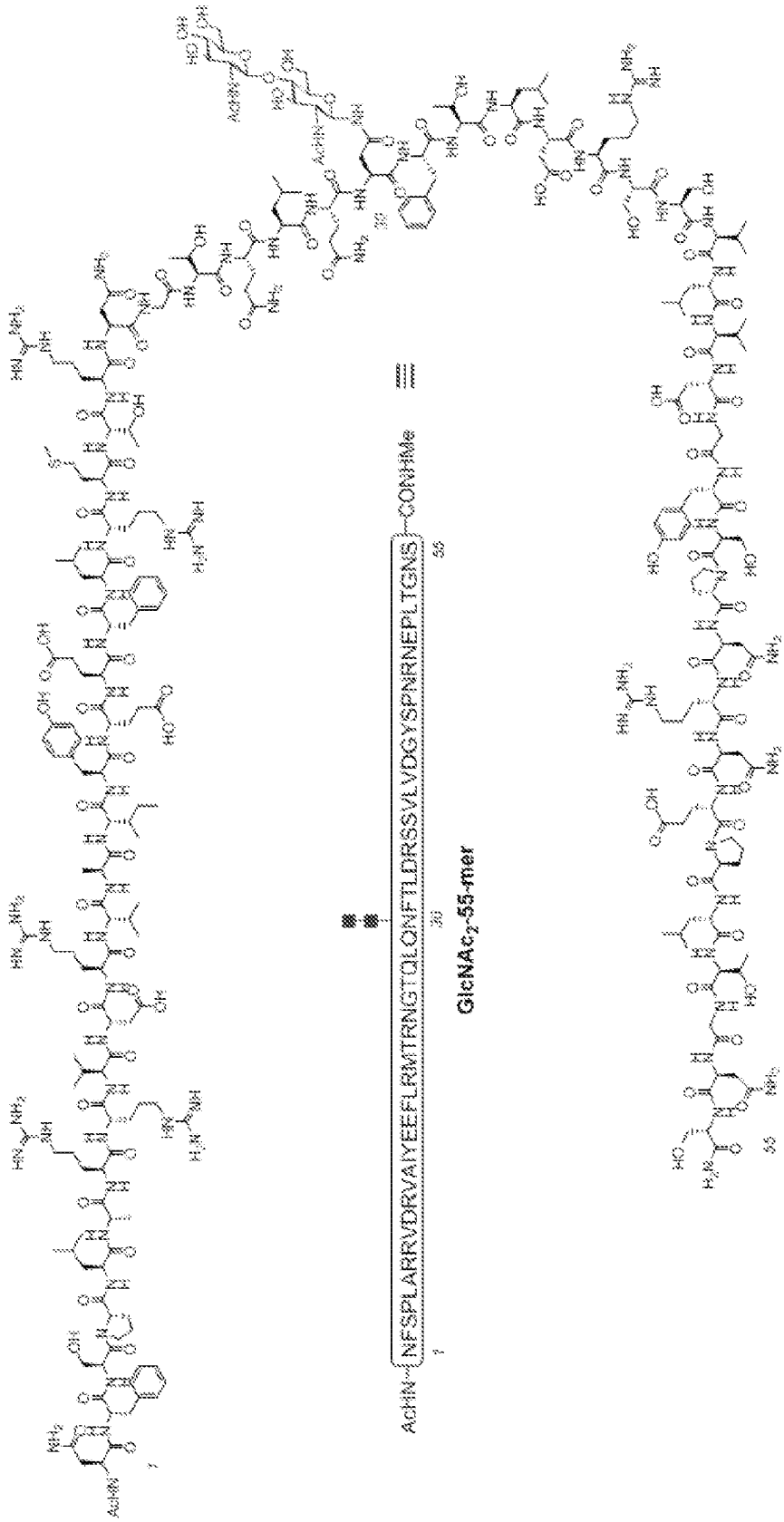

AcHN-
NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNS
CONHMe
GlcNAc2-55-mer

Fig. 28A

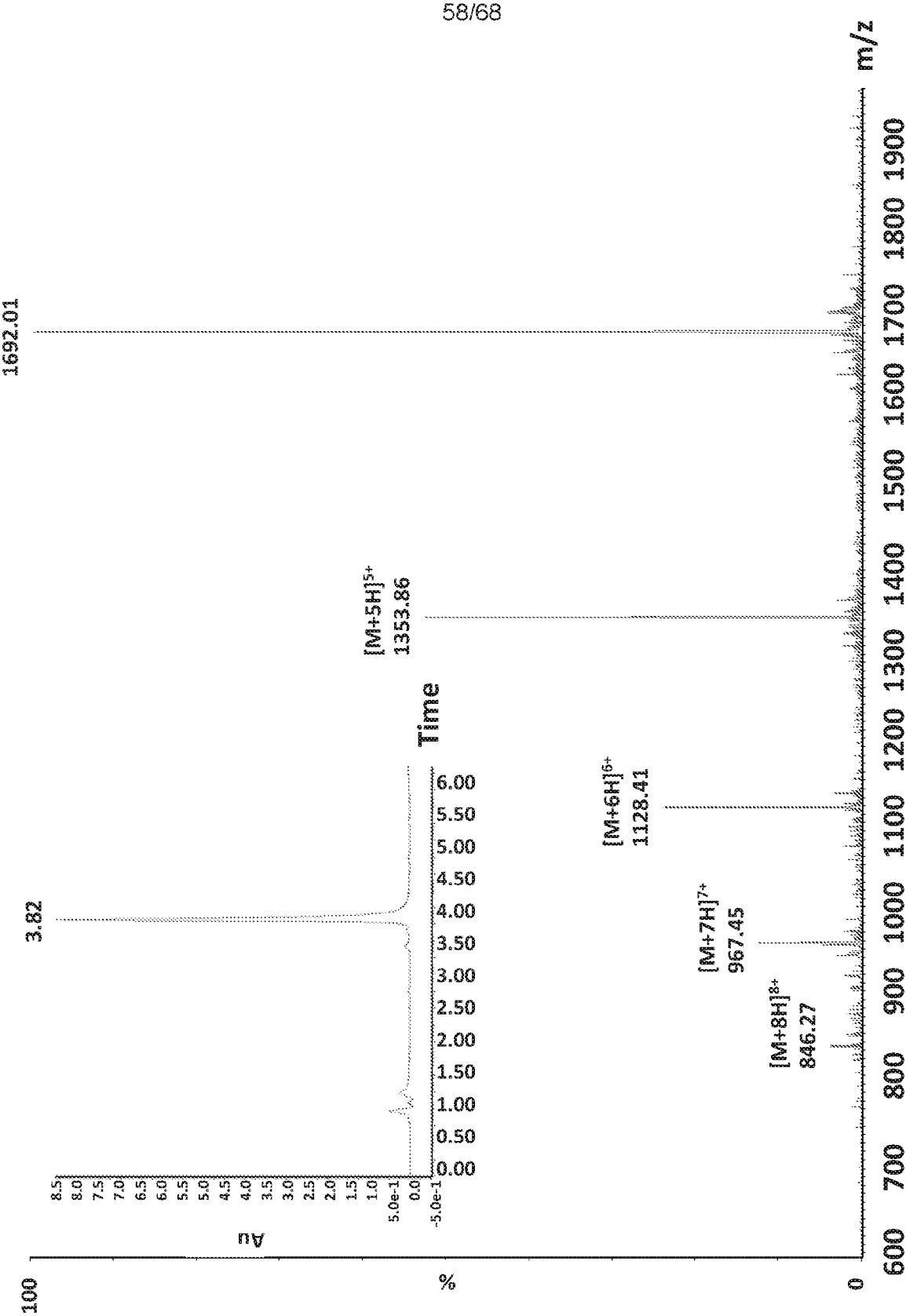

[M+4H]4+
1692.01
[M+5H]5+
1353.86
[M+6H]6+
1128.41
[M+7H]7+
967.45
[M+8H]8+
846.27
3.82
Time
AU
%
m/z
100
0
600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900
6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 0.50 0.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 5.0e-1 0.0 -5.0e-1

Fig. 28B

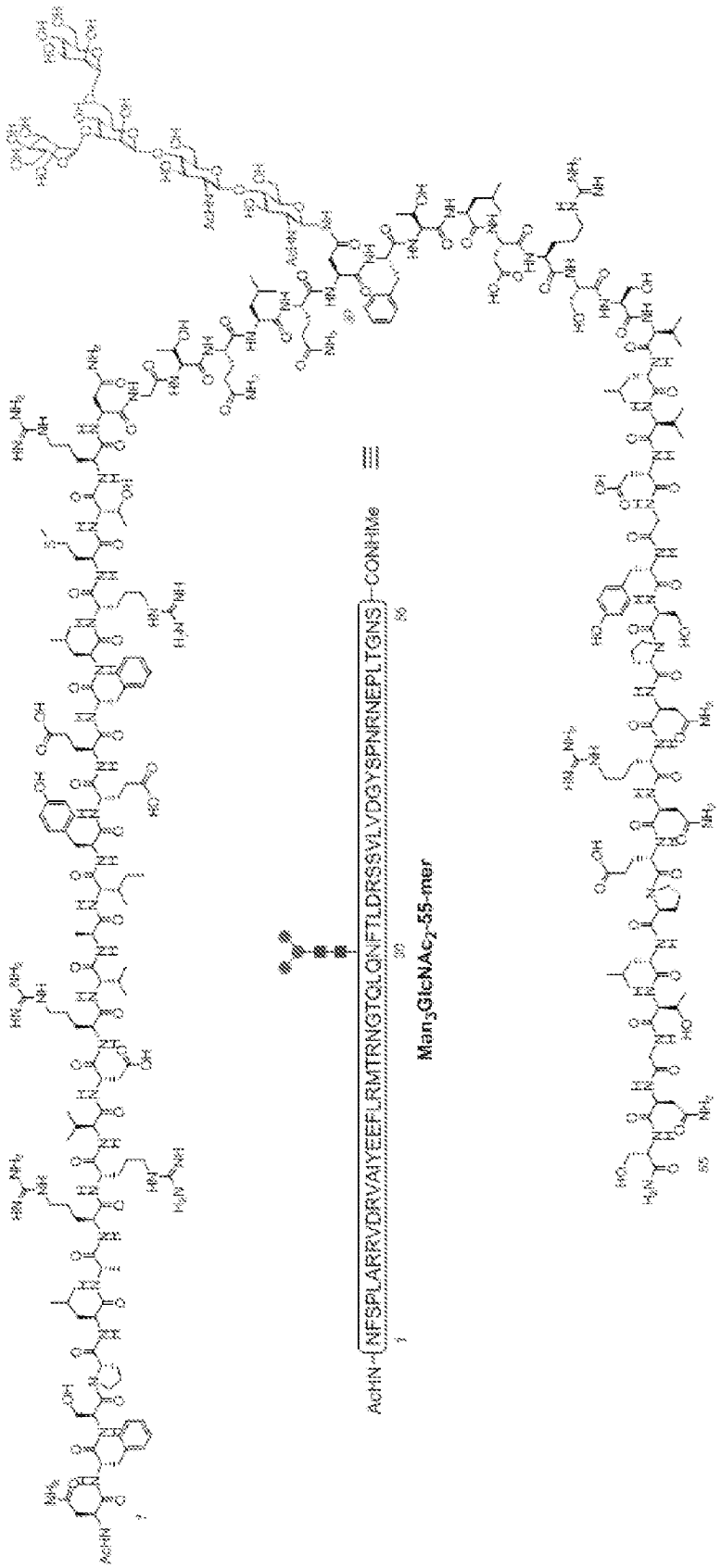

AcHN-{NFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDRSSVLVDGYSPNRNEPLTGNS}-CONHMe
1
99
55
Man3GlcNAc2-55-mer

Fig. 29A

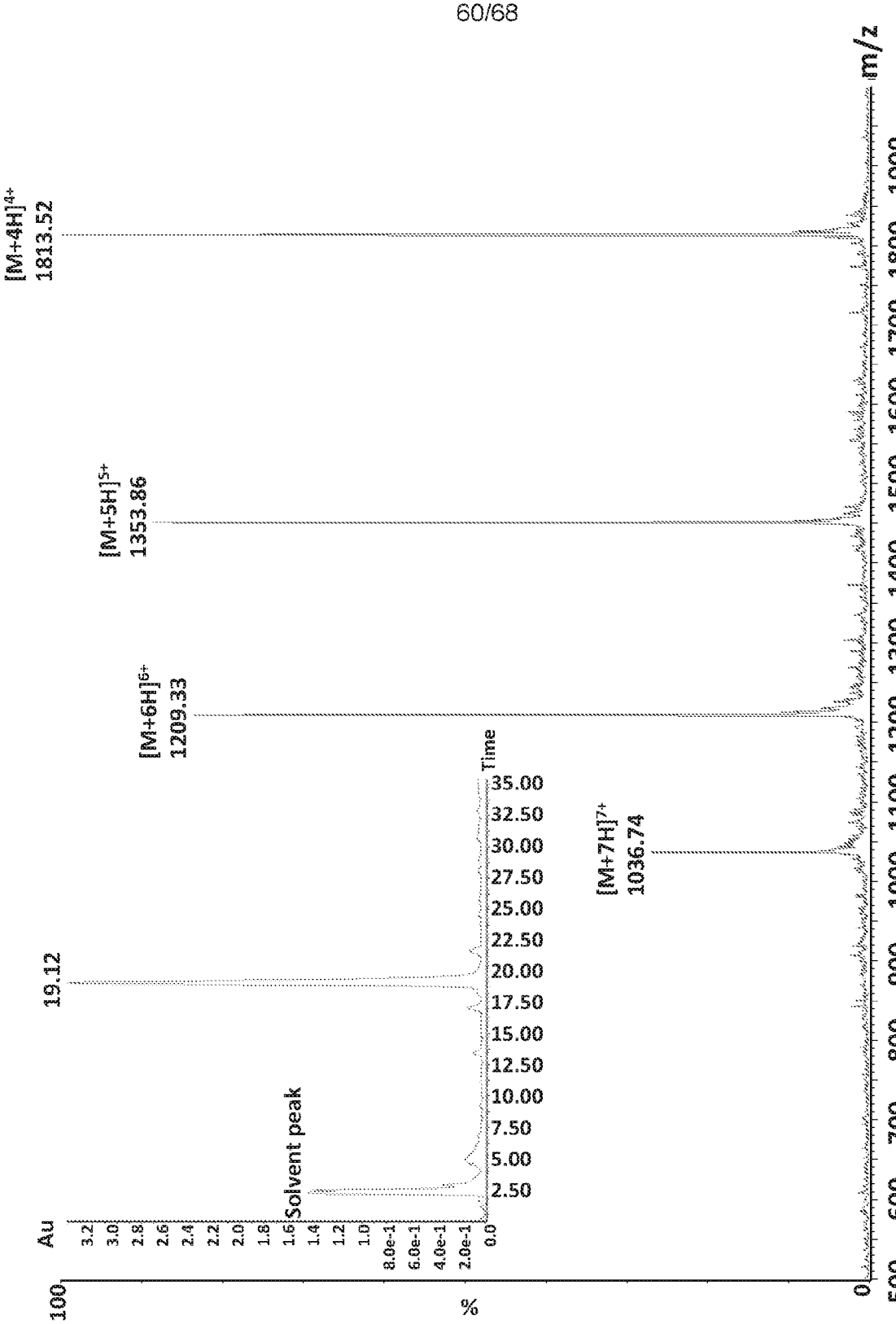

[M+4H]4+
1813.52
[M+5H]5+
1353.86
[M+6H]6+
1209.33
[M+7H]7+
1036.74
19.12
Solvent peak
Au
Time
m/z
%
100
0

Fig. 29B

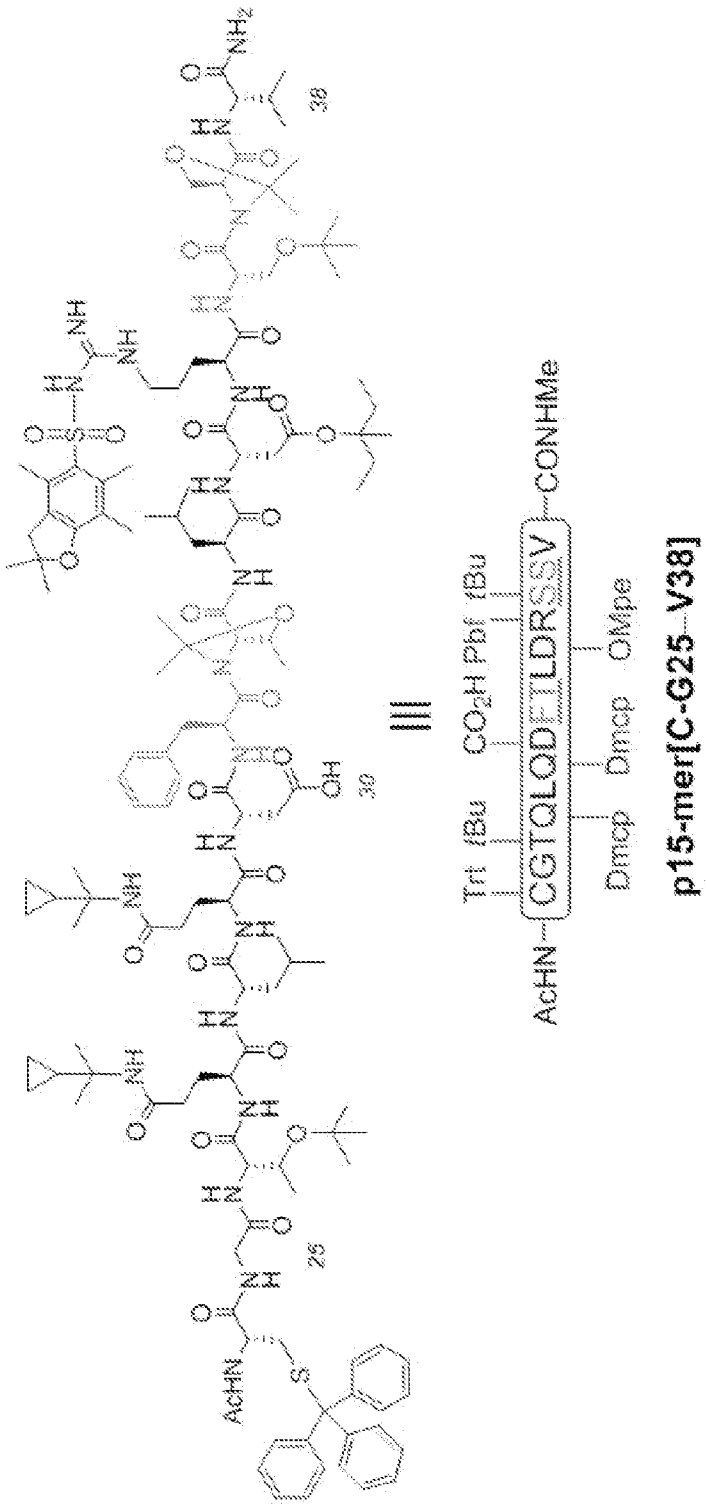

AcHN
Trt tBu CO2H Pbf tBu
CGTQLQDFTLDRSSV
CONHMe
Dmcp Dmcp OMpe
p15-mer[C-G25–V38]

Fig. 30A

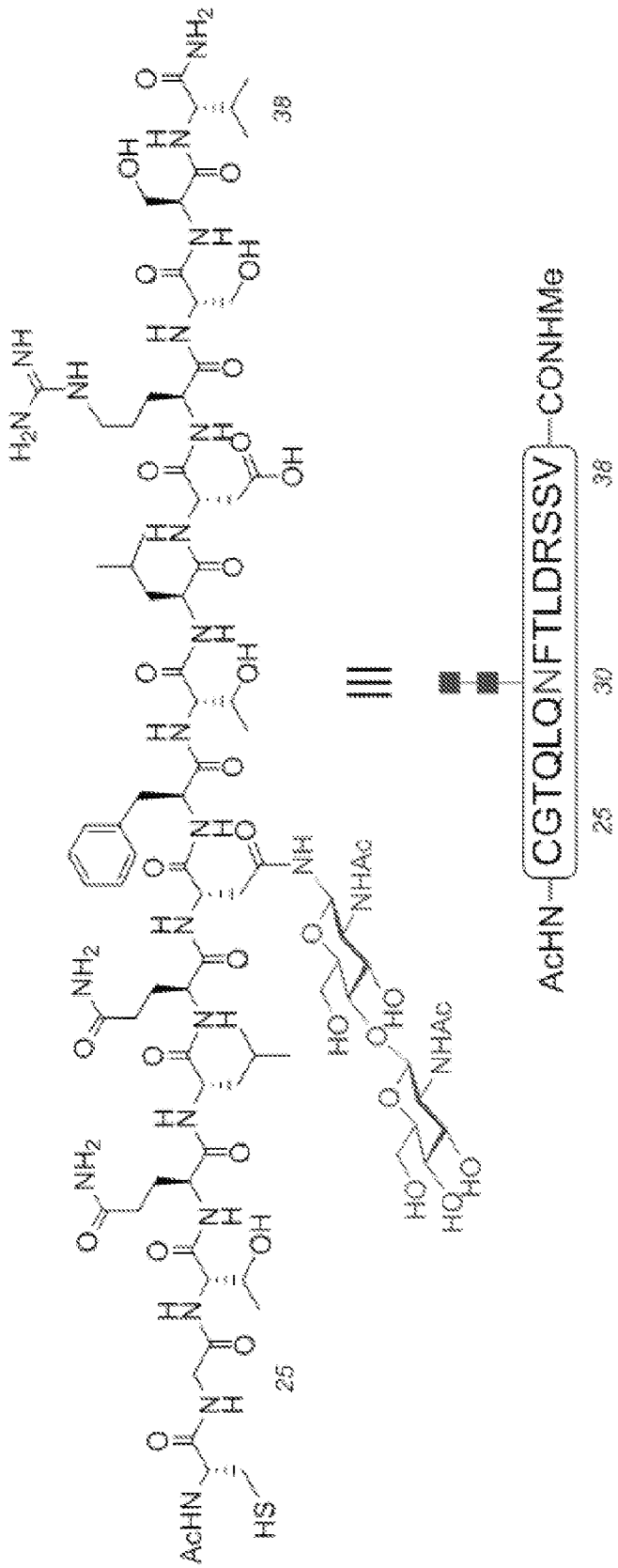


Fig. 30B

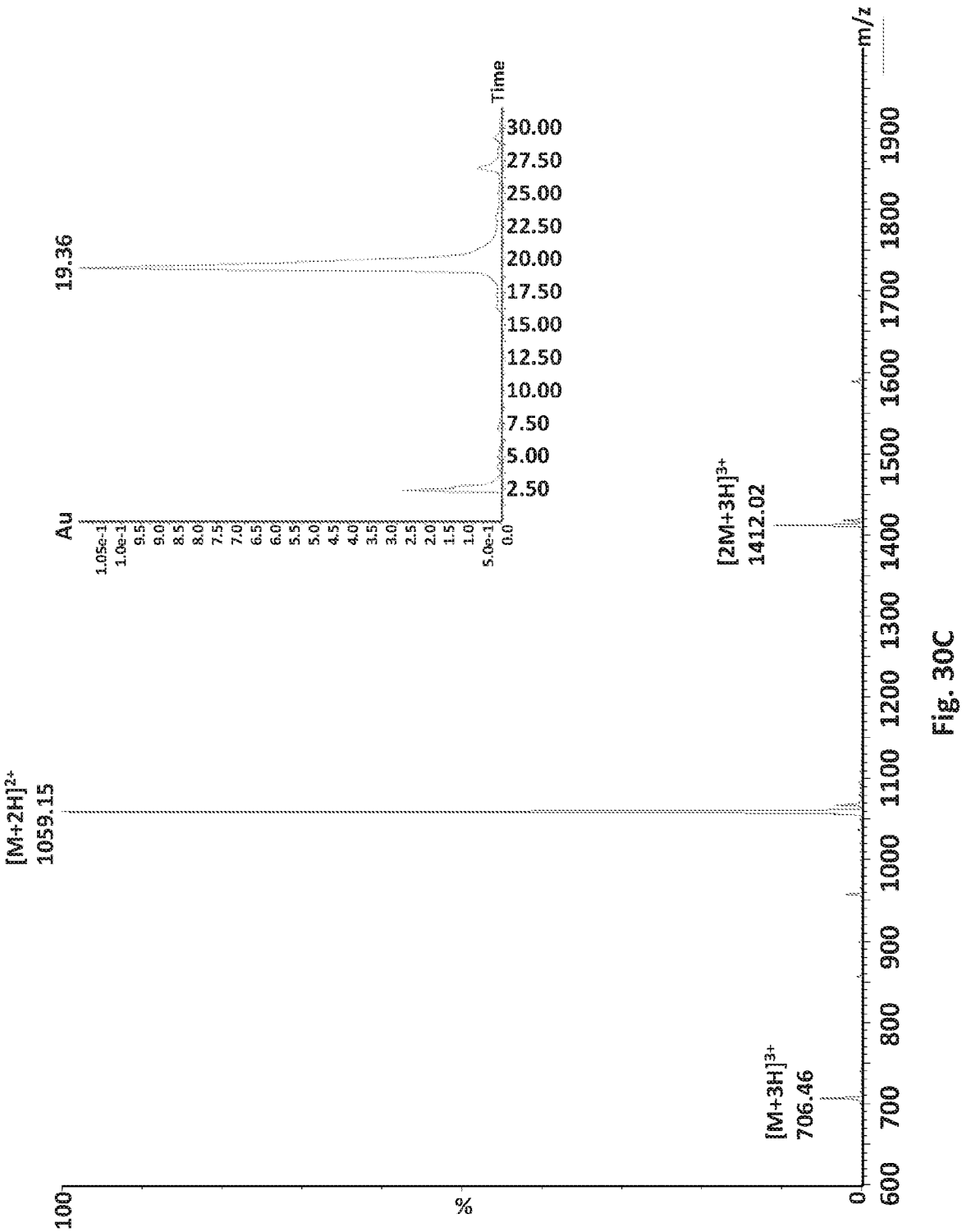

Time
30.00
27.50
25.00
22.50
20.00
17.50
15.00
12.50
10.00
7.50
5.00
2.50
19.36
Au
[M+2H]2+
1059.15
[2M+3H]3+
1412.02
[M+3H]3+
706.46
100
%
0
600 700 800 900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900
m/z

Fig. 30C

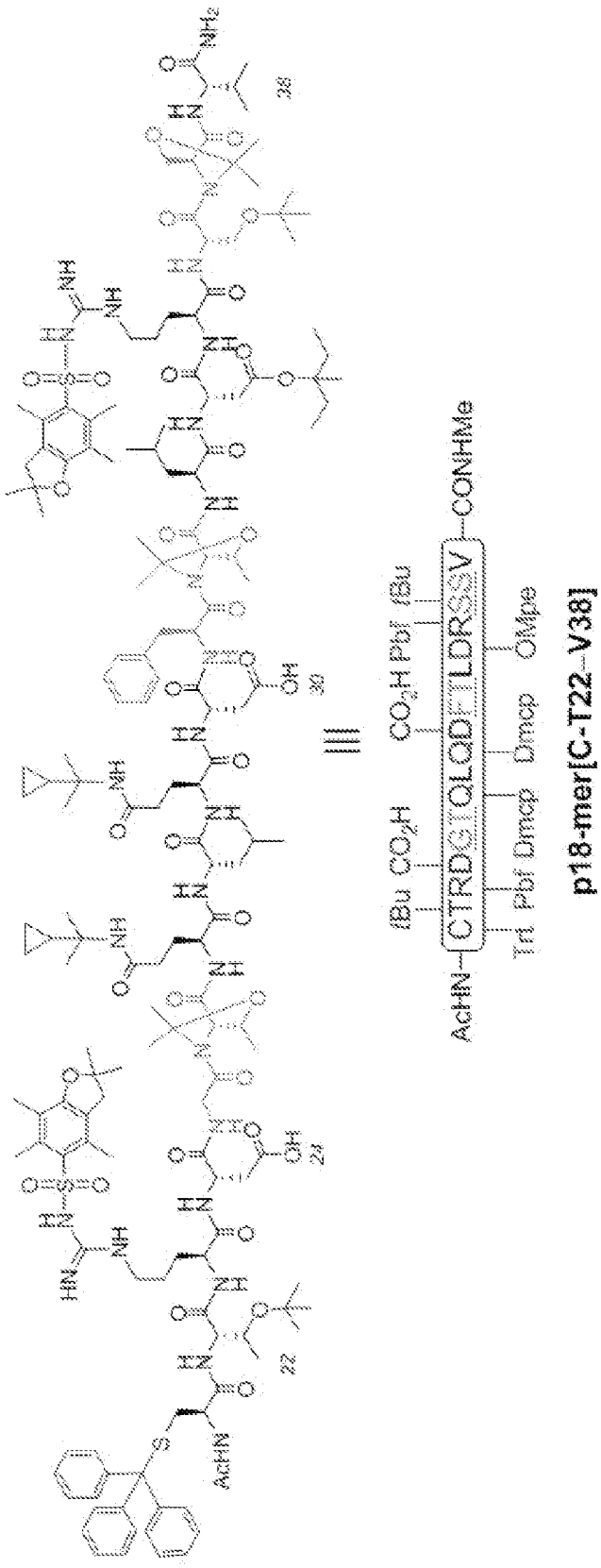

AcHN
CTRDGTQLQDFTLDRSSV
CONHMe
tBu CO2H
CO2H Pbf tBu
Trt Pbf Dmcp
Dmcp OMpe
p18-mer[C-T22–V38]

Fig. 31A

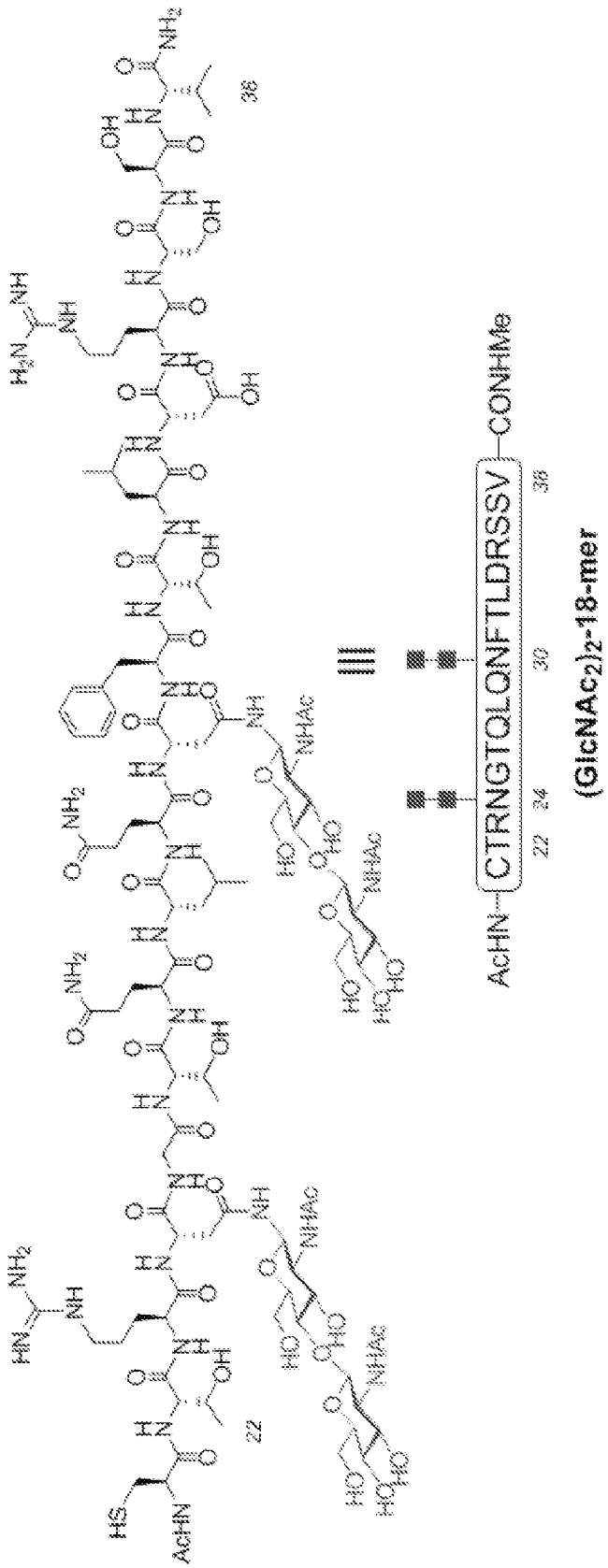


Fig. 31B

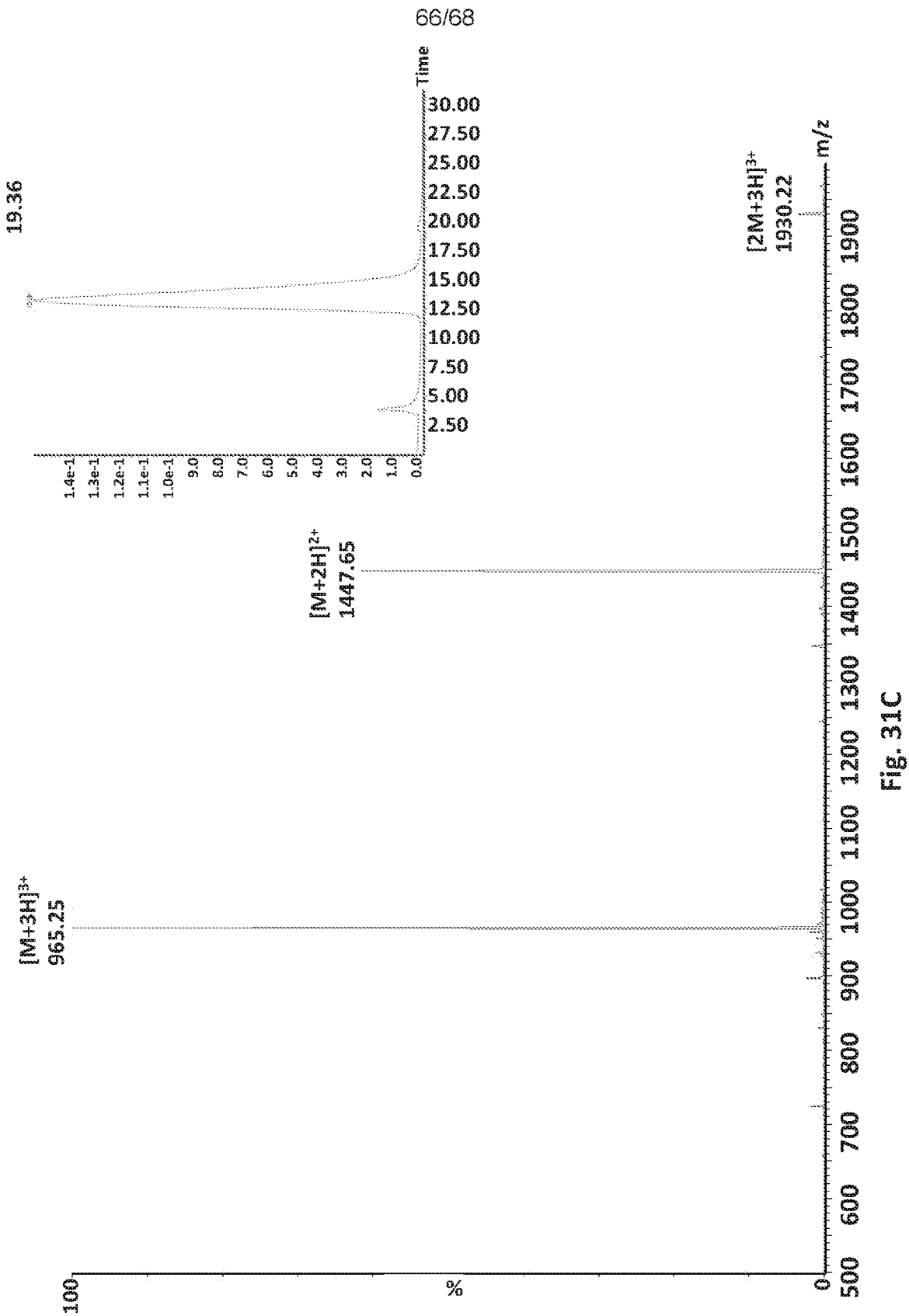

66/68
Time
30.00
27.50
25.00
22.50
20.00
17.50
15.00
12.50
10.00
7.50
5.00
2.50
19.36
1.4e-1
1.3e-1
1.2e-1
1.1e-1
1.0e-1
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
[M+3H]3+
965.25
[M+2H]2+
1447.65
[2M+3H]3+
1930.22
m/z
100
%
0
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900

Fig. 31C

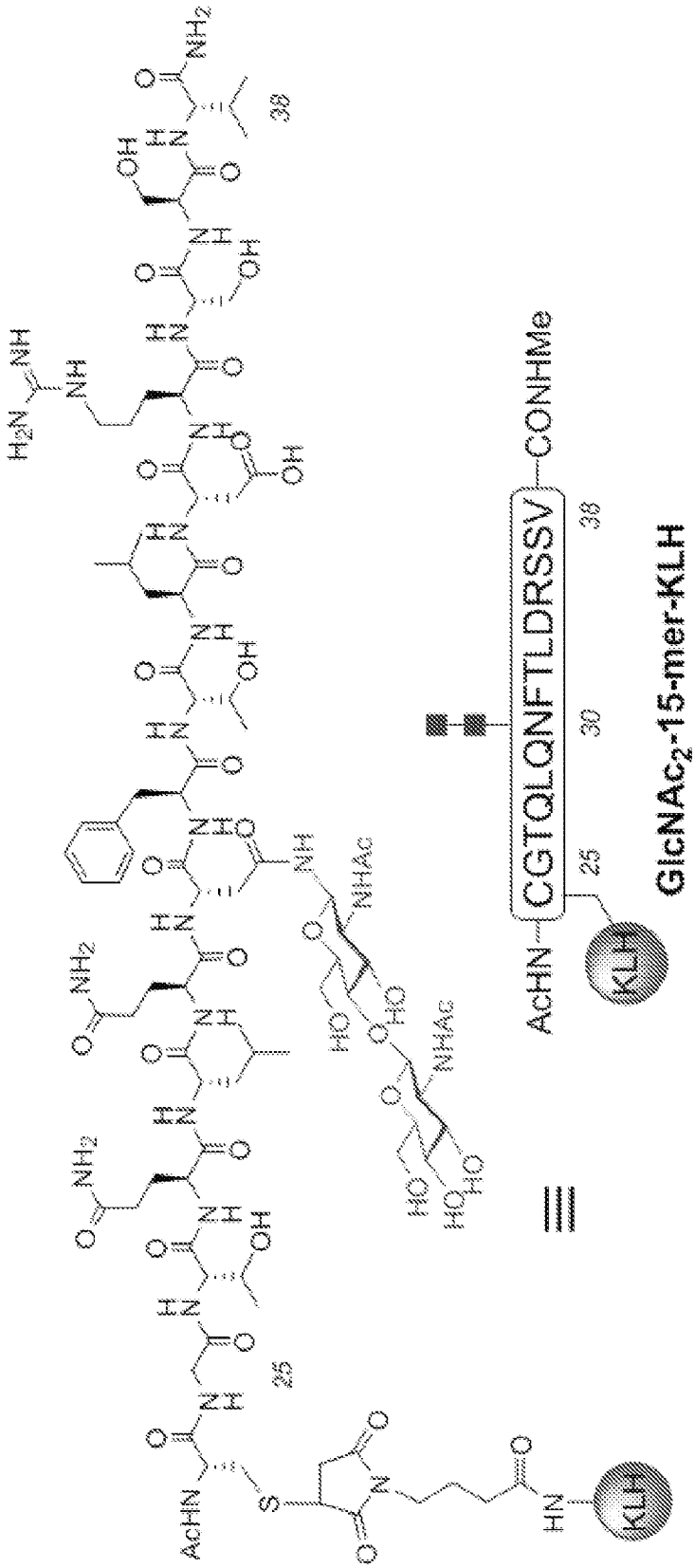


Fig. 32A

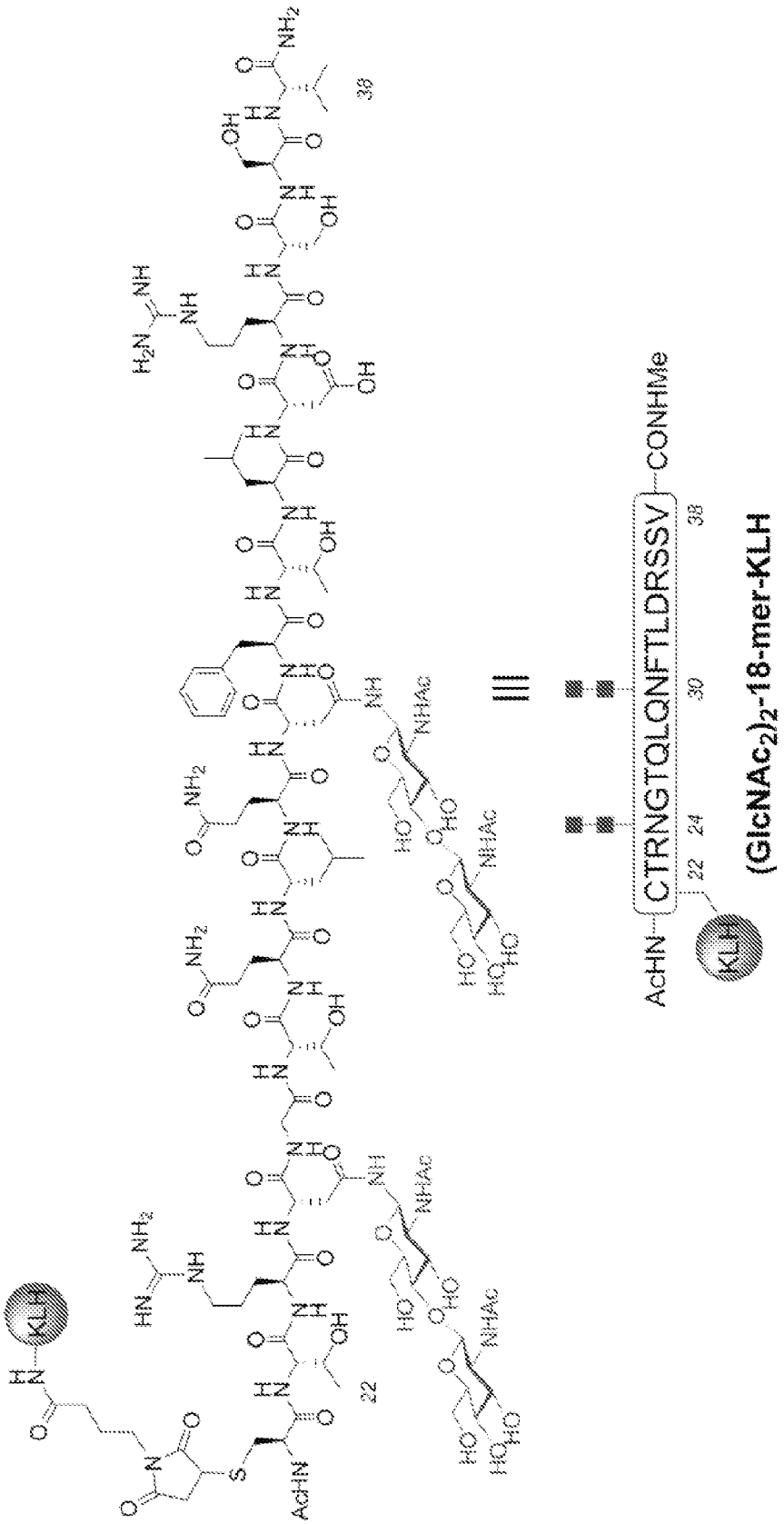

KLH
AcHN
CTRNGTQLQNFTLDRSSV
CONHMe
22
24
30
38
(GlcNAc2)2-18-mer-KLH

Fig. 32B

SEQUENCE LISTING

<110> MEMORIAL SLOAN-KETTERING CANCER CENTER

<120> ANTI-MUC16 ANTIBODIES AND USES THEREOF

<130> 13542-016-228

<150> 62/134,402
<151> 2015-03-17

<160> 175

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
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<400> 1
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1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Asn Thr Leu
20 25 30
Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ala
50 55 60
Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Ser Ser Lys Asn Gln Val
65 70 75 80
Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Ile Ala Thr Tyr Tyr
85 90 95
Cys Ser Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 2
<211> 109
<212> PRT
<213> Artificial Sequence

<220>

<223> 10C6 VL

<400> 2
Asp Ile Val Leu Thr Gln Ser Pro Ala Ser Leu Ala Val Ser Leu Gly
1 5 10 15
Gln Arg Ala Thr Ile Ser Tyr Arg Ala Ser Lys Ser Val Ser Thr Ser
20 25 30
Gly Tyr Ser Tyr Met His Trp Asn Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45
Arg Leu Leu Ile Tyr Leu Val Ser Asn Leu Glu Ser Gly Val Pro Ala
50 55 60
Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Asn Ile His
65 70 75 80
Pro Val Glu Glu Glu Asp Ala Ala Thr Tyr Tyr Cys Gln His Ile Arg
85 90 95
Glu Leu Thr Arg Ser Glu Gly Gly Pro Ser Trp Lys Asn
100 105

<210> 3
<211> 7
<212> PRT
<213> Artificial Sequence

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<400> 3
Thr Leu Gly Met Gly Val Gly
1 5

<210> 4
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 HCDR2 (KABAT)

<400> 4
His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ala Leu Lys Ser
1 5 10 15

<210> 5
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 HCDR3 (KABAT)

<400> 5
Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 6
<211> 15
<212> PRT
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<220>
<223> 10C6 LCDR1 (KABAT)

<400> 6
Arg Ala Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr Met His
1 5 10 15

<210> 7
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 LCDR2 (KABAT)

<400> 7
Leu Val Ser Asn Leu Glu Ser
1 5

<210> 8
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 LCDR3 (KABAT)

<400> 8
Gln His Ile Arg Glu Leu Thr Arg Ser
1 5

<210> 9
<211> 9
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<213> Artificial Sequence

<220>
<223> 10C6 HCDR1 (CHOTHIA)

<400> 9
Gly Phe Ser Leu Asn Thr Leu Gly Met
1 5

<210> 10
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 HCDR2 (CHOTHIA)

<400> 10
Trp Asp Asp
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<210> 11
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 HCDR3 (CHOTHIA)

<400> 11
Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp
1 5 10

<210> 12
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 LCDR1 (CHOTHIA)

<400> 12
Ser Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr
1 5 10

<210> 13

<211> 3
<212> PRT
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<220>
<223> 10C6 LCDR2 (CHOTHIA)

<400> 13
Leu Val Ser
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<210> 14
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 LCDR3 (CHOTHIA)

<400> 14
Ile Arg Glu Leu Thr Arg
1 5

<210> 15
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 HCDR1 (IMGT)

<400> 15
Gly Phe Ser Leu Asn Thr Leu Gly Met Gly
1 5 10

<210> 16
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 HCDR2 (IMGT)

<400> 16
Ile Trp Trp Asp Asp Asp Lys
1 5

<210> 17
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 HCDR3 (IMGT)

<400> 17
Ser Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 18
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 LCDR1 (IMGT)

<400> 18
Lys Ser Val Ser Thr Ser Gly Tyr Ser Tyr
1 5 10

<210> 19
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 LCDR2 (IMGT)

<400> 19
Leu Val Ser
1

<210> 20
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6 LCDR3 (IMGT)

<400> 20
Gln His Ile Arg Glu Leu Thr Arg Ser

1 5

<210> 21
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 VH

<400> 21
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Val
20 25 30
Gly Met Gly Val Gly Trp Ser Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Trp Trp Asp Asp Glu Asp Lys Tyr Tyr Asn Pro
50 55 60
Ala Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln
65 70 75 80
Val Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Ser Ala Thr Tyr
85 90 95
Tyr Cys Thr Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
100 105 110
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 22
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 VL

<400> 22
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Val Ser Val Thr Pro Gly
1 5 10 15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Arg Lys Ser
20 25 30
Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45
Pro Gln Arg Leu Ile Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu Arg Ile
65 70 75 80
Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ser

85 90 95
Leu Glu Tyr Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Lys Ile Lys
100 105 110

<210> 23
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR1 (KABAT)

<400> 23
Thr Val Gly Met Gly Val Gly
1 5

<210> 24
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR2 (KABAT)

<400> 24
His Ile Trp Trp Asp Asp Glu Asp Lys Tyr Tyr Asn Pro Ala Leu Lys
1 5 10 15
Ser

<210> 25
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR3 (KABAT)

<400> 25
Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 26
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR1 (KABAT)

<400> 26
Arg Ser Ser Lys Ser Leu Arg Lys Ser Asn Gly Asn Thr Tyr Leu Tyr
1 5 10 15

<210> 27
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR2 (KABAT)

<400> 27
Tyr Met Ser Asn Leu Ala Ser
1 5

<210> 28
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR3 (KABAT)

<400> 28
Met Gln Ser Leu Glu Tyr Pro Leu Thr
1 5

<210> 29
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR1 (CHOTHIA)

<400> 29
Gly Phe Ser Leu Ser Thr Val Gly Met
1 5

<210> 30
<211> 4

<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR2 (CHOTHIA)

<400> 30
Trp Asp Asp Glu
1

<210> 31
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR3 (CHOTHIA)

<400> 31
Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp
1 5 10

<210> 32
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR1 (CHOTHIA)

<400> 32
Ser Lys Ser Leu Arg Lys Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 33
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR2 (CHOTHIA)

<400> 33
Tyr Met Ser
1

<210> 34
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR3 (CHOTHIA)

<400> 34
Ser Leu Glu Tyr Pro Leu
1 5

<210> 35
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR1 (IMGT)

<400> 35
Gly Phe Ser Leu Ser Thr Val Gly Met Gly
1 5 10

<210> 36
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR2 (IMGT)

<400> 36
Ile Trp Trp Asp Asp Glu Asp Lys
1 5

<210> 37
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 HCDR3 (IMGT)

<400> 37
Thr Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr

1 5 10

<210> 38
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR1 (IMGT)

<400> 38
Lys Ser Leu Arg Lys Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 39
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR2 (IMGT)

<400> 39
Tyr Met Ser
1

<210> 40
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12 LCDR3 (IMGT)

<400> 40
Met Gln Ser Leu Glu Tyr Pro Leu Thr
1 5

<210> 41
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 VH

<400> 41
Gln Val Asn Leu Lys Glu Ser Gly Pro Gly Lys Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Leu
20 25 30
Gly Met Gly Val Gly Trp Ile Arg Gln Ser Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ala
50 55 60
Leu Lys Ser Arg Leu Thr Ile Ser Arg Ala Thr Ser Lys Asn Gln Val
65 70 75 80
Phe Leu Lys Ile Val Asn Val Gly Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Ala Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr Trp
100 105 110
Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 42
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 VL

<400> 42
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Ile Pro Val Thr Pro Gly
1 5 10 15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Leu His Ser
20 25 30
Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45
Pro Gln Arg Leu Ile Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80
Ser Arg Val Glu Ala Gly Asp Val Gly Val Tyr Tyr Cys Met Gln Gly
85 90 95
Leu Glu His Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 43
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> 19C11 HCDR1 (KABAT)

<400> 43
Thr Leu Gly Met Gly Val Gly
1 5

<210> 44
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 HCDR2 (KABAT)

<400> 44
His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Asn Pro Ala Leu Lys Ser
1 5 10 15

<210> 45
<211> 12
<212> PRT
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<220>
<223> 19C11 HCDR3 (KABAT)

<400> 45
Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 46
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 LCDR1 (KABAT)

<400> 46
Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr
1 5 10 15

<210> 47
<211> 7
<212> PRT
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<400> 47
Tyr Met Ser Asn Leu Ala Ser
1 5

<210> 48
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 LCDR3 (KABAT)

<400> 48
Met Gln Gly Leu Glu His Pro Leu Thr
1 5

<210> 49
<211> 9
<212> PRT
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<220>
<223> 19C11 HCDR1 (CHOTHIA)

<400> 49
Gly Phe Ser Leu Ser Thr Leu Gly Met
1 5

<210> 50
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 HCDR2 (CHOTHIA)

<400> 50
Trp Asp Asp
1

<210> 51
<211> 10

<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 HCDR3 (CHOTHIA)

<400> 51
Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp
1 5 10

<210> 52
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 LCDR1 (CHOTHIA)

<400> 52
Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 53
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 LCDR2 (CHOTHIA)

<400> 53
Tyr Met Ser
1

<210> 54
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 LCDR3 (CHOTHIA)

<400> 54
Gly Leu Glu His Pro Leu
1 5

<210> 55
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 HCDR1 (IMGT)

<400> 55
Gly Phe Ser Leu Ser Thr Leu Gly Met Gly
1 5 10

<210> 56
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 HCDR2 (IMGT)

<400> 56
Ile Trp Trp Asp Asp Asp Lys
1 5

<210> 57
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 HCDR3 (IMGT)

<400> 57
Ala Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 58
<211> 11
<212> PRT
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<220>
<223> 19C11 LCDR1 (IMGT)

<400> 58
Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 59
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 19C11 LCDR2 (IMGT)

<400> 59
Tyr Met Ser
1

<210> 60
<211> 9
<212> PRT
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<220>
<223> 19C11 LCDR3 (IMGT)

<400> 60
Met Gln Gly Leu Glu His Pro Leu Thr
1 5

<210> 61
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 VH

<400> 61
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Asn Thr Leu
20 25 30
Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Tyr Pro Ala
50 55 60
Leu Lys Ser Arg Leu Thr Ile Ser Arg Asp Thr Ser Lys Asn Gln Val
65 70 75 80
Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Ala Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr Trp

100 105 110
Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 62
<211> 109
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 VL

<400> 62
Glu Leu Asp Met Thr Gln Thr Pro Pro Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Glu Thr Val Arg Ile Arg Cys Leu Ala Ser Glu Asp Ile Tyr Ser Gly
20 25 30
Ile Ser Trp Tyr Gln Gln Lys Pro Gly Lys Pro Pro Thr Leu Leu Ile
35 40 45
Tyr Gly Ala Ser Asn Leu Glu Ser Gly Val Pro Pro Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Gly Gly Val Gln Ala
65 70 75 80
Glu Asp Ala Ala Thr Tyr Tyr Cys Leu Gly Gly Tyr Ser Tyr Ser Ser
85 90 95
Thr Leu Thr Phe Gly Ala Gly Thr Asn Val Glu Ile Lys
100 105

<210> 63
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR1 (KABAT)

<400> 63
Thr Leu Gly Met Gly Val Gly
1 5

<210> 64
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR2 (KABAT)

<400> 64
His Ile Trp Trp Asp Asp Asp Lys Tyr Tyr Tyr Pro Ala Leu Lys Ser
1 5 10 15

<210> 65
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR3 (KABAT)

<400> 65
Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 66
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR1 (KABAT)

<400> 66
Leu Ala Ser Glu Asp Ile Tyr Ser Gly Ile Ser
1 5 10

<210> 67
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR2 (KABAT)

<400> 67
Gly Ala Ser Asn Leu Glu Ser
1 5

<210> 68
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR3 (KABAT)

<400> 68
Leu Gly Gly Tyr Ser Tyr Ser Ser Thr Leu Thr
1 5 10

<210> 69
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR1 (CHOTHIA)

<400> 69
Gly Phe Ser Leu Asn Thr Leu Gly Met
1 5

<210> 70
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR2 (CHOTHIA)

<400> 70
Trp Asp Asp
1

<210> 71
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 71
Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp
1 5 10

<210> 72
<211> 7
<212> PRT

<213> Artificial Sequence

<220>
<223> 16C5 LCDR1 (CHOTHIA)

<400> 72
Ser Glu Asp Ile Tyr Ser Gly
1 5

<210> 73
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR2 (CHOTHIA)

<400> 73
Gly Ala Ser
1

<210> 74
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR3 (CHOTHIA)

<400> 74
Gly Tyr Ser Tyr Ser Ser Thr Leu
1 5

<210> 75
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR1 (IMGT)

<400> 75
Gly Phe Ser Leu Asn Thr Leu Gly Met Gly
1 5 10

<210> 76

<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR2 (IMGT)

<400> 76
Ile Trp Trp Asp Asp Asp Lys
1 5

<210> 77
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 HCDR3 (IMGT)

<400> 77
Ala Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 78
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR1 (IMGT)

<400> 78
Glu Asp Ile Tyr Ser Gly
1 5

<210> 79
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR2 (IMGT)

<400> 79
Gly Ala Ser
1

<210> 80
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 16C5 LCDR3 (IMGT)

<400> 80
Leu Gly Gly Tyr Ser Tyr Ser Ser Thr Leu Thr
1 5 10

<210> 81
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 VH

<400> 81
Gln Val Thr Leu Lys Glu Ser Gly Pro Gly Ile Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Val
20 25 30
Gly Met Gly Val Gly Trp Ser Arg Gln Pro Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Trp Trp Asp Asp Glu Asp Lys Tyr Tyr Asn Pro
50 55 60
Ala Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln
65 70 75 80
Val Phe Leu Lys Ile Ala Asn Val Asp Thr Ala Asp Thr Ala Thr Tyr
85 90 95
Tyr Cys Thr Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
100 105 110
Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 82
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 VL

<400> 82

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

<210> 83
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR1 (KABAT)

<400> 83
Thr Val Gly Met Gly Val Gly
1 5

<210> 84
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR2 (KABAT)

<400> 84
His Ile Trp Trp Asp Asp Glu Asp Lys Tyr Tyr Asn Pro Ala Leu Lys
1 5 10 15
Ser

<210> 85
<211> 12
<212> PRT
<213> Artificial Sequence

<220>

<223> 18C6 HCDR3 (KABAT)

<400> 85
Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 86
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR1 (KABAT)

<400> 86
Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr
1 5 10 15

<210> 87
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR2 (KABAT)

<400> 87
Tyr Met Ser Asn Leu Ala Ser
1 5

<210> 88
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR3 (KABAT)

<400> 88
Met Gln Ser Leu Glu Tyr Pro Leu Thr
1 5

<210> 89
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR1 (CHOTHIA)

<400> 89
Gly Phe Ser Leu Ser Thr Val Gly Met
1 5

<210> 90
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR2 (CHOTHIA)

<400> 90
Trp Asp Asp Glu
1

<210> 91
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR3 (CHOTHIA)

<400> 91
Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp
1 5 10

<210> 92
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR1 (CHOTHIA)

<400> 92
Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 93
<211> 3

<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR2 (CHOTHIA)

<400> 93
Tyr Met Ser
1

<210> 94
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR3 (CHOTHIA)

<400> 94
Ser Leu Glu Tyr Pro Leu
1 5

<210> 95
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR1 (IMGT)

<400> 95
Gly Phe Ser Leu Ser Thr Val Gly Met Gly
1 5 10

<210> 96
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR2 (IMGT)

<400> 96
Ile Trp Trp Asp Asp Glu Asp Lys
1 5

<210> 97
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 HCDR3 (IMGT)

<400> 97
Thr Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 98
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR1 (IMGT)

<400> 98
Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 99
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR2 (IMGT)

<400> 99
Tyr Met Ser
1

<210> 100
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 18C6 LCDR3 (IMGT)

<400> 100
Met Gln Ser Leu Glu Tyr Pro Leu Thr
1 5

<210> 101
<211> 123
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6-18C6 VH consensus

<220>
<221> VARIANT
<222> 3
<223> Xaa = Thr or Asn

<220>
<221> VARIANT
<222> 11
<223> Xaa = Ile or Lys

<220>
<221> VARIANT
<222> 30
<223> Xaa = Asn or Ser

<220>
<221> VARIANT
<222> 32
<223> Xaa = Val or Leu

<220>
<221> VARIANT
<222> 39
<223> Xaa = Ser or Ile

<220>
<221> VARIANT
<222> 42
<223> Xaa = Pro or Ser

<220>
<221> VARIANT
<222> 58
<223> Xaa = Glu or absent

<220>
<221> VARIANT
<222> 63
<223> Xaa = Asn or Tyr

<220>
<221> VARIANT
<222> 74
<223> Xaa = Lys or Arg

<220>
<221> VARIANT
<222> 75
<223> Xaa = Ala or Asp

<220>
<221> VARIANT
<222> 76
<223> Xaa = Thr or Ser

<220>
<221> VARIANT
<222> 86
<223> Xaa = Val or Ala

<220>
<221> VARIANT
<222> 89
<223> Xaa = Gly or Asp

<220>
<221> VARIANT
<222> 93
<223> Xaa = Thr, Ile or Ser

<220>
<221> VARIANT
<222> 99
<223> Xaa = Thr, Ser or Ala

<400> 101
Gln Val Xaa Leu Lys Glu Ser Gly Pro Gly Xaa Leu Gln Pro Ser Gln
1 5 10 15
Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Xaa Thr Xaa
20 25 30
Gly Met Gly Val Gly Trp Xaa Arg Gln Xaa Ser Gly Lys Gly Leu Glu
35 40 45
Trp Leu Ala His Ile Trp Trp Asp Asp Xaa Asp Lys Tyr Tyr Xaa Pro
50 55 60
Ala Leu Lys Ser Arg Leu Thr Ile Ser Xaa Xaa Xaa Ser Lys Asn Gln
65 70 75 80
Val Phe Leu Lys Ile Xaa Asn Val Xaa Thr Ala Asp Xaa Ala Thr Tyr
85 90 95
Tyr Cys Xaa Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
115 120

<210> 102
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 VL consensus

<220>
<221> VARIANT
<222> 11
<223> Xaa = Ile or Val

<220>
<221> VARIANT
<222> 12
<223> Xaa = Pro or Ser

<220>
<221> VARIANT
<222> 30
<223> Xaa = Arg or Leu

<220>
<221> VARIANT
<222> 31
<223> Xaa = Lys or His

<220>
<221> VARIANT
<222> 79
<223> Xaa = Arg or Lys

<220>
<221> VARIANT
<222> 86
<223> Xaa = Glu or Gly

<220>
<221> VARIANT
<222> 96
<223> Xaa = Ser or Gly

<220>
<221> VARIANT
<222> 99

<223> Xaa = Tyr or His

<400> 102
Asp Ile Val Met Thr Gln Ala Ala Pro Ser Xaa Xaa Val Thr Pro Gly
1 5 10 15
Glu Ser Val Ser Ile Ser Cys Arg Ser Ser Lys Ser Leu Xaa Xaa Ser
20 25 30
Asn Gly Asn Thr Tyr Leu Tyr Trp Phe Leu Gln Arg Pro Gly Gln Ser
35 40 45
Pro Gln Arg Leu Ile Tyr Tyr Met Ser Asn Leu Ala Ser Gly Val Pro
50 55 60
Asp Arg Phe Ser Gly Arg Gly Ser Gly Thr Asp Phe Thr Leu Xaa Ile
65 70 75 80
Ser Arg Val Glu Ala Xaa Asp Val Gly Val Tyr Tyr Cys Met Gln Xaa
85 90 95
Leu Glu Xaa Pro Leu Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 103
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> HCDR1 KABAT CONSENSUS

<220>
<221> VARIANT
<222> 2
<223> Xaa = Lue or Val

<400> 103
Thr Xaa Gly Met Gly Val Gly
1 5

<210> 104
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> HCDR2 KABAT CONSENSUS

<220>
<221> VARIANT
<222> 7
<223> Xaa = Glu or Absent

<220>
<221> VARIANT
<222> 12
<223> Xaa = Tyr or Asn

<400> 104
His Ile Trp Trp Asp Asp Xaa Asp Lys Tyr Tyr Xaa Pro Ala Leu Lys
 1 5 10 15
Ser

<210> 105
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> HCDR3 KABAT CONSENSUS

<400> 105
Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
 1 5 10

<210> 106
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR2 KABAT CONSENSUS

<220>
<221> VARIANT
<222> 7
<223> Xaa = Arg or Leu

<220>
<221> VARIANT
<222> 8
<223> Xaa = Lys or His

<400> 106
Arg Ser Ser Lys Ser Leu Xaa Xaa Ser Asn Gly Asn Thr Tyr Leu Tyr
 1 5 10 15

<210> 107
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR2 KABAT CONSENSUS

<400> 107
Tyr Met Ser Asn Leu Ala Ser
1 5

<210> 108
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR3 KABAT CONSENSUS

<220>
<221> VARIANT
<222> 3
<223> Xaa = Gly or Ser

<220>
<221> VARIANT
<222> 6
<223> Xaa = His or Tyr

<400> 108
Met Gln Xaa Leu Glu Xaa Pro Leu Thr
1 5

<210> 109
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6-18C6 HCDR1 CHOTHIA CONSENSUS

<220>
<221> VARIANT
<222> 5
<223> Xaa = Asn or Ser

<220>
<221> VARIANT
<222> 7

<223> Xaa = Leu or Val

<400> 109
Gly Phe Ser Leu Xaa Thr Xaa Gly Met
1 5

<210> 110
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6-18C6 HCDR2 CHOTHIA CONSENSUS

<220>
<221> VARIANT
<222> 4
<223> Xaa = Glu or Absent

<400> 110
Trp Asp Asp Xaa
1

<210> 111
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6-18C6 HCDR3 CHOTHIA CONSENSUS

<400> 111
Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp
1 5 10

<210> 112
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR1 CHOTHIA CONSENSUS

<220>
<221> VARIANT
<222> 5
<223> Xaa = Leu or Arg

<220>
<221> VARIANT
<222> 6
<223> Xaa = His or Lys

<400> 112
Ser Lys Ser Leu Xaa Xaa Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 113
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR2 CHOTHIA CONSENSUS

<400> 113
Tyr Met Ser
1

<210> 114
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR3 CHOTHIA CONSENSUS

<220>
<221> VARIANT
<222> 1
<223> Xaa = Gly or Ser

<220>
<221> VARIANT
<222> 4
<223> Xaa = His or Tyr

<400> 114
Xaa Leu Glu Xaa Pro Leu
1 5

<210> 115
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> 10C6-18C6 HCDR1 IMGT CONSENSUS

<220>
<221> VARIANT
<222> 5
<223> Xaa = Asn or Ser

<220>
<221> VARIANT
<222> 7
<223> Xaa = Val or Leu

<400> 115
Gly Phe Ser Leu Xaa Thr Xaa Gly Met Gly
1 5 10

<210> 116
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6-18C6 HCDR2 IMGT CONSENSUS

<220>
<221> VARIANT
<222> 6
<223> Xaa = Glu or Absent

<400> 116
Ile Trp Trp Asp Asp Xaa Asp Lys
1 5

<210> 117
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 10C6-18C6 HCDR3 IMGT CONSENSUS

<220>
<221> VARIANT
<222> 1
<223> Xaa = Thr, Ala or Ser

<400> 117
Xaa Arg Ile Gly Thr Ala Gln Ala Thr Asp Ala Leu Asp Tyr
1 5 10

<210> 118
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR1 IMGT CONSENSUS

<220>
<221> VARIANT
<222> 4
<223> Xaa = Val or Leu

<220>
<221> VARIANT
<222> 5
<223> Xaa = His or Lys

<400> 118
Lys Ser Leu Xaa Xaa Ser Asn Gly Asn Thr Tyr
1 5 10

<210> 119
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR2 IMGT CONSENSUS

<400> 119
Tyr Met Ser
1

<210> 120
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> 7B12, 19C11, 18C6 LCDR3 IMGT CONSENSUS

<400> 120
Met Gln Ser Leu Glu Tyr Pro Leu Thr
1 5

<210> 121
<211> 42
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114 F primer

<400> 121
Cys Cys Ala Thr Gly Cys Gly Ala Thr Ala Thr Cys Gly Cys Cys Ala
1 5 10 15
Cys Cys Ala Thr Gly Gly Thr Gly Ala Ala Cys Thr Thr Cys Thr Cys
20 25 30
Gly Cys Cys Ala Cys Thr Gly Gly Cys Thr
35 40

<210> 122
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114 R primer

<400> 122
Thr Ala Cys Gly Gly Cys Gly Gly Cys Cys Gly Cys Thr Thr Gly Cys
1 5 10 15
Ala Gly Ala Thr Cys Cys Thr Cys Cys Ala Gly Gly Thr Cys Thr Ala
20 25 30
Gly Gly

<210> 123
<211> 45
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c344 F primer

<400> 123
Cys Cys Ala Thr Gly Cys Gly Ala Thr Ala Thr Cys Gly Cys Cys Ala
1 5 10 15

Cys Cys Ala Thr Gly Gly Thr Gly Ala Cys Ala Gly Gly Cys Cys Cys
20 25 30
Thr Gly Gly Gly Cys Thr Gly Gly Ala Cys Ala Gly Ala
35 40 45

<210> 124
<211> 34
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c344 R primer

<400> 124
Thr Ala Cys Gly Gly Cys Gly Gly Cys Cys Gly Cys Thr Thr Gly Cys
1 5 10 15
Ala Gly Ala Thr Cys Cys Thr Cys Cys Ala Gly Gly Thr Cys Thr Ala
20 25 30
Gly Gly

<210> 125
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c57-114 F primer

<400> 125
Cys Cys Ala Thr Gly Cys Gly Ala Thr Ala Thr Cys Ala Ala Ala Cys
1 5 10 15
Thr Thr Cys Thr Cys Gly Cys Cys Ala Cys Thr Gly Gly Cys Thr
20 25 30

<210> 126
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c57-114 R primer

<400> 126
Ala Gly Ala Thr Cys Thr Ala Ala Cys Cys Ala Thr Gly Gly Gly Ala
1 5 10 15
Ala Gly Gly Thr Cys Ala Gly Ala Ala Thr Thr Cys Cys Cys Ala Gly

20 25 30
Thr

<210> 127
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> 117-244LGALS3 F primer

<400> 127
Cys Cys Ala Thr Gly Cys Gly Ala Thr Ala Thr Cys Ala Cys Cys Thr
1 5 10 15
Thr Ala Thr Ala Ala Cys Cys Thr Gly Cys Cys Thr Thr Thr Gly
20 25 30

<210> 128
<211> 30
<212> PRT
<213> Artificial Sequence

<220>
<223> 117-244LGALS3 R primer

<400> 128
Ala Gly Ala Thr Cys Thr Ala Ala Cys Cys Ala Thr Gly Gly Thr Ala
1 5 10 15
Thr Ala Thr Gly Ala Ala Gly Cys Ala Cys Thr Gly Gly Thr
20 25 30

<210> 129
<211> 55
<212> PRT
<213> Artificial Sequence

<220>
<223> 55mer immunizing peptide

<400> 129
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45

Glu Pro Leu Thr Gly Asn Ser
50 55

<210> 130
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> 18mer immunizing peptide

<400> 130
Cys Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser
1 5 10 15
Ser Val

<210> 131
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> 15mer immunizing peptide

<400> 131
Cys Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val
1 5 10 15

<210> 132
<211> 344
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c344

<400> 132
Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr
1 5 10 15
Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn
20 25 30
Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Gln
35 40 45
Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu
50 55 60
Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu

65 70 75 80
His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser
85 90 95
Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser
100 105 110
Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His
115 120 125
Gln Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met
130 135 140
Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His Phe
145 150 155 160
Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala
165 170 175
Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp
180 185 190
Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser
195 200 205
Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr
210 215 220
Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp
225 230 235 240
Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly Thr
245 250 255
Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly
260 265 270
Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro
275 280 285
Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile
290 295 300
Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys
305 310 315 320
Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser
325 330 335
His Leu Asp Leu Glu Asp Leu Gln
340

<210> 133
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114

<400> 133
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr
20 25 30

Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
50 55 60
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
65 70 75 80
Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
85 90 95
Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp
100 105 110
Leu Gln

<210> 134
<211> 80
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c86

<400> 134
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Asp Leu Pro Phe Trp Ala Val Ile Leu Ile Gly
20 25 30
Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu
35 40 45
Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln
50 55 60
Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
65 70 75 80

<210> 135
<211> 86
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c80

<400> 135
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45

Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
50 55 60
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
65 70 75 80
Asp Leu Glu Asp Leu Gln
85

<210> 136
<211> 14507
<212> PRT
<213> Homo sapiens

<220>
<223> Immature Human MUC16 amino acid sequence (NP_078966.2)

<400> 136

Met Leu Lys Pro Ser Gly Leu Pro Gly Ser Ser Ser Pro Thr Arg Ser
1 5 10 15
Leu Met Thr Gly Ser Arg Ser Thr Lys Ala Thr Pro Glu Met Asp Ser
20 25 30
Gly Leu Thr Gly Ala Thr Leu Ser Pro Lys Thr Ser Thr Gly Ala Ile
35 40 45
Val Val Thr Glu His Thr Leu Pro Phe Thr Ser Pro Asp Lys Thr Leu
50 55 60
Ala Ser Pro Thr Ser Ser Val Val Gly Arg Thr Thr Gln Ser Leu Gly
65 70 75 80
Val Met Ser Ser Ala Leu Pro Glu Ser Thr Ser Arg Gly Met Thr His
85 90 95
Ser Glu Gln Arg Thr Ser Pro Ser Leu Ser Pro Gln Val Asn Gly Thr
100 105 110
Pro Ser Arg Asn Tyr Pro Ala Thr Ser Met Val Ser Gly Leu Ser Ser
115 120 125
Pro Arg Thr Arg Thr Ser Ser Thr Glu Gly Asn Phe Thr Lys Glu Ala
130 135 140
Ser Thr Tyr Thr Leu Thr Val Glu Thr Thr Ser Gly Pro Val Thr Glu
145 150 155 160
Lys Tyr Thr Val Pro Thr Glu Thr Ser Thr Thr Glu Gly Asp Ser Thr
165 170 175
Glu Thr Pro Trp Asp Thr Arg Tyr Ile Pro Val Lys Ile Thr Ser Pro
180 185 190
Met Lys Thr Phe Ala Asp Ser Thr Ala Ser Lys Glu Asn Ala Pro Val
195 200 205
Ser Met Thr Pro Ala Glu Thr Thr Val Thr Asp Ser His Thr Pro Gly
210 215 220
Arg Thr Asn Pro Ser Phe Gly Thr Leu Tyr Ser Ser Phe Leu Asp Leu
225 230 235 240
Ser Pro Lys Gly Thr Pro Asn Ser Arg Gly Glu Thr Ser Leu Glu Leu
245 250 255

Ile Leu Ser Thr Thr Gly Tyr Pro Phe Ser Ser Pro Glu Pro Gly Ser
260 265 270
Ala Gly His Ser Arg Ile Ser Thr Ser Ala Pro Leu Ser Ser Ser Ala
275 280 285
Ser Val Leu Asp Asn Lys Ile Ser Glu Thr Ser Ile Phe Ser Gly Gln
290 295 300
Ser Leu Thr Ser Pro Leu Ser Pro Gly Val Pro Glu Ala Arg Ala Ser
305 310 315 320
Thr Met Pro Asn Ser Ala Ile Pro Phe Ser Met Thr Leu Ser Asn Ala
325 330 335
Glu Thr Ser Ala Glu Arg Val Arg Ser Thr Ile Ser Ser Leu Gly Thr
340 345 350
Pro Ser Ile Ser Thr Lys Gln Thr Ala Glu Thr Ile Leu Thr Phe His
355 360 365
Ala Phe Ala Glu Thr Met Asp Ile Pro Ser Thr His Ile Ala Lys Thr
370 375 380
Leu Ala Ser Glu Trp Leu Gly Ser Pro Gly Thr Leu Gly Gly Thr Ser
385 390 395 400
Thr Ser Ala Leu Thr Thr Thr Ser Pro Ser Thr Thr Leu Val Ser Glu
405 410 415
Glu Thr Asn Thr His His Ser Thr Ser Gly Lys Glu Thr Glu Gly Thr
420 425 430
Leu Asn Thr Ser Met Thr Pro Leu Glu Thr Ser Ala Pro Gly Glu Glu
435 440 445
Ser Glu Met Thr Ala Thr Leu Val Pro Thr Leu Gly Phe Thr Thr Leu
450 455 460
Asp Ser Lys Ile Arg Ser Pro Ser Gln Val Ser Ser Ser His Pro Thr
465 470 475 480
Arg Glu Leu Arg Thr Thr Gly Ser Thr Ser Gly Arg Gln Ser Ser Ser
485 490 495
Thr Ala Ala His Gly Ser Ser Asp Ile Leu Arg Ala Thr Thr Ser Ser
500 505 510
Thr Ser Lys Ala Ser Ser Trp Thr Ser Glu Ser Thr Ala Gln Gln Phe
515 520 525
Ser Glu Pro Gln His Thr Gln Trp Val Glu Thr Ser Pro Ser Met Lys
530 535 540
Thr Glu Arg Pro Pro Ala Ser Thr Ser Val Ala Ala Pro Ile Thr Thr
545 550 555 560
Ser Val Pro Ser Val Val Ser Gly Phe Thr Thr Leu Lys Thr Ser Ser
565 570 575
Thr Lys Gly Ile Trp Leu Glu Glu Thr Ser Ala Asp Thr Leu Ile Gly
580 585 590
Glu Ser Thr Ala Gly Pro Thr Thr His Gln Phe Ala Val Pro Thr Gly
595 600 605
Ile Ser Met Thr Gly Gly Ser Ser Thr Arg Gly Ser Gln Gly Thr Thr
610 615 620
His Leu Leu Thr Arg Ala Thr Ala Ser Ser Glu Thr Ser Ala Asp Leu
625 630 635 640
Thr Leu Ala Thr Asn Gly Val Pro Val Ser Val Ser Pro Ala Val Ser
645 650 655

Lys Thr Ala Ala Gly Ser Ser Pro Pro Gly Gly Thr Lys Pro Ser Tyr
660 665 670
Thr Met Val Ser Ser Val Ile Pro Glu Thr Ser Ser Leu Gln Ser Ser
675 680 685
Ala Phe Arg Glu Gly Thr Ser Leu Gly Leu Thr Pro Leu Asn Thr Arg
690 695 700
His Pro Phe Ser Ser Pro Glu Pro Asp Ser Ala Gly His Thr Lys Ile
705 710 715 720
Ser Thr Ser Ile Pro Leu Leu Ser Ser Ala Ser Val Leu Glu Asp Lys
725 730 735
Val Ser Ala Thr Ser Thr Phe Ser His His Lys Ala Thr Ser Ser Ile
740 745 750
Thr Thr Gly Thr Pro Glu Ile Ser Thr Lys Thr Lys Pro Ser Ser Ala
755 760 765
Val Leu Ser Ser Met Thr Leu Ser Asn Ala Ala Thr Ser Pro Glu Arg
770 775 780
Val Arg Asn Ala Thr Ser Pro Leu Thr His Pro Ser Pro Ser Gly Glu
785 790 795 800
Glu Thr Ala Gly Ser Val Leu Thr Leu Ser Thr Ser Ala Glu Thr Thr
805 810 815
Asp Ser Pro Asn Ile His Pro Thr Gly Thr Leu Thr Ser Glu Ser Ser
820 825 830
Glu Ser Pro Ser Thr Leu Ser Leu Pro Ser Val Ser Gly Val Lys Thr
835 840 845
Thr Phe Ser Ser Ser Thr Pro Ser Thr His Leu Phe Thr Ser Gly Glu
850 855 860
Glu Thr Glu Glu Thr Ser Asn Pro Ser Val Ser Gln Pro Glu Thr Ser
865 870 875 880
Val Ser Arg Val Arg Thr Thr Leu Ala Ser Thr Ser Val Pro Thr Pro
885 890 895
Val Phe Pro Thr Met Asp Thr Trp Pro Thr Arg Ser Ala Gln Phe Ser
900 905 910
Ser Ser His Leu Val Ser Glu Leu Arg Ala Thr Ser Ser Thr Ser Val
915 920 925
Thr Asn Ser Thr Gly Ser Ala Leu Pro Lys Ile Ser His Leu Thr Gly
930 935 940
Thr Ala Thr Met Ser Gln Thr Asn Arg Asp Thr Phe Asn Asp Ser Ala
945 950 955 960
Ala Pro Gln Ser Thr Thr Trp Pro Glu Thr Ser Pro Arg Phe Lys Thr
965 970 975
Gly Leu Pro Ser Ala Thr Thr Thr Val Ser Thr Ser Ala Thr Ser Leu
980 985 990
Ser Ala Thr Val Met Val Ser Lys Phe Thr Ser Pro Ala Thr Ser Ser
995 1000 1005
Met Glu Ala Thr Ser Ile Arg Glu Pro Ser Thr Thr Ile Leu Thr
1010 1015 1020
Thr Glu Thr Thr Asn Gly Pro Gly Ser Met Ala Val Ala Ser Thr
1025 1030 1035
Asn Ile Pro Ile Gly Lys Gly Tyr Ile Thr Glu Gly Arg Leu Asp
1040 1045 1050

Thr Ser His Leu Pro Ile Gly Thr Thr Ala Ser Ser Glu Thr Ser
1055 1060 1065
Met Asp Phe Thr Met Ala Lys Glu Ser Val Ser Met Ser Val Ser
1070 1075 1080
Pro Ser Gln Ser Met Asp Ala Ala Gly Ser Ser Thr Pro Gly Arg
1085 1090 1095
Thr Ser Gln Phe Val Asp Thr Phe Ser Asp Asp Val Tyr His Leu
1100 1105 1110
Thr Ser Arg Glu Ile Thr Ile Pro Arg Asp Gly Thr Ser Ser Ala
1115 1120 1125
Leu Thr Pro Gln Met Thr Ala Thr His Pro Pro Ser Pro Asp Pro
1130 1135 1140
Gly Ser Ala Arg Ser Thr Trp Leu Gly Ile Leu Ser Ser Ser Pro
1145 1150 1155
Ser Ser Pro Thr Pro Lys Val Thr Met Ser Ser Thr Phe Ser Thr
1160 1165 1170
Gln Arg Val Thr Thr Ser Met Ile Met Asp Thr Val Glu Thr Ser
1175 1180 1185
Arg Trp Asn Met Pro Asn Leu Pro Ser Thr Thr Ser Leu Thr Pro
1190 1195 1200
Ser Asn Ile Pro Thr Ser Gly Ala Ile Gly Lys Ser Thr Leu Val
1205 1210 1215
Pro Leu Asp Thr Pro Ser Pro Ala Thr Ser Leu Glu Ala Ser Glu
1220 1225 1230
Gly Gly Leu Pro Thr Leu Ser Thr Tyr Pro Glu Ser Thr Asn Thr
1235 1240 1245
Pro Ser Ile His Leu Gly Ala His Ala Ser Ser Glu Ser Pro Ser
1250 1255 1260
Thr Ile Lys Leu Thr Met Ala Ser Val Val Lys Pro Gly Ser Tyr
1265 1270 1275
Thr Pro Leu Thr Phe Pro Ser Ile Glu Thr His Ile His Val Ser
1280 1285 1290
Thr Ala Arg Met Ala Tyr Ser Ser Gly Ser Ser Pro Glu Met Thr
1295 1300 1305
Ala Pro Gly Glu Thr Asn Thr Gly Ser Thr Trp Asp Pro Thr Thr
1310 1315 1320
Tyr Ile Thr Thr Thr Asp Pro Lys Asp Thr Ser Ser Ala Gln Val
1325 1330 1335
Ser Thr Pro His Ser Val Arg Thr Leu Arg Thr Thr Glu Asn His
1340 1345 1350
Pro Lys Thr Glu Ser Ala Thr Pro Ala Ala Tyr Ser Gly Ser Pro
1355 1360 1365
Lys Ile Ser Ser Ser Pro Asn Leu Thr Ser Pro Ala Thr Lys Ala
1370 1375 1380
Trp Thr Ile Thr Asp Thr Thr Glu His Ser Thr Gln Leu His Tyr
1385 1390 1395
Thr Lys Leu Ala Glu Lys Ser Ser Gly Phe Glu Thr Gln Ser Ala
1400 1405 1410
Pro Gly Pro Val Ser Val Val Ile Pro Thr Ser Pro Thr Ile Gly
1415 1420 1425

Ser Ser Thr Leu Glu Leu Thr Ser Asp Val Pro Gly Glu Pro Leu
1430 1435 1440
Val Leu Ala Pro Ser Glu Gln Thr Thr Ile Thr Leu Pro Met Ala
1445 1450 1455
Thr Trp Leu Ser Thr Ser Leu Thr Glu Glu Met Ala Ser Thr Asp
1460 1465 1470
Leu Asp Ile Ser Ser Pro Ser Ser Pro Met Ser Thr Phe Ala Ile
1475 1480 1485
Phe Pro Pro Met Ser Thr Pro Ser His Glu Leu Ser Lys Ser Glu
1490 1495 1500
Ala Asp Thr Ser Ala Ile Arg Asn Thr Asp Ser Thr Thr Leu Asp
1505 1510 1515
Gln His Leu Gly Ile Arg Ser Leu Gly Arg Thr Gly Asp Leu Thr
1520 1525 1530
Thr Val Pro Ile Thr Pro Leu Thr Thr Thr Trp Thr Ser Val Ile
1535 1540 1545
Glu His Ser Thr Gln Ala Gln Asp Thr Leu Ser Ala Thr Met Ser
1550 1555 1560
Pro Thr His Val Thr Gln Ser Leu Lys Asp Gln Thr Ser Ile Pro
1565 1570 1575
Ala Ser Ala Ser Pro Ser His Leu Thr Glu Val Tyr Pro Glu Leu
1580 1585 1590
Gly Thr Gln Gly Arg Ser Ser Ser Glu Ala Thr Thr Phe Trp Lys
1595 1600 1605
Pro Ser Thr Asp Thr Leu Ser Arg Glu Ile Glu Thr Gly Pro Thr
1610 1615 1620
Asn Ile Gln Ser Thr Pro Pro Met Asp Asn Thr Thr Thr Gly Ser
1625 1630 1635
Ser Ser Ser Gly Val Thr Leu Gly Ile Ala His Leu Pro Ile Gly
1640 1645 1650
Thr Ser Ser Pro Ala Glu Thr Ser Thr Asn Met Ala Leu Glu Arg
1655 1660 1665
Arg Ser Ser Thr Ala Thr Val Ser Met Ala Gly Thr Met Gly Leu
1670 1675 1680
Leu Val Thr Ser Ala Pro Gly Arg Ser Ile Ser Gln Ser Leu Gly
1685 1690 1695
Arg Val Ser Ser Val Leu Ser Glu Ser Thr Thr Glu Gly Val Thr
1700 1705 1710
Asp Ser Ser Lys Gly Ser Ser Pro Arg Leu Asn Thr Gln Gly Asn
1715 1720 1725
Thr Ala Leu Ser Ser Ser Leu Glu Pro Ser Tyr Ala Glu Gly Ser
1730 1735 1740
Gln Met Ser Thr Ser Ile Pro Leu Thr Ser Ser Pro Thr Thr Pro
1745 1750 1755
Asp Val Glu Phe Ile Gly Gly Ser Thr Phe Trp Thr Lys Glu Val
1760 1765 1770
Thr Thr Val Met Thr Ser Asp Ile Ser Lys Ser Ser Ala Arg Thr
1775 1780 1785
Glu Ser Ser Ser Ala Thr Leu Met Ser Thr Ala Leu Gly Ser Thr
1790 1795 1800

Glu Asn Thr Gly Lys Glu Lys Leu Arg Thr Ala Ser Met Asp Leu
1805 1810 1815
Pro Ser Pro Thr Pro Ser Met Glu Val Thr Pro Trp Ile Ser Leu
1820 1825 1830
Thr Leu Ser Asn Ala Pro Asn Thr Thr Asp Ser Leu Asp Leu Ser
1835 1840 1845
His Gly Val His Thr Ser Ser Ala Gly Thr Leu Ala Thr Asp Arg
1850 1855 1860
Ser Leu Asn Thr Gly Val Thr Arg Ala Ser Arg Leu Glu Asn Gly
1865 1870 1875
Ser Asp Thr Ser Ser Lys Ser Leu Ser Met Gly Asn Ser Thr His
1880 1885 1890
Thr Ser Met Thr Tyr Thr Glu Lys Ser Glu Val Ser Ser Ser Ile
1895 1900 1905
His Pro Arg Pro Glu Thr Ser Ala Pro Gly Ala Glu Thr Thr Leu
1910 1915 1920
Thr Ser Thr Pro Gly Asn Arg Ala Ile Ser Leu Thr Leu Pro Phe
1925 1930 1935
Ser Ser Ile Pro Val Glu Glu Val Ile Ser Thr Gly Ile Thr Ser
1940 1945 1950
Gly Pro Asp Ile Asn Ser Ala Pro Met Thr His Ser Pro Ile Thr
1955 1960 1965
Pro Pro Thr Ile Val Trp Thr Ser Thr Gly Thr Ile Glu Gln Ser
1970 1975 1980
Thr Gln Pro Leu His Ala Val Ser Ser Glu Lys Val Ser Val Gln
1985 1990 1995
Thr Gln Ser Thr Pro Tyr Val Asn Ser Val Ala Val Ser Ala Ser
2000 2005 2010
Pro Thr His Glu Asn Ser Val Ser Ser Gly Ser Ser Thr Ser Ser
2015 2020 2025
Pro Tyr Ser Ser Ala Ser Leu Glu Ser Leu Asp Ser Thr Ile Ser
2030 2035 2040
Arg Arg Asn Ala Ile Thr Ser Trp Leu Trp Asp Leu Thr Thr Ser
2045 2050 2055
Leu Pro Thr Thr Thr Trp Pro Ser Thr Ser Leu Ser Glu Ala Leu
2060 2065 2070
Ser Ser Gly His Ser Gly Val Ser Asn Pro Ser Ser Thr Thr Thr
2075 2080 2085
Glu Phe Pro Leu Phe Ser Ala Ala Ser Thr Ser Ala Ala Lys Gln
2090 2095 2100
Arg Asn Pro Glu Thr Glu Thr His Gly Pro Gln Asn Thr Ala Ala
2105 2110 2115
Ser Thr Leu Asn Thr Asp Ala Ser Ser Val Thr Gly Leu Ser Glu
2120 2125 2130
Thr Pro Val Gly Ala Ser Ile Ser Ser Glu Val Pro Leu Pro Met
2135 2140 2145
Ala Ile Thr Ser Arg Ser Asp Val Ser Gly Leu Thr Ser Glu Ser
2150 2155 2160
Thr Ala Asn Pro Ser Leu Gly Thr Ala Ser Ser Ala Gly Thr Lys
2165 2170 2175

Leu Thr Arg Thr Ile Ser Leu Pro Thr Ser Glu Ser Leu Val Ser
2180 2185 2190
Phe Arg Met Asn Lys Asp Pro Trp Thr Val Ser Ile Pro Leu Gly
2195 2200 2205
Ser His Pro Thr Thr Asn Thr Glu Thr Ser Ile Pro Val Asn Ser
2210 2215 2220
Ala Gly Pro Pro Gly Leu Ser Thr Val Ala Ser Asp Val Ile Asp
2225 2230 2235
Thr Pro Ser Asp Gly Ala Glu Ser Ile Pro Thr Val Ser Phe Ser
2240 2245 2250
Pro Ser Pro Asp Thr Glu Val Thr Thr Ile Ser His Phe Pro Glu
2255 2260 2265
Lys Thr Thr His Ser Phe Arg Thr Ile Ser Ser Leu Thr His Glu
2270 2275 2280
Leu Thr Ser Arg Val Thr Pro Ile Pro Gly Asp Trp Met Ser Ser
2285 2290 2295
Ala Met Ser Thr Lys Pro Thr Gly Ala Ser Pro Ser Ile Thr Leu
2300 2305 2310
Gly Glu Arg Arg Thr Ile Thr Ser Ala Ala Pro Thr Thr Ser Pro
2315 2320 2325
Ile Val Leu Thr Ala Ser Phe Thr Glu Thr Ser Thr Val Ser Leu
2330 2335 2340
Asp Asn Glu Thr Thr Val Lys Thr Ser Asp Ile Leu Asp Ala Arg
2345 2350 2355
Lys Thr Asn Glu Leu Pro Ser Asp Ser Ser Ser Ser Ser Asp Leu
2360 2365 2370
Ile Asn Thr Ser Ile Ala Ser Ser Thr Met Asp Val Thr Lys Thr
2375 2380 2385
Ala Ser Ile Ser Pro Thr Ser Ile Ser Gly Met Thr Ala Ser Ser
2390 2395 2400
Ser Pro Ser Leu Phe Ser Ser Asp Arg Pro Gln Val Pro Thr Ser
2405 2410 2415
Thr Thr Glu Thr Asn Thr Ala Thr Ser Pro Ser Val Ser Ser Asn
2420 2425 2430
Thr Tyr Ser Leu Asp Gly Gly Ser Asn Val Gly Gly Thr Pro Ser
2435 2440 2445
Thr Leu Pro Pro Phe Thr Ile Thr His Pro Val Glu Thr Ser Ser
2450 2455 2460
Ala Leu Leu Ala Trp Ser Arg Pro Val Arg Thr Phe Ser Thr Met
2465 2470 2475
Val Ser Thr Asp Thr Ala Ser Gly Glu Asn Pro Thr Ser Ser Asn
2480 2485 2490
Ser Val Val Thr Ser Val Pro Ala Pro Gly Thr Trp Thr Ser Val
2495 2500 2505
Gly Ser Thr Thr Asp Leu Pro Ala Met Gly Phe Leu Lys Thr Ser
2510 2515 2520
Pro Ala Gly Glu Ala His Ser Leu Leu Ala Ser Thr Ile Glu Pro
2525 2530 2535
Ala Thr Ala Phe Thr Pro His Leu Ser Ala Ala Val Val Thr Gly
2540 2545 2550

Ser Ser Ala Thr Ser Glu Ala Ser Leu Leu Thr Thr Ser Glu Ser
2555 2560 2565
Lys Ala Ile His Ser Ser Pro Gln Thr Pro Thr Thr Pro Thr Ser
2570 2575 2580
Gly Ala Asn Trp Glu Thr Ser Ala Thr Pro Glu Ser Leu Leu Val
2585 2590 2595
Val Thr Glu Thr Ser Asp Thr Thr Leu Thr Ser Lys Ile Leu Val
2600 2605 2610
Thr Asp Thr Ile Leu Phe Ser Thr Val Ser Thr Pro Pro Ser Lys
2615 2620 2625
Phe Pro Ser Thr Gly Thr Leu Ser Gly Ala Ser Phe Pro Thr Leu
2630 2635 2640
Leu Pro Asp Thr Pro Ala Ile Pro Leu Thr Ala Thr Glu Pro Thr
2645 2650 2655
Ser Ser Leu Ala Thr Ser Phe Asp Ser Thr Pro Leu Val Thr Ile
2660 2665 2670
Ala Ser Asp Ser Leu Gly Thr Val Pro Glu Thr Thr Leu Thr Met
2675 2680 2685
Ser Glu Thr Ser Asn Gly Asp Ala Leu Val Leu Lys Thr Val Ser
2690 2695 2700
Asn Pro Asp Arg Ser Ile Pro Gly Ile Thr Ile Gln Gly Val Thr
2705 2710 2715
Glu Ser Pro Leu His Pro Ser Ser Thr Ser Pro Ser Lys Ile Val
2720 2725 2730
Ala Pro Arg Asn Thr Thr Tyr Glu Gly Ser Ile Thr Val Ala Leu
2735 2740 2745
Ser Thr Leu Pro Ala Gly Thr Thr Gly Ser Leu Val Phe Ser Gln
2750 2755 2760
Ser Ser Glu Asn Ser Glu Thr Thr Ala Leu Val Asp Ser Ser Ala
2765 2770 2775
Gly Leu Glu Arg Ala Ser Val Met Pro Leu Thr Thr Gly Ser Gln
2780 2785 2790
Gly Met Ala Ser Ser Gly Gly Ile Arg Ser Gly Ser Thr His Ser
2795 2800 2805
Thr Gly Thr Lys Thr Phe Ser Ser Leu Pro Leu Thr Met Asn Pro
2810 2815 2820
Gly Glu Val Thr Ala Met Ser Glu Ile Thr Thr Asn Arg Leu Thr
2825 2830 2835
Ala Thr Gln Ser Thr Ala Pro Lys Gly Ile Pro Val Lys Pro Thr
2840 2845 2850
Ser Ala Glu Ser Gly Leu Leu Thr Pro Val Ser Ala Ser Ser Ser
2855 2860 2865
Pro Ser Lys Ala Phe Ala Ser Leu Thr Thr Ala Pro Pro Thr Trp
2870 2875 2880
Gly Ile Pro Gln Ser Thr Leu Thr Phe Glu Phe Ser Glu Val Pro
2885 2890 2895
Ser Leu Asp Thr Lys Ser Ala Ser Leu Pro Thr Pro Gly Gln Ser
2900 2905 2910
Leu Asn Thr Ile Pro Asp Ser Asp Ala Ser Thr Ala Ser Ser Ser
2915 2920 2925

Leu Ser Lys Ser Pro Glu Lys Asn Pro Arg Ala Arg Met Met Thr
2930 2935 2940
Ser Thr Lys Ala Ile Ser Ala Ser Ser Phe Gln Ser Thr Gly Phe
2945 2950 2955
Thr Glu Thr Pro Glu Gly Ser Ala Ser Pro Ser Met Ala Gly His
2960 2965 2970
Glu Pro Arg Val Pro Thr Ser Gly Thr Gly Asp Pro Arg Tyr Ala
2975 2980 2985
Ser Glu Ser Met Ser Tyr Pro Asp Pro Ser Lys Ala Ser Ser Ala
2990 2995 3000
Met Thr Ser Thr Ser Leu Ala Ser Lys Leu Thr Thr Leu Phe Ser
3005 3010 3015
Thr Gly Gln Ala Ala Arg Ser Gly Ser Ser Ser Ser Pro Ile Ser
3020 3025 3030
Leu Ser Thr Glu Lys Glu Thr Ser Phe Leu Ser Pro Thr Ala Ser
3035 3040 3045
Thr Ser Arg Lys Thr Ser Leu Phe Leu Gly Pro Ser Met Ala Arg
3050 3055 3060
Gln Pro Asn Ile Leu Val His Leu Gln Thr Ser Ala Leu Thr Leu
3065 3070 3075
Ser Pro Thr Ser Thr Leu Asn Met Ser Gln Glu Glu Pro Pro Glu
3080 3085 3090
Leu Thr Ser Ser Gln Thr Ile Ala Glu Glu Glu Gly Thr Thr Ala
3095 3100 3105
Glu Thr Gln Thr Leu Thr Phe Thr Pro Ser Glu Thr Pro Thr Ser
3110 3115 3120
Leu Leu Pro Val Ser Ser Pro Thr Glu Pro Thr Ala Arg Arg Lys
3125 3130 3135
Ser Ser Pro Glu Thr Trp Ala Ser Ser Ile Ser Val Pro Ala Lys
3140 3145 3150
Thr Ser Leu Val Glu Thr Thr Asp Gly Thr Leu Val Thr Thr Ile
3155 3160 3165
Lys Met Ser Ser Gln Ala Ala Gln Gly Asn Ser Thr Trp Pro Ala
3170 3175 3180
Pro Ala Glu Glu Thr Gly Ser Ser Pro Ala Gly Thr Ser Pro Gly
3185 3190 3195
Ser Pro Glu Met Ser Thr Thr Leu Lys Ile Met Ser Ser Lys Glu
3200 3205 3210
Pro Ser Ile Ser Pro Glu Ile Arg Ser Thr Val Arg Asn Ser Pro
3215 3220 3225
Trp Lys Thr Pro Glu Thr Thr Val Pro Met Glu Thr Thr Val Glu
3230 3235 3240
Pro Val Thr Leu Gln Ser Thr Ala Leu Gly Ser Gly Ser Thr Ser
3245 3250 3255
Ile Ser His Leu Pro Thr Gly Thr Thr Ser Pro Thr Lys Ser Pro
3260 3265 3270
Thr Glu Asn Met Leu Ala Thr Glu Arg Val Ser Leu Ser Pro Ser
3275 3280 3285
Pro Pro Glu Ala Trp Thr Asn Leu Tyr Ser Gly Thr Pro Gly Gly
3290 3295 3300

Thr Arg Gln Ser Leu Ala Thr Met Ser Ser Val Ser Leu Glu Ser
3305 3310 3315
Pro Thr Ala Arg Ser Ile Thr Gly Thr Gly Gln Gln Ser Ser Pro
3320 3325 3330
Glu Leu Val Ser Lys Thr Thr Gly Met Glu Phe Ser Met Trp His
3335 3340 3345
Gly Ser Thr Gly Gly Thr Thr Gly Asp Thr His Val Ser Leu Ser
3350 3355 3360
Thr Ser Ser Asn Ile Leu Glu Asp Pro Val Thr Ser Pro Asn Ser
3365 3370 3375
Val Ser Ser Leu Thr Asp Lys Ser Lys His Lys Thr Glu Thr Trp
3380 3385 3390
Val Ser Thr Thr Ala Ile Pro Ser Thr Val Leu Asn Asn Lys Ile
3395 3400 3405
Met Ala Ala Glu Gln Gln Thr Ser Arg Ser Val Asp Glu Ala Tyr
3410 3415 3420
Ser Ser Thr Ser Ser Trp Ser Asp Gln Thr Ser Gly Ser Asp Ile
3425 3430 3435
Thr Leu Gly Ala Ser Pro Asp Val Thr Asn Thr Leu Tyr Ile Thr
3440 3445 3450
Ser Thr Ala Gln Thr Thr Ser Leu Val Ser Leu Pro Ser Gly Asp
3455 3460 3465
Gln Gly Ile Thr Ser Leu Thr Asn Pro Ser Gly Gly Lys Thr Ser
3470 3475 3480
Ser Ala Ser Ser Val Thr Ser Pro Ser Ile Gly Leu Glu Thr Leu
3485 3490 3495
Arg Ala Asn Val Ser Ala Val Lys Ser Asp Ile Ala Pro Thr Ala
3500 3505 3510
Gly His Leu Ser Gln Thr Ser Ser Pro Ala Glu Val Ser Ile Leu
3515 3520 3525
Asp Val Thr Thr Ala Pro Thr Pro Gly Ile Ser Thr Thr Ile Thr
3530 3535 3540
Thr Met Gly Thr Asn Ser Ile Ser Thr Thr Thr Pro Asn Pro Glu
3545 3550 3555
Val Gly Met Ser Thr Met Asp Ser Thr Pro Ala Thr Glu Arg Arg
3560 3565 3570
Thr Thr Ser Thr Glu His Pro Ser Thr Trp Ser Ser Thr Ala Ala
3575 3580 3585
Ser Asp Ser Trp Thr Val Thr Asp Met Thr Ser Asn Leu Lys Val
3590 3595 3600
Ala Arg Ser Pro Gly Thr Ile Ser Thr Met His Thr Thr Ser Phe
3605 3610 3615
Leu Ala Ser Ser Thr Glu Leu Asp Ser Met Ser Thr Pro His Gly
3620 3625 3630
Arg Ile Thr Val Ile Gly Thr Ser Leu Val Thr Pro Ser Ser Asp
3635 3640 3645
Ala Ser Ala Val Lys Thr Glu Thr Ser Thr Ser Glu Arg Thr Leu
3650 3655 3660
Ser Pro Ser Asp Thr Thr Ala Ser Thr Pro Ile Ser Thr Phe Ser
3665 3670 3675

Arg Val Gln Arg Met Ser Ile Ser Val Pro Asp Ile Leu Ser Thr
3680 3685 3690
Ser Trp Thr Pro Ser Ser Thr Glu Ala Glu Asp Val Pro Val Ser
3695 3700 3705
Met Val Ser Thr Asp His Ala Ser Thr Lys Thr Asp Pro Asn Thr
3710 3715 3720
Pro Leu Ser Thr Phe Leu Phe Asp Ser Leu Ser Thr Leu Asp Trp
3725 3730 3735
Asp Thr Gly Arg Ser Leu Ser Ser Ala Thr Ala Thr Thr Ser Ala
3740 3745 3750
Pro Gln Gly Ala Thr Thr Pro Gln Glu Leu Thr Leu Glu Thr Met
3755 3760 3765
Ile Ser Pro Ala Thr Ser Gln Leu Pro Phe Ser Ile Gly His Ile
3770 3775 3780
Thr Ser Ala Val Thr Pro Ala Ala Met Ala Arg Ser Ser Gly Val
3785 3790 3795
Thr Phe Ser Arg Pro Asp Pro Thr Ser Lys Lys Ala Glu Gln Thr
3800 3805 3810
Ser Thr Gln Leu Pro Thr Thr Thr Ser Ala His Pro Gly Gln Val
3815 3820 3825
Pro Arg Ser Ala Ala Thr Thr Leu Asp Val Ile Pro His Thr Ala
3830 3835 3840
Lys Thr Pro Asp Ala Thr Phe Gln Arg Gln Gly Gln Thr Ala Leu
3845 3850 3855
Thr Thr Glu Ala Arg Ala Thr Ser Asp Ser Trp Asn Glu Lys Glu
3860 3865 3870
Lys Ser Thr Pro Ser Ala Pro Trp Ile Thr Glu Met Met Asn Ser
3875 3880 3885
Val Ser Glu Asp Thr Ile Lys Glu Val Thr Ser Ser Ser Ser Val
3890 3895 3900
Leu Arg Thr Leu Asn Thr Leu Asp Ile Asn Leu Glu Ser Gly Thr
3905 3910 3915
Thr Ser Ser Pro Ser Trp Lys Ser Ser Pro Tyr Glu Arg Ile Ala
3920 3925 3930
Pro Ser Glu Ser Thr Thr Asp Lys Glu Ala Ile His Pro Ser Thr
3935 3940 3945
Asn Thr Val Glu Thr Thr Gly Trp Val Thr Ser Ser Glu His Ala
3950 3955 3960
Ser His Ser Thr Ile Pro Ala His Ser Ala Ser Ser Lys Leu Thr
3965 3970 3975
Ser Pro Val Val Thr Thr Ser Thr Arg Glu Gln Ala Ile Val Ser
3980 3985 3990
Met Ser Thr Thr Thr Trp Pro Glu Ser Thr Arg Ala Arg Thr Glu
3995 4000 4005
Pro Asn Ser Phe Leu Thr Ile Glu Leu Arg Asp Val Ser Pro Tyr
4010 4015 4020
Met Asp Thr Ser Ser Thr Thr Gln Thr Ser Ile Ile Ser Ser Pro
4025 4030 4035
Gly Ser Thr Ala Ile Thr Lys Gly Pro Arg Thr Glu Ile Thr Ser
4040 4045 4050

Ser Lys Arg Ile Ser Ser Ser Phe Leu Ala Gln Ser Met Arg Ser
4055 4060 4065
Ser Asp Ser Pro Ser Glu Ala Ile Thr Arg Leu Ser Asn Phe Pro
4070 4075 4080
Ala Met Thr Glu Ser Gly Gly Met Ile Leu Ala Met Gln Thr Ser
4085 4090 4095
Pro Pro Gly Ala Thr Ser Leu Ser Ala Pro Thr Leu Asp Thr Ser
4100 4105 4110
Ala Thr Ala Ser Trp Thr Gly Thr Pro Leu Ala Thr Thr Gln Arg
4115 4120 4125
Phe Thr Tyr Ser Glu Lys Thr Thr Leu Phe Ser Lys Gly Pro Glu
4130 4135 4140
Asp Thr Ser Gln Pro Ser Pro Pro Ser Val Glu Glu Thr Ser Ser
4145 4150 4155
Ser Ser Ser Leu Val Pro Ile His Ala Thr Thr Ser Pro Ser Asn
4160 4165 4170
Ile Leu Leu Thr Ser Gln Gly His Ser Pro Ser Ser Thr Pro Pro
4175 4180 4185
Val Thr Ser Val Phe Leu Ser Glu Thr Ser Gly Leu Gly Lys Thr
4190 4195 4200
Thr Asp Met Ser Arg Ile Ser Leu Glu Pro Gly Thr Ser Leu Pro
4205 4210 4215
Pro Asn Leu Ser Ser Thr Ala Gly Glu Ala Leu Ser Thr Tyr Glu
4220 4225 4230
Ala Ser Arg Asp Thr Lys Ala Ile His His Ser Ala Asp Thr Ala
4235 4240 4245
Val Thr Asn Met Glu Ala Thr Ser Ser Glu Tyr Ser Pro Ile Pro
4250 4255 4260
Gly His Thr Lys Pro Ser Lys Ala Thr Ser Pro Leu Val Thr Ser
4265 4270 4275
His Ile Met Gly Asp Ile Thr Ser Ser Thr Ser Val Phe Gly Ser
4280 4285 4290
Ser Glu Thr Thr Glu Ile Glu Thr Val Ser Ser Val Asn Gln Gly
4295 4300 4305
Leu Gln Glu Arg Ser Thr Ser Gln Val Ala Ser Ser Ala Thr Glu
4310 4315 4320
Thr Ser Thr Val Ile Thr His Val Ser Ser Gly Asp Ala Thr Thr
4325 4330 4335
His Val Thr Lys Thr Gln Ala Thr Phe Ser Ser Gly Thr Ser Ile
4340 4345 4350
Ser Ser Pro His Gln Phe Ile Thr Ser Thr Asn Thr Phe Thr Asp
4355 4360 4365
Val Ser Thr Asn Pro Ser Thr Ser Leu Ile Met Thr Glu Ser Ser
4370 4375 4380
Gly Val Thr Ile Thr Thr Gln Thr Gly Pro Thr Gly Ala Ala Thr
4385 4390 4395
Gln Gly Pro Tyr Leu Leu Asp Thr Ser Thr Met Pro Tyr Leu Thr
4400 4405 4410
Glu Thr Pro Leu Ala Val Thr Pro Asp Phe Met Gln Ser Glu Lys
4415 4420 4425

Thr Thr Leu Ile Ser Lys Gly Pro Lys Asp Val Ser Trp Thr Ser
4430 4435 4440
Pro Pro Ser Val Ala Glu Thr Ser Tyr Pro Ser Ser Leu Thr Pro
4445 4450 4455
Phe Leu Val Thr Thr Ile Pro Pro Ala Thr Ser Thr Leu Gln Gly
4460 4465 4470
Gln His Thr Ser Ser Pro Val Ser Ala Thr Ser Val Leu Thr Ser
4475 4480 4485
Gly Leu Val Lys Thr Thr Asp Met Leu Asn Thr Ser Met Glu Pro
4490 4495 4500
Val Thr Asn Ser Pro Gln Asn Leu Asn Asn Pro Ser Asn Glu Ile
4505 4510 4515
Leu Ala Thr Leu Ala Ala Thr Thr Asp Ile Glu Thr Ile His Pro
4520 4525 4530
Ser Ile Asn Lys Ala Val Thr Asn Met Gly Thr Ala Ser Ser Ala
4535 4540 4545
His Val Leu His Ser Thr Leu Pro Val Ser Ser Glu Pro Ser Thr
4550 4555 4560
Ala Thr Ser Pro Met Val Pro Ala Ser Ser Met Gly Asp Ala Leu
4565 4570 4575
Ala Ser Ile Ser Ile Pro Gly Ser Glu Thr Thr Asp Ile Glu Gly
4580 4585 4590
Glu Pro Thr Ser Ser Leu Thr Ala Gly Arg Lys Glu Asn Ser Thr
4595 4600 4605
Leu Gln Glu Met Asn Ser Thr Thr Glu Ser Asn Ile Ile Leu Ser
4610 4615 4620
Asn Val Ser Val Gly Ala Ile Thr Glu Ala Thr Lys Met Glu Val
4625 4630 4635
Pro Ser Phe Asp Ala Thr Phe Ile Pro Thr Pro Ala Gln Ser Thr
4640 4645 4650
Lys Phe Pro Asp Ile Phe Ser Val Ala Ser Ser Arg Leu Ser Asn
4655 4660 4665
Ser Pro Pro Met Thr Ile Ser Thr His Met Thr Thr Thr Gln Thr
4670 4675 4680
Gly Ser Ser Gly Ala Thr Ser Lys Ile Pro Leu Ala Leu Asp Thr
4685 4690 4695
Ser Thr Leu Glu Thr Ser Ala Gly Thr Pro Ser Val Val Thr Glu
4700 4705 4710
Gly Phe Ala His Ser Lys Ile Thr Thr Ala Met Asn Asn Asp Val
4715 4720 4725
Lys Asp Val Ser Gln Thr Asn Pro Pro Phe Gln Asp Glu Ala Ser
4730 4735 4740
Ser Pro Ser Ser Gln Ala Pro Val Leu Val Thr Thr Leu Pro Ser
4745 4750 4755
Ser Val Ala Phe Thr Pro Gln Trp His Ser Thr Ser Ser Pro Val
4760 4765 4770
Ser Met Ser Ser Val Leu Thr Ser Ser Leu Val Lys Thr Ala Gly
4775 4780 4785
Lys Val Asp Thr Ser Leu Glu Thr Val Thr Ser Ser Pro Gln Ser
4790 4795 4800

Met Ser Asn Thr Leu Asp Asp Ile Ser Val Thr Ser Ala Ala Thr
4805 4810 4815
Thr Asp Ile Glu Thr Thr His Pro Ser Ile Asn Thr Val Val Thr
4820 4825 4830
Asn Val Gly Thr Thr Gly Ser Ala Phe Glu Ser His Ser Thr Val
4835 4840 4845
Ser Ala Tyr Pro Glu Pro Ser Lys Val Thr Ser Pro Asn Val Thr
4850 4855 4860
Thr Ser Thr Met Glu Asp Thr Thr Ile Ser Arg Ser Ile Pro Lys
4865 4870 4875
Ser Ser Lys Thr Thr Arg Thr Glu Thr Glu Thr Thr Ser Ser Leu
4880 4885 4890
Thr Pro Lys Leu Arg Glu Thr Ser Ile Ser Gln Glu Ile Thr Ser
4895 4900 4905
Ser Thr Glu Thr Ser Thr Val Pro Tyr Lys Glu Leu Thr Gly Ala
4910 4915 4920
Thr Thr Glu Val Ser Arg Thr Asp Val Thr Ser Ser Ser Ser Thr
4925 4930 4935
Ser Phe Pro Gly Pro Asp Gln Ser Thr Val Ser Leu Asp Ile Ser
4940 4945 4950
Thr Glu Thr Asn Thr Arg Leu Ser Thr Ser Pro Ile Met Thr Glu
4955 4960 4965
Ser Ala Glu Ile Thr Ile Thr Thr Gln Thr Gly Pro His Gly Ala
4970 4975 4980
Thr Ser Gln Asp Thr Phe Thr Met Asp Pro Ser Asn Thr Thr Pro
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Gln Ala Gly Ile His Ser Ala Met Thr His Gly Phe Ser Gln Leu
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Asp Val Thr Thr Leu Met Ser Arg Ile Pro Gln Asp Val Ser Trp
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Thr Ser Pro Pro Ser Val Asp Lys Thr Ser Ser Pro Ser Ser Phe
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Leu Ser Ser Pro Ala Met Thr Thr Pro Ser Leu Ile Ser Ser Thr
5045 5050 5055
Leu Pro Glu Asp Lys Leu Ser Ser Pro Met Thr Ser Leu Leu Thr
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Ser Gly Leu Val Lys Ile Thr Asp Ile Leu Arg Thr Arg Leu Glu
5075 5080 5085
Pro Val Thr Ser Ser Leu Pro Asn Phe Ser Ser Thr Ser Asp Lys
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Ile Leu Ala Thr Ser Lys Asp Ser Lys Asp Thr Lys Glu Ile Phe
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Pro Ser Ile Asn Thr Glu Glu Thr Asn Val Lys Ala Asn Asn Ser
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Gly His Glu Ser His Ser Pro Ala Leu Ala Asp Ser Glu Thr Pro
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Lys Ala Thr Thr Gln Met Val Ile Thr Thr Thr Val Gly Asp Pro
5150 5155 5160
Ala Pro Ser Thr Ser Met Pro Val His Gly Ser Ser Glu Thr Thr
5165 5170 5175

Asn Ile Lys Arg Glu Pro Thr Tyr Phe Leu Thr Pro Arg Leu Arg
5180 5185 5190
Glu Thr Ser Thr Ser Gln Glu Ser Ser Phe Pro Thr Asp Thr Ser
5195 5200 5205
Phe Leu Leu Ser Lys Val Pro Thr Gly Thr Ile Thr Glu Val Ser
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Ser Thr Gly Val Asn Ser Ser Ser Lys Ile Ser Thr Pro Asp His
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Asp Lys Ser Thr Val Pro Pro Asp Thr Phe Thr Gly Glu Ile Pro
5240 5245 5250
Arg Val Phe Thr Ser Ser Ile Lys Thr Lys Ser Ala Glu Met Thr
5255 5260 5265
Ile Thr Thr Gln Ala Ser Pro Pro Glu Ser Ala Ser His Ser Thr
5270 5275 5280
Leu Pro Leu Asp Thr Ser Thr Thr Leu Ser Gln Gly Gly Thr His
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Ser Thr Val Thr Gln Gly Phe Pro Tyr Ser Glu Val Thr Thr Leu
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Met Gly Met Gly Pro Gly Asn Val Ser Trp Met Thr Thr Pro Pro
5315 5320 5325
Val Glu Glu Thr Ser Ser Val Ser Ser Leu Met Ser Ser Pro Ala
5330 5335 5340
Met Thr Ser Pro Ser Pro Val Ser Ser Thr Ser Pro Gln Ser Ile
5345 5350 5355
Pro Ser Ser Pro Leu Pro Val Thr Ala Leu Pro Thr Ser Val Leu
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Val Thr Thr Thr Asp Val Leu Gly Thr Thr Ser Pro Glu Ser Val
5375 5380 5385
Thr Ser Ser Pro Pro Asn Leu Ser Ser Ile Thr His Glu Arg Pro
5390 5395 5400
Ala Thr Tyr Lys Asp Thr Ala His Thr Glu Ala Ala Met His His
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Ser Thr Asn Thr Ala Val Thr Asn Val Gly Thr Ser Gly Ser Gly
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His Lys Ser Gln Ser Ser Val Leu Ala Asp Ser Glu Thr Ser Lys
5435 5440 5445
Ala Thr Pro Leu Met Ser Thr Thr Ser Thr Leu Gly Asp Thr Ser
5450 5455 5460
Val Ser Thr Ser Thr Pro Asn Ile Ser Gln Thr Asn Gln Ile Gln
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Thr Glu Pro Thr Ala Ser Leu Ser Pro Arg Leu Arg Glu Ser Ser
5480 5485 5490
Thr Ser Glu Lys Thr Ser Ser Thr Thr Glu Thr Asn Thr Ala Phe
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Ser Tyr Val Pro Thr Gly Ala Ile Thr Gln Ala Ser Arg Thr Glu
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Ile Ser Ser Ser Arg Thr Ser Ile Ser Asp Leu Asp Arg Pro Thr
5525 5530 5535
Ile Ala Pro Asp Ile Ser Thr Gly Met Ile Thr Arg Leu Phe Thr
5540 5545 5550

Ser Pro Ile Met Thr Lys Ser Ala Glu Met Thr Val Thr Thr Gln
5555 5560 5565
Thr Thr Thr Pro Gly Ala Thr Ser Gln Gly Ile Leu Pro Trp Asp
5570 5575 5580
Thr Ser Thr Thr Leu Phe Gln Gly Gly Thr His Ser Thr Val Ser
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Gln Gly Phe Pro His Ser Glu Ile Thr Thr Leu Arg Ser Arg Thr
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Pro Gly Asp Val Ser Trp Met Thr Thr Pro Pro Val Glu Glu Thr
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Pro Val Ser Ser Thr Ser Pro Glu Ser Ile Pro Ser Ser Pro Leu
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Pro Val Thr Ala Leu Leu Thr Ser Val Leu Val Thr Thr Thr Asn
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Val Leu Gly Thr Thr Ser Pro Glu Pro Val Thr Ser Ser Pro Pro
5675 5680 5685
Asn Leu Ser Ser Pro Thr Gln Glu Arg Leu Thr Thr Tyr Lys Asp
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Thr Ala His Thr Glu Ala Met His Ala Ser Met His Thr Asn Thr
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Ala Val Ala Asn Val Gly Thr Ser Ile Ser Gly His Glu Ser Gln
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Ser Ser Val Pro Ala Asp Ser His Thr Ser Lys Ala Thr Ser Pro
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Met Gly Ile Thr Phe Ala Met Gly Asp Thr Ser Val Ser Thr Ser
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Thr Pro Ala Phe Phe Glu Thr Arg Ile Gln Thr Glu Ser Thr Ser
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Ser Leu Ile Pro Gly Leu Arg Asp Thr Arg Thr Ser Glu Glu Ile
5780 5785 5790
Asn Thr Val Thr Glu Thr Ser Thr Val Leu Ser Glu Val Pro Thr
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Thr Thr Thr Thr Glu Val Ser Arg Thr Glu Val Ile Thr Ser Ser
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Arg Thr Thr Ile Ser Gly Pro Asp His Ser Lys Met Ser Pro Tyr
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Ile Ser Thr Glu Thr Ile Thr Arg Leu Ser Thr Phe Pro Phe Val
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Thr Gly Ser Thr Glu Met Ala Ile Thr Asn Gln Thr Gly Pro Ile
5855 5860 5865
Gly Thr Ile Ser Gln Ala Thr Leu Thr Leu Asp Thr Ser Ser Thr
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Ala Ser Trp Glu Gly Thr His Ser Pro Val Thr Gln Arg Phe Pro
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His Ser Glu Glu Thr Thr Thr Met Ser Arg Ser Thr Lys Gly Val
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Ser Trp Gln Ser Pro Pro Ser Val Glu Glu Thr Ser Ser Pro Ser
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Ser Pro Val Pro Leu Pro Ala Ile Thr Ser His Ser Ser Leu Tyr
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Ser Ala Val Ser Gly Ser Ser Pro Thr Ser Ala Leu Pro Val Thr
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Ser Leu Leu Thr Ser Gly Arg Arg Lys Thr Ile Asp Met Leu Asp
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Thr His Ser Glu Leu Val Thr Ser Ser Leu Pro Ser Ala Ser Ser
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Phe Ser Gly Glu Ile Leu Thr Ser Glu Ala Ser Thr Asn Thr Glu
5990 5995 6000
Thr Ile His Phe Ser Glu Asn Thr Ala Glu Thr Asn Met Gly Thr
6005 6010 6015
Thr Asn Ser Met His Lys Leu His Ser Ser Val Ser Ile His Ser
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Gln Pro Ser Gly His Thr Pro Pro Lys Val Thr Gly Ser Met Met
6035 6040 6045
Glu Asp Ala Ile Val Ser Thr Ser Thr Pro Gly Ser Pro Glu Thr
6050 6055 6060
Lys Asn Val Asp Arg Asp Ser Thr Ser Pro Leu Thr Pro Glu Leu
6065 6070 6075
Lys Glu Asp Ser Thr Ala Leu Val Met Asn Ser Thr Thr Glu Ser
6080 6085 6090
Asn Thr Val Phe Ser Ser Val Ser Leu Asp Ala Ala Thr Glu Val
6095 6100 6105
Ser Arg Ala Glu Val Thr Tyr Tyr Asp Pro Thr Phe Met Pro Ala
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Ser Ala Gln Ser Thr Lys Ser Pro Asp Ile Ser Pro Glu Ala Ser
6125 6130 6135
Ser Ser His Ser Asn Ser Pro Pro Leu Thr Ile Ser Thr His Lys
6140 6145 6150
Thr Ile Ala Thr Gln Thr Gly Pro Ser Gly Val Thr Ser Leu Gly
6155 6160 6165
Gln Leu Thr Leu Asp Thr Ser Thr Ile Ala Thr Ser Ala Gly Thr
6170 6175 6180
Pro Ser Ala Arg Thr Gln Asp Phe Val Asp Ser Glu Thr Thr Ser
6185 6190 6195
Val Met Asn Asn Asp Leu Asn Asp Val Leu Lys Thr Ser Pro Phe
6200 6205 6210
Ser Ala Glu Glu Ala Asn Ser Leu Ser Ser Gln Ala Pro Leu Leu
6215 6220 6225
Val Thr Thr Ser Pro Ser Pro Val Thr Ser Thr Leu Gln Glu His
6230 6235 6240
Ser Thr Ser Ser Leu Val Ser Val Thr Ser Val Pro Thr Pro Thr
6245 6250 6255
Leu Ala Lys Ile Thr Asp Met Asp Thr Asn Leu Glu Pro Val Thr
6260 6265 6270
Arg Ser Pro Gln Asn Leu Arg Asn Thr Leu Ala Thr Ser Glu Ala
6275 6280 6285
Thr Thr Asp Thr His Thr Met His Pro Ser Ile Asn Thr Ala Val
6290 6295 6300

Ala Asn Val Gly Thr Thr Ser Ser Pro Asn Glu Phe Tyr Phe Thr
6305 6310 6315
Val Ser Pro Asp Ser Asp Pro Tyr Lys Ala Thr Ser Ala Val Val
6320 6325 6330
Ile Thr Ser Thr Ser Gly Asp Ser Ile Val Ser Thr Ser Met Pro
6335 6340 6345
Arg Ser Ser Ala Met Lys Lys Ile Glu Ser Glu Thr Thr Phe Ser
6350 6355 6360
Leu Ile Phe Arg Leu Arg Glu Thr Ser Thr Ser Gln Lys Ile Gly
6365 6370 6375
Ser Ser Ser Asp Thr Ser Thr Val Phe Asp Lys Ala Phe Thr Ala
6380 6385 6390
Ala Thr Thr Glu Val Ser Arg Thr Glu Leu Thr Ser Ser Ser Arg
6395 6400 6405
Thr Ser Ile Gln Gly Thr Glu Lys Pro Thr Met Ser Pro Asp Thr
6410 6415 6420
Ser Thr Arg Ser Val Thr Met Leu Ser Thr Phe Ala Gly Leu Thr
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Lys Ser Glu Glu Arg Thr Ile Ala Thr Gln Thr Gly Pro His Arg
6440 6445 6450
Ala Thr Ser Gln Gly Thr Leu Thr Trp Asp Thr Ser Ile Thr Thr
6455 6460 6465
Ser Gln Ala Gly Thr His Ser Ala Met Thr His Gly Phe Ser Gln
6470 6475 6480
Leu Asp Leu Ser Thr Leu Thr Ser Arg Val Pro Glu Tyr Ile Ser
6485 6490 6495
Gly Thr Ser Pro Pro Ser Val Glu Lys Thr Ser Ser Ser Ser Ser
6500 6505 6510
Leu Leu Ser Leu Pro Ala Ile Thr Ser Pro Ser Pro Val Pro Thr
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Thr Leu Pro Glu Ser Arg Pro Ser Ser Pro Val His Leu Thr Ser
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Leu Pro Thr Ser Gly Leu Val Lys Thr Thr Asp Met Leu Ala Ser
6545 6550 6555
Val Ala Ser Leu Pro Pro Asn Leu Gly Ser Thr Ser His Lys Ile
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Pro Thr Thr Ser Glu Asp Ile Lys Asp Thr Glu Lys Met Tyr Pro
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Ser Thr Asn Ile Ala Val Thr Asn Val Gly Thr Thr Thr Ser Glu
6590 6595 6600
Lys Glu Ser Tyr Ser Ser Val Pro Ala Tyr Ser Glu Pro Pro Lys
6605 6610 6615
Val Thr Ser Pro Met Val Thr Ser Phe Asn Ile Arg Asp Thr Ile
6620 6625 6630
Val Ser Thr Ser Met Pro Gly Ser Ser Glu Ile Thr Arg Ile Glu
6635 6640 6645
Met Glu Ser Thr Phe Ser Leu Ala His Gly Leu Lys Gly Thr Ser
6650 6655 6660
Thr Ser Gln Asp Pro Ile Val Ser Thr Glu Lys Ser Ala Val Leu
6665 6670 6675

His Lys Leu Thr Thr Gly Ala Thr Glu Thr Ser Arg Thr Glu Val
6680 6685 6690
Ala Ser Ser Arg Arg Thr Ser Ile Pro Gly Pro Asp His Ser Thr
6695 6700 6705
Glu Ser Pro Asp Ile Ser Thr Glu Val Ile Pro Ser Leu Pro Ile
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Ser Leu Gly Ile Thr Glu Ser Ser Asn Met Thr Ile Ile Thr Arg
6725 6730 6735
Thr Gly Pro Pro Leu Gly Ser Thr Ser Gln Gly Thr Phe Thr Leu
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Asp Thr Pro Thr Thr Ser Ser Arg Ala Gly Thr His Ser Met Ala
6755 6760 6765
Thr Gln Glu Phe Pro His Ser Glu Met Thr Thr Val Met Asn Lys
6770 6775 6780
Asp Pro Glu Ile Leu Ser Trp Thr Ile Pro Pro Ser Ile Glu Lys
6785 6790 6795
Thr Ser Phe Ser Ser Ser Leu Met Pro Ser Pro Ala Met Thr Ser
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Pro Pro Val Ser Ser Thr Leu Pro Lys Thr Ile His Thr Thr Pro
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Ser Pro Met Thr Ser Leu Leu Thr Pro Ser Leu Val Met Thr Thr
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Asp Thr Leu Gly Thr Ser Pro Glu Pro Thr Thr Ser Ser Pro Pro
6845 6850 6855
Asn Leu Ser Ser Thr Ser His Glu Ile Leu Thr Thr Asp Glu Asp
6860 6865 6870
Thr Thr Ala Ile Glu Ala Met His Pro Ser Thr Ser Thr Ala Ala
6875 6880 6885
Thr Asn Val Glu Thr Thr Ser Ser Gly His Gly Ser Gln Ser Ser
6890 6895 6900
Val Leu Ala Asp Ser Glu Lys Thr Lys Ala Thr Ala Pro Met Asp
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Thr Thr Ser Thr Met Gly His Thr Thr Val Ser Thr Ser Met Ser
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Val Ser Ser Glu Thr Thr Lys Ile Lys Arg Glu Ser Thr Tyr Ser
6935 6940 6945
Leu Thr Pro Gly Leu Arg Glu Thr Ser Ile Ser Gln Asn Ala Ser
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Phe Ser Thr Asp Thr Ser Ile Val Leu Ser Glu Val Pro Thr Gly
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Thr Thr Ala Glu Val Ser Arg Thr Glu Val Thr Ser Ser Gly Arg
6980 6985 6990
Thr Ser Ile Pro Gly Pro Ser Gln Ser Thr Val Leu Pro Glu Ile
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Ser Thr Arg Thr Met Thr Arg Leu Phe Ala Ser Pro Thr Met Thr
7010 7015 7020
Glu Ser Ala Glu Met Thr Ile Pro Thr Gln Thr Gly Pro Ser Gly
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Ser Thr Ser Gln Asp Thr Leu Thr Leu Asp Thr Ser Thr Thr Lys
7040 7045 7050

Ser Gln Ala Lys Thr His Ser Thr Leu Thr Gln Arg Phe Pro His
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Ser Glu Met Thr Thr Leu Met Ser Arg Gly Pro Gly Asp Met Ser
7070 7075 7080
Trp Gln Ser Ser Pro Ser Leu Glu Asn Pro Ser Ser Leu Pro Ser
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Thr Leu Pro Val Thr Ile Ser Ser Ser Pro Leu Pro Val Thr Ser
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Leu Leu Thr Ser Ser Pro Val Thr Thr Thr Asp Met Leu His Thr
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Ser Pro Glu Leu Val Thr Ser Ser Pro Pro Lys Leu Ser His Thr
7145 7150 7155
Ser Asp Glu Arg Leu Thr Thr Gly Lys Asp Thr Thr Asn Thr Glu
7160 7165 7170
Ala Val His Pro Ser Thr Asn Thr Ala Ala Ser Asn Val Glu Ile
7175 7180 7185
Pro Ser Ser Gly His Glu Ser Pro Ser Ser Ala Leu Ala Asp Ser
7190 7195 7200
Glu Thr Ser Lys Ala Thr Ser Pro Met Phe Ile Thr Ser Thr Gln
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Glu Asp Thr Thr Val Ala Ile Ser Thr Pro His Phe Leu Glu Thr
7220 7225 7230
Ser Arg Ile Gln Lys Glu Ser Ile Ser Ser Leu Ser Pro Lys Leu
7235 7240 7245
Arg Glu Thr Gly Ser Ser Val Glu Thr Ser Ser Ala Ile Glu Thr
7250 7255 7260
Ser Ala Val Leu Ser Glu Val Ser Ile Gly Ala Thr Thr Glu Ile
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Ser Arg Thr Glu Val Thr Ser Ser Ser Arg Thr Ser Ile Ser Gly
7280 7285 7290
Ser Ala Glu Ser Thr Met Leu Pro Glu Ile Ser Thr Thr Arg Lys
7295 7300 7305
Ile Ile Lys Phe Pro Thr Ser Pro Ile Leu Ala Glu Ser Ser Glu
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Met Thr Ile Lys Thr Gln Thr Ser Pro Pro Gly Ser Thr Ser Glu
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Ser Thr Phe Thr Leu Asp Thr Ser Thr Thr Pro Ser Leu Val Ile
7340 7345 7350
Thr His Ser Thr Met Thr Gln Arg Leu Pro His Ser Glu Ile Thr
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Thr Leu Val Ser Arg Gly Ala Gly Asp Val Pro Arg Pro Ser Ser
7370 7375 7380
Leu Pro Val Glu Glu Thr Ser Pro Pro Ser Ser Gln Leu Ser Leu
7385 7390 7395
Ser Ala Met Ile Ser Pro Ser Pro Val Ser Ser Thr Leu Pro Ala
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Ser Ser His Ser Ser Ser Ala Ser Val Thr Ser Leu Leu Thr Pro
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Gly Gln Val Lys Thr Thr Glu Val Leu Asp Ala Ser Ala Glu Pro
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Glu Thr Ser Ser Pro Pro Ser Leu Ser Ser Thr Ser Val Glu Ile
7445 7450 7455
Leu Ala Thr Ser Glu Val Thr Thr Asp Thr Glu Lys Ile His Pro
7460 7465 7470
Phe Ser Asn Thr Ala Val Thr Lys Val Gly Thr Ser Ser Ser Gly
7475 7480 7485
His Glu Ser Pro Ser Ser Val Leu Pro Asp Ser Glu Thr Thr Lys
7490 7495 7500
Ala Thr Ser Ala Met Gly Thr Ile Ser Ile Met Gly Asp Thr Ser
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Val Ser Thr Leu Thr Pro Ala Leu Ser Asn Thr Arg Lys Ile Gln
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Ser Glu Pro Ala Ser Ser Leu Thr Thr Arg Leu Arg Glu Thr Ser
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Thr Ser Glu Glu Thr Ser Leu Ala Thr Glu Ala Asn Thr Val Leu
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Ser Lys Val Ser Thr Gly Ala Thr Thr Glu Val Ser Arg Thr Glu
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Ala Ile Ser Phe Ser Arg Thr Ser Met Ser Gly Pro Glu Gln Ser
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Thr Met Ser Gln Asp Ile Ser Ile Gly Thr Ile Pro Arg Ile Ser
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Ala Ser Ser Val Leu Thr Glu Ser Ala Lys Met Thr Ile Thr Thr
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Gln Thr Gly Pro Ser Glu Ser Thr Leu Glu Ser Thr Leu Asn Leu
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Asn Thr Ala Thr Thr Pro Ser Trp Val Glu Thr His Ser Ile Val
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Ile Gln Gly Phe Pro His Pro Glu Met Thr Thr Ser Met Gly Arg
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Pro His Pro Val Ser Thr Thr Phe Leu Ala His Ile Pro Pro Ser
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Pro Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Pro Ala Thr Thr
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Gly Thr Asn Val Ala Thr Thr Ser Ser Gly Tyr Lys Ser Gln Ser
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Ser Val Leu Ala Asp Ser Ser Pro Met Cys Thr Thr Ser Thr Met
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Gly Asp Thr Ser Val Leu Thr Ser Thr Pro Ala Phe Leu Glu Thr
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Arg Arg Ile Gln Thr Glu Leu Ala Ser Ser Leu Thr Pro Gly Leu
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Arg Glu Ser Ser Gly Ser Glu Gly Thr Ser Ser Gly Thr Lys Met
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Ser Lys Glu Asp Val Thr Ser Ile Pro Gly Pro Ala Gln Ser Thr
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Ser Pro Val Met Thr Glu Ser Ala Glu Ile Thr Met Asn Thr His
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Thr Ser Pro Leu Gly Ala Thr Thr Gln Gly Thr Ser Thr Leu Asp
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Thr Ser Ser Thr Thr Ser Leu Thr Met Thr His Ser Thr Ile Ser
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Gln Gly Phe Ser His Ser Gln Met Ser Thr Leu Met Arg Arg Gly
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Pro Glu Asp Val Ser Trp Met Ser Pro Pro Leu Leu Glu Lys Thr
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Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Leu Ala Lys Thr Thr
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Asp Met Leu His Lys Ser Ser Glu Pro Val Thr Asn Ser Pro Ala
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Thr Asp Val Gly Thr Ser Ser Ser Gly His Glu Ser Thr Ser Phe
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Val Leu Ala Asp Ser Gln Thr Ser Lys Val Thr Ser Pro Met Val
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Gly Phe Phe Glu Thr Ser Arg Ile Gln Thr Glu Pro Thr Ser Ser
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Ser His Glu Arg Leu Thr Thr Leu Glu Asp Thr Val Asp Thr Glu
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Asp Met Gln Pro Ser Thr His Thr Ala Val Thr Asn Val Arg Thr
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Gly Glu Thr Ser Val Ser Ile Ser Thr Ser Asp Phe Phe Glu Thr
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Ser Arg Thr Glu Val Ile Ser Ser Arg Gly Thr Ser Met Ser Gly
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Pro Asp Gln Phe Thr Ile Ser Pro Asp Ile Ser Thr Glu Ala Ile
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Ala Ile Thr Ile Glu Thr Gly Ser Pro Gly Ala Thr Ser Glu Gly
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His Ser Thr Ala Ser Pro Gly Phe Ser His Ser Glu Met Thr Thr
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Leu Met Ser Arg Thr Pro Gly Asp Val Pro Trp Pro Ser Leu Pro
8540 8545 8550

Ser Val Glu Glu Ala Ser Ser Val Ser Ser Ser Leu Ser Ser Pro
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Ala Met Thr Ser Thr Ser Phe Phe Ser Thr Leu Pro Glu Ser Ile
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Ser Ser Ser Pro His Pro Val Thr Ala Leu Leu Thr Leu Gly Pro
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Val Lys Thr Thr Asp Met Leu Arg Thr Ser Ser Glu Pro Glu Thr
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Ser Ser Pro Pro Asn Leu Ser Ser Thr Ser Ala Glu Ile Leu Ala
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Thr Ser Glu Val Thr Lys Asp Arg Glu Lys Ile His Pro Ser Ser
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Asn Thr Pro Val Val Asn Val Gly Thr Val Ile Tyr Lys His Leu
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Ser Pro Met Ala Thr Thr Ser Thr Leu Gly Asn Thr Ser Val Ser
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Thr Ser Thr Pro Ala Phe Pro Glu Thr Met Met Thr Gln Pro Thr
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Ser Ser Leu Thr Ser Gly Leu Arg Glu Ile Ser Thr Ser Gln Glu
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Thr Ser Ser Ala Thr Glu Arg Ser Ala Ser Leu Ser Gly Met Pro
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Thr Gly Ala Thr Thr Lys Val Ser Arg Thr Glu Ala Leu Ser Leu
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Gly Arg Thr Ser Thr Pro Gly Pro Ala Gln Ser Thr Ile Ser Pro
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Glu Ile Ser Thr Glu Thr Ile Thr Arg Ile Ser Thr Pro Leu Thr
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Thr Thr Gly Ser Ala Glu Met Thr Ile Thr Pro Lys Thr Gly His
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Ser Gly Ala Ser Ser Gln Gly Thr Phe Thr Leu Asp Thr Ser Ser
8795 8800 8805
Arg Ala Ser Trp Pro Gly Thr His Ser Ala Ala Thr His Arg Ser
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Pro His Ser Gly Met Thr Thr Pro Met Ser Arg Gly Pro Glu Asp
8825 8830 8835
Val Ser Trp Pro Ser Arg Pro Ser Val Glu Lys Thr Ser Pro Pro
8840 8845 8850
Ser Ser Leu Val Ser Leu Ser Ala Val Thr Ser Pro Ser Pro Leu
8855 8860 8865
Tyr Ser Thr Pro Ser Glu Ser Ser His Ser Ser Pro Leu Arg Val
8870 8875 8880
Thr Ser Leu Phe Thr Pro Val Met Met Lys Thr Thr Asp Met Leu
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Asp Thr Ser Leu Glu Pro Val Thr Thr Ser Pro Pro Ser Met Asn
8900 8905 8910
Ile Thr Ser Asp Glu Ser Leu Ala Thr Ser Lys Ala Thr Met Glu
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Thr Glu Ala Ile Gln Leu Ser Glu Asn Thr Ala Val Thr Gln Met
8930 8935 8940
Gly Thr Ile Ser Ala Arg Gln Glu Phe Tyr Ser Ser Tyr Pro Gly
8945 8950 8955
Leu Pro Glu Pro Ser Lys Val Thr Ser Pro Val Val Thr Ser Ser
8960 8965 8970
Thr Ile Lys Asp Ile Val Ser Thr Thr Ile Pro Ala Ser Ser Glu
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Ile Thr Arg Ile Glu Met Glu Ser Thr Ser Thr Leu Thr Pro Thr
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Pro Arg Glu Thr Ser Thr Ser Gln Glu Ile His Ser Ala Thr Lys
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Pro Ser Thr Val Pro Tyr Lys Ala Leu Thr Ser Ala Thr Ile Glu
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Asp Ser Met Thr Gln Val Met Ser Ser Ser Arg Gly Pro Ser Pro
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Asp Gln Ser Thr Met Ser Gln Asp Ile Ser Thr Glu Val Ile Thr
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Arg Leu Ser Thr Ser Pro Ile Lys Thr Glu Ser Thr Glu Met Thr
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Ile Thr Thr Gln Thr Gly Ser Pro Gly Ala Thr Ser Arg Gly Thr
9080 9085 9090
Leu Thr Leu Asp Thr Ser Thr Thr Phe Met Ser Gly Thr His Ser
9095 9100 9105
Thr Ala Ser Gln Gly Phe Ser His Ser Gln Met Thr Ala Leu Met
9110 9115 9120
Ser Arg Thr Pro Gly Asp Val Pro Trp Leu Ser His Pro Ser Val
9125 9130 9135
Glu Glu Ala Ser Ser Ala Ser Phe Ser Leu Ser Ser Pro Val Met
9140 9145 9150
Thr Ser Ser Ser Pro Val Ser Ser Thr Leu Pro Asp Ser Ile His
9155 9160 9165
Ser Ser Ser Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Leu Val
9170 9175 9180
Lys Thr Thr Glu Leu Leu Gly Thr Ser Ser Glu Pro Glu Thr Ser
9185 9190 9195
Ser Pro Pro Asn Leu Ser Ser Thr Ser Ala Glu Ile Leu Ala Ile
9200 9205 9210
Thr Glu Val Thr Thr Asp Thr Glu Lys Leu Glu Met Thr Asn Val
9215 9220 9225
Val Thr Ser Gly Tyr Thr His Glu Ser Pro Ser Ser Val Leu Ala
9230 9235 9240
Asp Ser Val Thr Thr Lys Ala Thr Ser Ser Met Gly Ile Thr Tyr
9245 9250 9255
Pro Thr Gly Asp Thr Asn Val Leu Thr Ser Thr Pro Ala Phe Ser
9260 9265 9270
Asp Thr Ser Arg Ile Gln Thr Lys Ser Lys Leu Ser Leu Thr Pro
9275 9280 9285
Gly Leu Met Glu Thr Ser Ile Ser Glu Glu Thr Ser Ser Ala Thr
9290 9295 9300

Glu Lys Ser Thr Val Leu Ser Ser Val Pro Thr Gly Ala Thr Thr
9305 9310 9315
Glu Val Ser Arg Thr Glu Ala Ile Ser Ser Ser Arg Thr Ser Ile
9320 9325 9330
Pro Gly Pro Ala Gln Ser Thr Met Ser Ser Asp Thr Ser Met Glu
9335 9340 9345
Thr Ile Thr Arg Ile Ser Thr Pro Leu Thr Arg Lys Glu Ser Thr
9350 9355 9360
Asp Met Ala Ile Thr Pro Lys Thr Gly Pro Ser Gly Ala Thr Ser
9365 9370 9375
Gln Gly Thr Phe Thr Leu Asp Ser Ser Ser Thr Ala Ser Trp Pro
9380 9385 9390
Gly Thr His Ser Ala Thr Thr Gln Arg Phe Pro Gln Ser Val Val
9395 9400 9405
Thr Thr Pro Met Ser Arg Gly Pro Glu Asp Val Ser Trp Pro Ser
9410 9415 9420
Pro Leu Ser Val Glu Lys Asn Ser Pro Pro Ser Ser Leu Val Ser
9425 9430 9435
Ser Ser Ser Val Thr Ser Pro Ser Pro Leu Tyr Ser Thr Pro Ser
9440 9445 9450
Gly Ser Ser His Ser Ser Pro Val Pro Val Thr Ser Leu Phe Thr
9455 9460 9465
Ser Ile Met Met Lys Ala Thr Asp Met Leu Asp Ala Ser Leu Glu
9470 9475 9480
Pro Glu Thr Thr Ser Ala Pro Asn Met Asn Ile Thr Ser Asp Glu
9485 9490 9495
Ser Leu Ala Ala Ser Lys Ala Thr Thr Glu Thr Glu Ala Ile His
9500 9505 9510
Val Phe Glu Asn Thr Ala Ala Ser His Val Glu Thr Thr Ser Ala
9515 9520 9525
Thr Glu Glu Leu Tyr Ser Ser Ser Pro Gly Phe Ser Glu Pro Thr
9530 9535 9540
Lys Val Ile Ser Pro Val Val Thr Ser Ser Ser Ile Arg Asp Asn
9545 9550 9555
Met Val Ser Thr Thr Met Pro Gly Ser Ser Gly Ile Thr Arg Ile
9560 9565 9570
Glu Ile Glu Ser Met Ser Ser Leu Thr Pro Gly Leu Arg Glu Thr
9575 9580 9585
Arg Thr Ser Gln Asp Ile Thr Ser Ser Thr Glu Thr Ser Thr Val
9590 9595 9600
Leu Tyr Lys Met Pro Ser Gly Ala Thr Pro Glu Val Ser Arg Thr
9605 9610 9615
Glu Val Met Pro Ser Ser Arg Thr Ser Ile Pro Gly Pro Ala Gln
9620 9625 9630
Ser Thr Met Ser Leu Asp Ile Ser Asp Glu Val Val Thr Arg Leu
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Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ile Thr Ile Thr
9650 9655 9660
Thr Gln Thr Gly Tyr Ser Leu Ala Thr Ser Gln Val Thr Leu Pro
9665 9670 9675

Leu Gly Thr Ser Met Thr Phe Leu Ser Gly Thr His Ser Thr Met
9680 9685 9690
Ser Gln Gly Leu Ser His Ser Glu Met Thr Asn Leu Met Ser Arg
9695 9700 9705
Gly Pro Glu Ser Leu Ser Trp Thr Ser Pro Arg Phe Val Glu Thr
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Leu Ser Pro Val Ser Ser Thr Leu Leu Asp Ser Ser Pro Ser Ser
9740 9745 9750
Pro Leu Pro Val Thr Ser Leu Ile Leu Pro Gly Leu Val Lys Thr
9755 9760 9765
Thr Glu Val Leu Asp Thr Ser Ser Glu Pro Lys Thr Ser Ser Ser
9770 9775 9780
Pro Asn Leu Ser Ser Thr Ser Val Glu Ile Pro Ala Thr Ser Glu
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Ile Met Thr Asp Thr Glu Lys Ile His Pro Ser Ser Asn Thr Ala
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Val Ala Lys Val Arg Thr Ser Ser Ser Val His Glu Ser His Ser
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Gly Ile Thr Ser Ala Val Asp Asp Thr Thr Val Phe Thr Ser Asn
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Pro Ala Phe Ser Glu Thr Arg Arg Ile Pro Thr Glu Pro Thr Phe
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Ser Leu Thr Pro Gly Phe Arg Glu Thr Ser Thr Ser Glu Glu Thr
9875 9880 9885
Thr Ser Ile Thr Glu Thr Ser Ala Val Leu Tyr Gly Val Pro Thr
9890 9895 9900
Ser Ala Thr Thr Glu Val Ser Met Thr Glu Ile Met Ser Ser Asn
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Arg Ile His Ile Pro Asp Ser Asp Gln Ser Thr Met Ser Pro Asp
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Ile Ile Thr Glu Val Ile Thr Arg Leu Ser Ser Ser Ser Met Met
9935 9940 9945
Ser Glu Ser Thr Gln Met Thr Ile Thr Thr Gln Lys Ser Ser Pro
9950 9955 9960
Gly Ala Thr Ala Gln Ser Thr Leu Thr Leu Ala Thr Thr Thr Ala
9965 9970 9975
Pro Leu Ala Arg Thr His Ser Thr Val Pro Pro Arg Phe Leu His
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Ser Glu Met Thr Thr Leu Met Ser Arg Ser Pro Glu Asn Pro Ser
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Trp Lys Ser Ser Leu Phe Val Glu Lys Thr Ser Ser Ser Ser Ser
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Leu Pro Gln Ser Ile Pro Ser Ser Ser Phe Ser Val Thr Ser Leu
10040 10045 10050

Leu Thr Pro Gly Met Val Lys Thr Thr Asp Thr Ser Thr Glu Pro
10055 10060 10065
Gly Thr Ser Leu Ser Pro Asn Leu Ser Gly Thr Ser Val Glu Ile
10070 10075 10080
Leu Ala Ala Ser Glu Val Thr Thr Asp Thr Glu Lys Ile His Pro
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Ser Ser Ser Met Ala Val Thr Asn Val Gly Thr Thr Ser Ser Gly
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His Glu Leu Tyr Ser Ser Val Ser Ile His Ser Glu Pro Ser Lys
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Ile Ser Thr Ser Met Pro Ala Asn Phe Glu Thr Thr Gly Phe Glu
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Ala Glu Pro Phe Ser His Leu Thr Ser Gly Phe Arg Lys Thr Asn
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Met Ser Leu Asp Thr Ser Ser Val Thr Pro Thr Asn Thr Pro Ser
10175 10180 10185
Ser Pro Gly Ser Thr His Leu Leu Gln Ser Ser Lys Thr Asp Phe
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Thr Ser Ser Ala Lys Thr Ser Ser Pro Asp Trp Pro Pro Ala Ser
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Gln Tyr Thr Glu Ile Pro Val Asp Ile Ile Thr Pro Phe Asn Ala
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Glu Ser Gly Pro Gly Asp Ala Thr Leu Ser Thr Ile Ala Glu Ser
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Leu Pro Ser Ser Thr Pro Val Pro Phe Ser Ser Ser Thr Phe Thr
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Thr Thr Asp Ser Ser Thr Ile Pro Ala Leu His Glu Ile Thr Ser
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Ser Ser Ala Thr Pro Tyr Arg Val Asp Thr Ser Leu Gly Thr Glu
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Ser Ser Thr Thr Glu Gly Arg Leu Val Met Val Ser Thr Leu Asp
10370 10375 10380
Thr Ser Ser Gln Pro Gly Arg Thr Ser Ser Ser Pro Ile Leu Asp
10385 10390 10395
Thr Arg Met Thr Glu Ser Val Glu Leu Gly Thr Val Thr Ser Ala
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Tyr Gln Val Pro Ser Leu Ser Thr Arg Leu Thr Arg Thr Asp Gly
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Ile Met Glu His Ile Thr Lys Ile Pro Asn Glu Ala Ala His Arg
10430 10435 10440
Gly Thr Ile Arg Pro Val Lys Gly Pro Gln Thr Ser Thr Ser Pro
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Ala Ser Pro Lys Gly Leu His Thr Gly Gly Thr Lys Arg Met Glu
10460 10465 10470
Thr Thr Thr Thr Ala Leu Lys Thr Thr Thr Thr Ala Leu Lys Thr
10475 10480 10485
Thr Ser Arg Ala Thr Leu Thr Thr Ser Val Tyr Thr Pro Thr Leu
10490 10495 10500
Gly Thr Leu Thr Pro Leu Asn Ala Ser Met Gln Met Ala Ser Thr
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Ile Pro Thr Glu Met Met Ile Thr Thr Pro Tyr Val Phe Pro Asp
10520 10525 10530
Val Pro Glu Thr Thr Ser Ser Leu Ala Thr Ser Leu Gly Ala Glu
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Thr Ser Thr Ala Leu Pro Arg Thr Thr Pro Ser Val Phe Asn Arg
10550 10555 10560
Glu Ser Glu Thr Thr Ala Ser Leu Val Ser Arg Ser Gly Ala Glu
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Arg Ser Pro Val Ile Gln Thr Leu Asp Val Ser Ser Ser Glu Pro
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Asp Thr Thr Ala Ser Trp Val Ile His Pro Ala Glu Thr Ile Pro
10595 10600 10605
Thr Val Ser Lys Thr Thr Pro Asn Phe Phe His Ser Glu Leu Asp
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Thr Val Ser Ser Thr Ala Thr Ser His Gly Ala Asp Val Ser Ser
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Ala Ile Pro Thr Asn Ile Ser Pro Ser Glu Leu Asp Ala Leu Thr
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Pro Leu Val Thr Ile Ser Gly Thr Asp Thr Ser Thr Thr Phe Pro
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Thr Leu Thr Lys Ser Pro His Glu Thr Glu Thr Arg Thr Thr Trp
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Leu Thr His Pro Ala Glu Thr Ser Ser Thr Ile Pro Arg Thr Ile
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Pro Asn Phe Ser His His Glu Ser Asp Ala Thr Pro Ser Ile Ala
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Thr Ser Pro Gly Ala Glu Thr Ser Ser Ala Ile Pro Ile Met Thr
10715 10720 10725
Val Ser Pro Gly Ala Glu Asp Leu Val Thr Ser Gln Val Thr Ser
10730 10735 10740
Ser Gly Thr Asp Arg Asn Met Thr Ile Pro Thr Leu Thr Leu Ser
10745 10750 10755
Pro Gly Glu Pro Lys Thr Ile Ala Ser Leu Val Thr His Pro Glu
10760 10765 10770
Ala Gln Thr Ser Ser Ala Ile Pro Thr Ser Thr Ile Ser Pro Ala
10775 10780 10785
Val Ser Arg Leu Val Thr Ser Met Val Thr Ser Leu Ala Ala Lys
10790 10795 10800

Thr Ser Thr Thr Asn Arg Ala Leu Thr Asn Ser Pro Gly Glu Pro
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Ala Thr Thr Val Ser Leu Val Thr His Pro Ala Gln Thr Ser Pro
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Thr Val Pro Trp Thr Thr Ser Ile Phe Phe His Ser Lys Ser Asp
10835 10840 10845
Thr Thr Pro Ser Met Thr Thr Ser His Gly Ala Glu Ser Ser Ser
10850 10855 10860
Ala Val Pro Thr Pro Thr Val Ser Thr Glu Val Pro Gly Val Val
10865 10870 10875
Thr Pro Leu Val Thr Ser Ser Arg Ala Val Ile Ser Thr Thr Ile
10880 10885 10890
Pro Ile Leu Thr Leu Ser Pro Gly Glu Pro Glu Thr Thr Pro Ser
10895 10900 10905
Met Ala Thr Ser His Gly Glu Glu Ala Ser Ser Ala Ile Pro Thr
10910 10915 10920
Pro Thr Val Ser Pro Gly Val Pro Gly Val Val Thr Ser Leu Val
10925 10930 10935
Thr Ser Ser Arg Ala Val Thr Ser Thr Thr Ile Pro Ile Leu Thr
10940 10945 10950
Phe Ser Leu Gly Glu Pro Glu Thr Thr Pro Ser Met Ala Thr Ser
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His Gly Thr Glu Ala Gly Ser Ala Val Pro Thr Val Leu Pro Glu
10970 10975 10980
Val Pro Gly Met Val Thr Ser Leu Val Ala Ser Ser Arg Ala Val
10985 10990 10995
Thr Ser Thr Thr Leu Pro Thr Leu Thr Leu Ser Pro Gly Glu Pro
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Glu Thr Thr Pro Ser Met Ala Thr Ser His Gly Ala Glu Ala Ser
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Ser Leu Val Thr Ser Ser Ser Gly Val Asn Ser Thr Ser Ile Pro
11045 11050 11055
Thr Leu Ile Leu Ser Pro Gly Glu Leu Glu Thr Thr Pro Ser Met
11060 11065 11070
Ala Thr Ser His Gly Ala Glu Ala Ser Ser Ala Val Pro Thr Pro
11075 11080 11085
Thr Val Ser Pro Gly Val Ser Gly Val Val Thr Pro Leu Val Thr
11090 11095 11100
Ser Ser Arg Ala Val Thr Ser Thr Thr Ile Pro Ile Leu Thr Leu
11105 11110 11115
Ser Ser Ser Glu Pro Glu Thr Thr Pro Ser Met Ala Thr Ser His
11120 11125 11130
Gly Val Glu Ala Ser Ser Ala Val Leu Thr Val Ser Pro Glu Val
11135 11140 11145
Pro Gly Met Val Thr Ser Leu Val Thr Ser Ser Arg Ala Val Thr
11150 11155 11160
Ser Thr Thr Ile Pro Thr Leu Thr Ile Ser Ser Asp Glu Pro Glu
11165 11170 11175

Thr Thr Thr Ser Leu Val Thr His Ser Glu Ala Lys Met Ile Ser
11180 11185 11190
Ala Ile Pro Thr Leu Ala Val Ser Pro Thr Val Gln Gly Leu Val
11195 11200 11205
Thr Ser Leu Val Thr Ser Ser Gly Ser Glu Thr Ser Ala Phe Ser
11210 11215 11220
Asn Leu Thr Val Ala Ser Ser Gln Pro Glu Thr Ile Asp Ser Trp
11225 11230 11235
Val Ala His Pro Gly Thr Glu Ala Ser Ser Val Val Pro Thr Leu
11240 11245 11250
Thr Val Ser Thr Gly Glu Pro Phe Thr Asn Ile Ser Leu Val Thr
11255 11260 11265
His Pro Ala Glu Ser Ser Ser Thr Leu Pro Arg Thr Thr Ser Arg
11270 11275 11280
Phe Ser His Ser Glu Leu Asp Thr Met Pro Ser Thr Val Thr Ser
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Pro Glu Ala Glu Ser Ser Ser Ala Ile Ser Thr Thr Ile Ser Pro
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Gly Ile Pro Gly Val Leu Thr Ser Leu Val Thr Ser Ser Gly Arg
11315 11320 11325
Asp Ile Ser Ala Thr Phe Pro Thr Val Pro Glu Ser Pro His Glu
11330 11335 11340
Ser Glu Ala Thr Ala Ser Trp Val Thr His Pro Ala Val Thr Ser
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Thr Thr Val Pro Arg Thr Thr Pro Asn Tyr Ser His Ser Glu Pro
11360 11365 11370
Asp Thr Thr Pro Ser Ile Ala Thr Ser Pro Gly Ala Glu Ala Thr
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Ser Asp Phe Pro Thr Ile Thr Val Ser Pro Asp Val Pro Asp Met
11390 11395 11400
Val Thr Ser Gln Val Thr Ser Ser Gly Thr Asp Thr Ser Ile Thr
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Ile Pro Thr Leu Thr Leu Ser Ser Gly Glu Pro Glu Thr Thr Thr
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Ser Phe Ile Thr Tyr Ser Glu Thr His Thr Ser Ser Ala Ile Pro
11435 11440 11445
Thr Leu Pro Val Ser Pro Gly Ala Ser Lys Met Leu Thr Ser Leu
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Val Ile Ser Ser Gly Thr Asp Ser Thr Thr Thr Phe Pro Thr Leu
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Thr Glu Thr Pro Tyr Glu Pro Glu Thr Thr Ala Ile Gln Leu Ile
11480 11485 11490
His Pro Ala Glu Thr Asn Thr Met Val Pro Arg Thr Thr Pro Lys
11495 11500 11505
Phe Ser His Ser Lys Ser Asp Thr Thr Leu Pro Val Ala Ile Thr
11510 11515 11520
Ser Pro Gly Pro Glu Ala Ser Ser Ala Val Ser Thr Thr Thr Ile
11525 11530 11535
Ser Pro Asp Met Ser Asp Leu Val Thr Ser Leu Val Pro Ser Ser
11540 11545 11550

Gly Thr Asp Thr Ser Thr Thr Phe Pro Thr Leu Ser Glu Thr Pro
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Tyr Glu Pro Glu Thr Thr Ala Thr Trp Leu Thr His Pro Ala Glu
11570 11575 11580
Thr Ser Thr Thr Val Ser Gly Thr Ile Pro Asn Phe Ser His Arg
11585 11590 11595
Gly Ser Asp Thr Ala Pro Ser Met Val Thr Ser Pro Gly Val Asp
11600 11605 11610
Thr Arg Ser Gly Val Pro Thr Thr Thr Ile Pro Pro Ser Ile Pro
11615 11620 11625
Gly Val Val Thr Ser Gln Val Thr Ser Ser Ala Thr Asp Thr Ser
11630 11635 11640
Thr Ala Ile Pro Thr Leu Thr Pro Ser Pro Gly Glu Pro Glu Thr
11645 11650 11655
Thr Ala Ser Ser Ala Thr His Pro Gly Thr Gln Thr Gly Phe Thr
11660 11665 11670
Val Pro Ile Arg Thr Val Pro Ser Ser Glu Pro Asp Thr Met Ala
11675 11680 11685
Ser Trp Val Thr His Pro Pro Gln Thr Ser Thr Pro Val Ser Arg
11690 11695 11700
Thr Thr Ser Ser Phe Ser His Ser Ser Pro Asp Ala Thr Pro Val
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Met Ala Thr Ser Pro Arg Thr Glu Ala Ser Ser Ala Val Leu Thr
11720 11725 11730
Thr Ile Ser Pro Gly Ala Pro Glu Met Val Thr Ser Gln Ile Thr
11735 11740 11745
Ser Ser Gly Ala Ala Thr Ser Thr Thr Val Pro Thr Leu Thr His
11750 11755 11760
Ser Pro Gly Met Pro Glu Thr Thr Ala Leu Leu Ser Thr His Pro
11765 11770 11775
Arg Thr Glu Thr Ser Lys Thr Phe Pro Ala Ser Thr Val Phe Pro
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Gln Val Ser Glu Thr Thr Ala Ser Leu Thr Ile Arg Pro Gly Ala
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Glu Thr Ser Thr Ala Leu Pro Thr Gln Thr Thr Ser Ser Leu Phe
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Thr Leu Leu Val Thr Gly Thr Ser Arg Val Asp Leu Ser Pro Thr
11825 11830 11835
Ala Ser Pro Gly Val Ser Ala Lys Thr Ala Pro Leu Ser Thr His
11840 11845 11850
Pro Gly Thr Glu Thr Ser Thr Met Ile Pro Thr Ser Thr Leu Ser
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Leu Gly Leu Leu Glu Thr Thr Gly Leu Leu Ala Thr Ser Ser Ser
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Ala Glu Thr Ser Thr Ser Thr Leu Thr Leu Thr Val Ser Pro Ala
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Val Ser Gly Leu Ser Ser Ala Ser Ile Thr Thr Asp Lys Pro Gln
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Thr Val Thr Ser Trp Asn Thr Glu Thr Ser Pro Ser Val Thr Ser
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Val Gly Pro Pro Glu Phe Ser Arg Thr Val Thr Gly Thr Thr Met
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Thr Leu Ile Pro Ser Glu Met Pro Thr Pro Pro Lys Thr Ser His
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Gly Glu Gly Val Ser Pro Thr Thr Ile Leu Arg Thr Thr Met Val
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Glu Ala Thr Asn Leu Ala Thr Thr Gly Ser Ser Pro Thr Val Ala
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Lys Thr Thr Thr Thr Phe Asn Thr Leu Ala Gly Ser Leu Phe Thr
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Ser Ser Tyr Asn Arg Arg Tyr Trp Thr Pro Ala Thr Ser Thr Pro
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Val Thr Ser Thr Phe Ser Pro Gly Ile Ser Thr Ser Ser Ile Pro
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Ser Ser Thr Ala Ala Thr Val Pro Phe Met Val Pro Phe Thr Leu
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Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asp Met Arg His
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Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu Arg Glu Leu Gln Gly
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Leu Leu Lys Pro Leu Phe Arg Asn Ser Ser Leu Glu Tyr Leu Tyr
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Ala Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu
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Asp Leu Gly Leu Asp Arg Glu Arg Leu Tyr Trp Glu Leu Ser Asn
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Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr
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Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr
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His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu
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Tyr Trp Glu Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly
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Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr
12335 12340 12345
His Gln Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Ser Thr
12350 12355 12360
Val Asp Leu Arg Thr Ser Gly Thr Pro Ser Ser Leu Ser Ser Pro
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Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly His Pro
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Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu
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Leu Gly Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser
12425 12430 12435
Gly Cys Arg Leu Thr Ser Leu Arg Ser Glu Lys Asp Gly Ala Ala
12440 12445 12450
Thr Gly Val Asp Ala Ile Cys Ile His His Leu Asp Pro Lys Ser
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Pro Gly Leu Asn Arg Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu
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Thr Asn Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn
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Ser Leu Tyr Val Asn Gly Phe Thr His Arg Thr Ser Val Pro Thr
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Ser Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Thr Ser Gly
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Val Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Lys Tyr Glu
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Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu
12560 12565 12570
Arg Val Leu Gln Thr Leu Leu Gly Pro Met Phe Lys Asn Thr Ser
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Val Gly Leu Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Ser
12590 12595 12600
Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His
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Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr
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Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His
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Asn Leu Lys Tyr Glu Glu Asp Met His Cys Pro Gly Ser Arg Lys
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Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu
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Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp
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Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val
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His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln
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Gly Leu Leu Gly Pro Met Phe Lys Asn Thr Ser Val Gly Leu Leu
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Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asn Gly
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Ala Ala Thr Gly Met Asp Ala Ile Cys Ser His Arg Leu Asp Pro
12920 12925 12930
Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu Tyr Trp Glu Leu Ser
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Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp
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Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His Arg Ser Ser Val
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Ala Pro Thr Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Thr
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Ser Gly Thr Pro Ser Ser Leu Pro Ser Pro Thr Thr Ala Val Pro
12995 13000 13005
Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln
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Tyr Gly Glu Asp Met Arg His Pro Gly Ser Arg Lys Phe Asn Thr
13025 13030 13035
Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu Phe Lys Asn
13040 13045 13050

Ser Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Ile Ser Leu
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Arg Ser Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys
13070 13075 13080
Thr His His Leu Asn Pro Gln Ser Pro Gly Leu Asp Arg Glu Gln
13085 13090 13095
Leu Tyr Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu
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Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe
13115 13120 13125
Thr His Arg Ser Ser Gly Leu Thr Thr Ser Thr Pro Trp Thr Ser
13130 13135 13140
Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser
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Pro Thr Thr Thr Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe
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Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asn Met Gly His Pro Gly
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Ser Arg Lys Phe Asn Ile Thr Glu Ser Val Leu Gln Gly Leu Leu
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Lys Pro Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly
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Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Val Ala Thr
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Arg Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Lys Ile Pro
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Gly Leu Asp Arg Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr
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His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser
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Leu Tyr Val Asn Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr
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Ser Thr Pro Gly Thr Phe Thr Val Gln Pro Glu Thr Ser Glu Thr
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Pro Ser Ser Leu Pro Gly Pro Thr Ala Thr Gly Pro Val Leu Leu
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Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu
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Asp Met Arg Arg Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg
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Val Leu Gln Gly Leu Leu Met Pro Leu Phe Lys Asn Thr Ser Val
13355 13360 13365
Ser Ser Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu
13370 13375 13380
Lys Asp Gly Ala Ala Thr Arg Val Asp Ala Val Cys Thr His Arg
13385 13390 13395
Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Arg Leu Tyr Trp
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Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly Pro Tyr
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Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly Phe Thr His Gln
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Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser Thr Met His
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Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro Met Thr
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Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile Thr
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<211> 518
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific

<400> 138
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Val Thr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45
Tyr Ser Ala Ser Asn Arg Tyr Ser Gly Val Pro Ala Arg Phe Ser Gly
50 55 60
Ser Gly Tyr Gly Thr Glu Phe Thr Phe Thr Ile Ser Ser Val Gln Ser
65 70 75 80
Glu Asp Phe Ala Val Tyr Phe Cys Gln Gln Asp Tyr Ser Ser Phe Gly
85 90 95
Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val
100 105 110
Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser
115 120 125
Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln
130 135 140
Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val
145 150 155 160
Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu
165 170 175
Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu
180 185 190
Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg
195 200 205
Gly Glu Cys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Val Gln
210 215 220
Leu Val Gln Ser Gly Gly Gly Leu Thr Leu Ser Lys Ala Asp Tyr Glu
225 230 235 240
Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
245 250 255
Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys Gly Gly Gly Gly Ser
260 265 270
Gly Gly Gly Gly Ser Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val
275 280 285
Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Lys Ala Ser Gly Tyr
290 295 300
Thr Phe Thr Arg Tyr Thr Met His Trp Val Arg Gln Ala Pro Gly Lys
305 310 315 320
Cys Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr Thr Asn
325 330 335
Tyr Asn Gln Lys Phe Lys Asp Arg Phe Thr Ile Ser Arg Asp Asn Ser
340 345 350
Lys Asn Thr Ala Phe Leu Gln Met Asp Ser Leu Arg Pro Glu Asp Thr
355 360 365
Gly Val Tyr Phe Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys Leu Asp
370 375 380
Tyr Trp Gly Gln Gly Thr Pro Val Thr Val Ser Ser Gly Gly Gly Gly
385 390 395 400
Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr
405 410 415

Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile
420 425 430
Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr Gln Gln
435 440 445
Thr Pro Gly Lys Ala Pro Lys Arg Trp Ile Tyr Asp Thr Ser Lys Leu
450 455 460
Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
465 470 475 480
Tyr Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr
485 490 495
Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Cys Gly Thr
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Lys Leu Gln Ile Thr Arg
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<210> 139
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114-N3

<400> 139
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35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
50 55 60
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
65 70 75 80
Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
85 90 95
Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp
100 105 110
Leu Gln

<210> 140
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> 10C6 VH NUCLEIC ACID

<400> 140
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cagccttcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgataagtac 180
tataacccag ccctgaagag tcggctcaca atctccaagg attcctccaa aaaccaggtt 240
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tcctca 366

<210> 141
<211> 330
<212> DNA
<213> Artificial Sequence

<220>
<223> 10C6 VL NUCLEIC ACID

<400> 141
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caacagaaac caggacagcc acccagactc ctcatctatc ttgtatccaa cctagaatct 180
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tcggaggggg gaccaagctg gaaataaaac 330

<210> 142
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> 7B12 VH NUCLEIC ACID

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cagccctcag ggaagggtct ggagtggctg gcacacatct ggtgggatga tgaagataag 180
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atcgggacag ctcaggctac ggatgctttg gactactggg gtcaaggaac ctcagtcacc 360
gtctcctca 369

<210> 143
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> 7B12 VL NUCLEIC ACID

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ctcacgttcg gaggggggac taagctaaaa ataaaa 336

<210> 144
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> 19C11 VH NUCLEIC ACID

<400> 144
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cagtcttcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgataagtac 180
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tcctca 366

<210> 145
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> 19C11 VL NUCLEIC ACID

<400> 145
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<210> 146
<211> 366
<212> DNA
<213> Artificial Sequence

<220>
<223> 16C5 VH NUCLEIC ACID

<400> 146
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cagccttcag ggaagggtct ggagtggctg gcacacattt ggtgggatga tgataagtac 180
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tcctca 366

<210> 147
<211> 327
<212> DNA
<213> Artificial Sequence

<220>
<223> 16C5 VL NUCLEIC ACID

<400> 147
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ggagctggca ccaatgtgga aatcaaa 327

<210> 148
<211> 369
<212> DNA
<213> Artificial Sequence

<220>
<223> 18C6 VH NUCLEIC ACID

<400> 148
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gtctcctca 369

<210> 149
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> 18C6 VL NUCLEIC ACID

<400> 149
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<210> 150
<211> 14447
<212> PRT
<213> Homo sapiens

<220>
<223> Mature Human MUC16 amino acid sequence

<400> 150

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Gln Ser Leu Gly Val Met Ser Ser Ala Leu Pro Glu Ser Thr Ser Arg
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Gly Met Thr His Ser Glu Gln Arg Thr Ser Pro Ser Leu Ser Pro Gln
35 40 45
Val Asn Gly Thr Pro Ser Arg Asn Tyr Pro Ala Thr Ser Met Val Ser
50 55 60
Gly Leu Ser Ser Pro Arg Thr Arg Thr Ser Ser Thr Glu Gly Asn Phe
65 70 75 80
Thr Lys Glu Ala Ser Thr Tyr Thr Leu Thr Val Glu Thr Thr Ser Gly
85 90 95
Pro Val Thr Glu Lys Tyr Thr Val Pro Thr Glu Thr Ser Thr Thr Glu
100 105 110
Gly Asp Ser Thr Glu Thr Pro Trp Asp Thr Arg Tyr Ile Pro Val Lys
115 120 125
Ile Thr Ser Pro Met Lys Thr Phe Ala Asp Ser Thr Ala Ser Lys Glu
130 135 140
Asn Ala Pro Val Ser Met Thr Pro Ala Glu Thr Thr Val Thr Asp Ser
145 150 155 160
His Thr Pro Gly Arg Thr Asn Pro Ser Phe Gly Thr Leu Tyr Ser Ser
165 170 175
Phe Leu Asp Leu Ser Pro Lys Gly Thr Pro Asn Ser Arg Gly Glu Thr
180 185 190
Ser Leu Glu Leu Ile Leu Ser Thr Thr Gly Tyr Pro Phe Ser Ser Pro
195 200 205
Glu Pro Gly Ser Ala Gly His Ser Arg Ile Ser Thr Ser Ala Pro Leu
210 215 220
Ser Ser Ser Ala Ser Val Leu Asp Asn Lys Ile Ser Glu Thr Ser Ile
225 230 235 240
Phe Ser Gly Gln Ser Leu Thr Ser Pro Leu Ser Pro Gly Val Pro Glu
245 250 255

Ala Arg Ala Ser Thr Met Pro Asn Ser Ala Ile Pro Phe Ser Met Thr
260 265 270
Leu Ser Asn Ala Glu Thr Ser Ala Glu Arg Val Arg Ser Thr Ile Ser
275 280 285
Ser Leu Gly Thr Pro Ser Ile Ser Thr Lys Gln Thr Ala Glu Thr Ile
290 295 300
Leu Thr Phe His Ala Phe Ala Glu Thr Met Asp Ile Pro Ser Thr His
305 310 315 320
Ile Ala Lys Thr Leu Ala Ser Glu Trp Leu Gly Ser Pro Gly Thr Leu
325 330 335
Gly Gly Thr Ser Thr Ser Ala Leu Thr Thr Thr Ser Pro Ser Thr Thr
340 345 350
Leu Val Ser Glu Glu Thr Asn Thr His His Ser Thr Ser Gly Lys Glu
355 360 365
Thr Glu Gly Thr Leu Asn Thr Ser Met Thr Pro Leu Glu Thr Ser Ala
370 375 380
Pro Gly Glu Glu Ser Glu Met Thr Ala Thr Leu Val Pro Thr Leu Gly
385 390 395 400
Phe Thr Thr Leu Asp Ser Lys Ile Arg Ser Pro Ser Gln Val Ser Ser
405 410 415
Ser His Pro Thr Arg Glu Leu Arg Thr Thr Gly Ser Thr Ser Gly Arg
420 425 430
Gln Ser Ser Ser Thr Ala Ala His Gly Ser Ser Asp Ile Leu Arg Ala
435 440 445
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450 455 460
Ala Gln Gln Phe Ser Glu Pro Gln His Thr Gln Trp Val Glu Thr Ser
465 470 475 480
Pro Ser Met Lys Thr Glu Arg Pro Pro Ala Ser Thr Ser Val Ala Ala
485 490 495
Pro Ile Thr Thr Ser Val Pro Ser Val Val Ser Gly Phe Thr Thr Leu
500 505 510
Lys Thr Ser Ser Thr Lys Gly Ile Trp Leu Glu Glu Thr Ser Ala Asp
515 520 525
Thr Leu Ile Gly Glu Ser Thr Ala Gly Pro Thr Thr His Gln Phe Ala
530 535 540
Val Pro Thr Gly Ile Ser Met Thr Gly Gly Ser Ser Thr Arg Gly Ser
545 550 555 560
Gln Gly Thr Thr His Leu Leu Thr Arg Ala Thr Ala Ser Ser Glu Thr
565 570 575
Ser Ala Asp Leu Thr Leu Ala Thr Asn Gly Val Pro Val Ser Val Ser
580 585 590
Pro Ala Val Ser Lys Thr Ala Ala Gly Ser Ser Pro Pro Gly Gly Thr
595 600 605
Lys Pro Ser Tyr Thr Met Val Ser Ser Val Ile Pro Glu Thr Ser Ser
610 615 620
Leu Gln Ser Ser Ala Phe Arg Glu Gly Thr Ser Leu Gly Leu Thr Pro
625 630 635 640
Leu Asn Thr Arg His Pro Phe Ser Ser Pro Glu Pro Asp Ser Ala Gly
645 650 655

His Thr Lys Ile Ser Thr Ser Ile Pro Leu Leu Ser Ser Ala Ser Val
660 665 670
Leu Glu Asp Lys Val Ser Ala Thr Ser Thr Phe Ser His His Lys Ala
675 680 685
Thr Ser Ser Ile Thr Thr Gly Thr Pro Glu Ile Ser Thr Lys Thr Lys
690 695 700
Pro Ser Ser Ala Val Leu Ser Ser Met Thr Leu Ser Asn Ala Ala Thr
705 710 715 720
Ser Pro Glu Arg Val Arg Asn Ala Thr Ser Pro Leu Thr His Pro Ser
725 730 735
Pro Ser Gly Glu Glu Thr Ala Gly Ser Val Leu Thr Leu Ser Thr Ser
740 745 750
Ala Glu Thr Thr Asp Ser Pro Asn Ile His Pro Thr Gly Thr Leu Thr
755 760 765
Ser Glu Ser Ser Glu Ser Pro Ser Thr Leu Ser Leu Pro Ser Val Ser
770 775 780
Gly Val Lys Thr Thr Phe Ser Ser Ser Thr Pro Ser Thr His Leu Phe
785 790 795 800
Thr Ser Gly Glu Glu Thr Glu Glu Thr Ser Asn Pro Ser Val Ser Gln
805 810 815
Pro Glu Thr Ser Val Ser Arg Val Arg Thr Thr Leu Ala Ser Thr Ser
820 825 830
Val Pro Thr Pro Val Phe Pro Thr Met Asp Thr Trp Pro Thr Arg Ser
835 840 845
Ala Gln Phe Ser Ser Ser His Leu Val Ser Glu Leu Arg Ala Thr Ser
850 855 860
Ser Thr Ser Val Thr Asn Ser Thr Gly Ser Ala Leu Pro Lys Ile Ser
865 870 875 880
His Leu Thr Gly Thr Ala Thr Met Ser Gln Thr Asn Arg Asp Thr Phe
885 890 895
Asn Asp Ser Ala Ala Pro Gln Ser Thr Thr Trp Pro Glu Thr Ser Pro
900 905 910
Arg Phe Lys Thr Gly Leu Pro Ser Ala Thr Thr Thr Val Ser Thr Ser
915 920 925
Ala Thr Ser Leu Ser Ala Thr Val Met Val Ser Lys Phe Thr Ser Pro
930 935 940
Ala Thr Ser Ser Met Glu Ala Thr Ser Ile Arg Glu Pro Ser Thr Thr
945 950 955 960
Ile Leu Thr Thr Glu Thr Thr Asn Gly Pro Gly Ser Met Ala Val Ala
965 970 975
Ser Thr Asn Ile Pro Ile Gly Lys Gly Tyr Ile Thr Glu Gly Arg Leu
980 985 990
Asp Thr Ser His Leu Pro Ile Gly Thr Thr Ala Ser Ser Glu Thr Ser
995 1000 1005
Met Asp Phe Thr Met Ala Lys Glu Ser Val Ser Met Ser Val Ser
1010 1015 1020
Pro Ser Gln Ser Met Asp Ala Ala Gly Ser Ser Thr Pro Gly Arg
1025 1030 1035
Thr Ser Gln Phe Val Asp Thr Phe Ser Asp Asp Val Tyr His Leu
1040 1045 1050

Thr Ser Arg Glu Ile Thr Ile Pro Arg Asp Gly Thr Ser Ser Ala
1055 1060 1065
Leu Thr Pro Gln Met Thr Ala Thr His Pro Pro Ser Pro Asp Pro
1070 1075 1080
Gly Ser Ala Arg Ser Thr Trp Leu Gly Ile Leu Ser Ser Ser Pro
1085 1090 1095
Ser Ser Pro Thr Pro Lys Val Thr Met Ser Ser Thr Phe Ser Thr
1100 1105 1110
Gln Arg Val Thr Thr Ser Met Ile Met Asp Thr Val Glu Thr Ser
1115 1120 1125
Arg Trp Asn Met Pro Asn Leu Pro Ser Thr Thr Ser Leu Thr Pro
1130 1135 1140
Ser Asn Ile Pro Thr Ser Gly Ala Ile Gly Lys Ser Thr Leu Val
1145 1150 1155
Pro Leu Asp Thr Pro Ser Pro Ala Thr Ser Leu Glu Ala Ser Glu
1160 1165 1170
Gly Gly Leu Pro Thr Leu Ser Thr Tyr Pro Glu Ser Thr Asn Thr
1175 1180 1185
Pro Ser Ile His Leu Gly Ala His Ala Ser Ser Glu Ser Pro Ser
1190 1195 1200
Thr Ile Lys Leu Thr Met Ala Ser Val Val Lys Pro Gly Ser Tyr
1205 1210 1215
Thr Pro Leu Thr Phe Pro Ser Ile Glu Thr His Ile His Val Ser
1220 1225 1230
Thr Ala Arg Met Ala Tyr Ser Ser Gly Ser Ser Pro Glu Met Thr
1235 1240 1245
Ala Pro Gly Glu Thr Asn Thr Gly Ser Thr Trp Asp Pro Thr Thr
1250 1255 1260
Tyr Ile Thr Thr Thr Asp Pro Lys Asp Thr Ser Ser Ala Gln Val
1265 1270 1275
Ser Thr Pro His Ser Val Arg Thr Leu Arg Thr Thr Glu Asn His
1280 1285 1290
Pro Lys Thr Glu Ser Ala Thr Pro Ala Ala Tyr Ser Gly Ser Pro
1295 1300 1305
Lys Ile Ser Ser Ser Pro Asn Leu Thr Ser Pro Ala Thr Lys Ala
1310 1315 1320
Trp Thr Ile Thr Asp Thr Thr Glu His Ser Thr Gln Leu His Tyr
1325 1330 1335
Thr Lys Leu Ala Glu Lys Ser Ser Gly Phe Glu Thr Gln Ser Ala
1340 1345 1350
Pro Gly Pro Val Ser Val Val Ile Pro Thr Ser Pro Thr Ile Gly
1355 1360 1365
Ser Ser Thr Leu Glu Leu Thr Ser Asp Val Pro Gly Glu Pro Leu
1370 1375 1380
Val Leu Ala Pro Ser Glu Gln Thr Thr Ile Thr Leu Pro Met Ala
1385 1390 1395
Thr Trp Leu Ser Thr Ser Leu Thr Glu Glu Met Ala Ser Thr Asp
1400 1405 1410
Leu Asp Ile Ser Ser Pro Ser Ser Pro Met Ser Thr Phe Ala Ile
1415 1420 1425

Phe Pro Pro Met Ser Thr Pro Ser His Glu Leu Ser Lys Ser Glu
1430 1435 1440
Ala Asp Thr Ser Ala Ile Arg Asn Thr Asp Ser Thr Thr Leu Asp
1445 1450 1455
Gln His Leu Gly Ile Arg Ser Leu Gly Arg Thr Gly Asp Leu Thr
1460 1465 1470
Thr Val Pro Ile Thr Pro Leu Thr Thr Thr Trp Thr Ser Val Ile
1475 1480 1485
Glu His Ser Thr Gln Ala Gln Asp Thr Leu Ser Ala Thr Met Ser
1490 1495 1500
Pro Thr His Val Thr Gln Ser Leu Lys Asp Gln Thr Ser Ile Pro
1505 1510 1515
Ala Ser Ala Ser Pro Ser His Leu Thr Glu Val Tyr Pro Glu Leu
1520 1525 1530
Gly Thr Gln Gly Arg Ser Ser Ser Glu Ala Thr Thr Phe Trp Lys
1535 1540 1545
Pro Ser Thr Asp Thr Leu Ser Arg Glu Ile Glu Thr Gly Pro Thr
1550 1555 1560
Asn Ile Gln Ser Thr Pro Pro Met Asp Asn Thr Thr Thr Gly Ser
1565 1570 1575
Ser Ser Ser Gly Val Thr Leu Gly Ile Ala His Leu Pro Ile Gly
1580 1585 1590
Thr Ser Ser Pro Ala Glu Thr Ser Thr Asn Met Ala Leu Glu Arg
1595 1600 1605
Arg Ser Ser Thr Ala Thr Val Ser Met Ala Gly Thr Met Gly Leu
1610 1615 1620
Leu Val Thr Ser Ala Pro Gly Arg Ser Ile Ser Gln Ser Leu Gly
1625 1630 1635
Arg Val Ser Ser Val Leu Ser Glu Ser Thr Thr Glu Gly Val Thr
1640 1645 1650
Asp Ser Ser Lys Gly Ser Ser Pro Arg Leu Asn Thr Gln Gly Asn
1655 1660 1665
Thr Ala Leu Ser Ser Ser Leu Glu Pro Ser Tyr Ala Glu Gly Ser
1670 1675 1680
Gln Met Ser Thr Ser Ile Pro Leu Thr Ser Ser Pro Thr Thr Pro
1685 1690 1695
Asp Val Glu Phe Ile Gly Gly Ser Thr Phe Trp Thr Lys Glu Val
1700 1705 1710
Thr Thr Val Met Thr Ser Asp Ile Ser Lys Ser Ser Ala Arg Thr
1715 1720 1725
Glu Ser Ser Ser Ala Thr Leu Met Ser Thr Ala Leu Gly Ser Thr
1730 1735 1740
Glu Asn Thr Gly Lys Glu Lys Leu Arg Thr Ala Ser Met Asp Leu
1745 1750 1755
Pro Ser Pro Thr Pro Ser Met Glu Val Thr Pro Trp Ile Ser Leu
1760 1765 1770
Thr Leu Ser Asn Ala Pro Asn Thr Thr Asp Ser Leu Asp Leu Ser
1775 1780 1785
His Gly Val His Thr Ser Ser Ala Gly Thr Leu Ala Thr Asp Arg
1790 1795 1800

Ser Leu Asn Thr Gly Val Thr Arg Ala Ser Arg Leu Glu Asn Gly
1805 1810 1815
Ser Asp Thr Ser Ser Lys Ser Leu Ser Met Gly Asn Ser Thr His
1820 1825 1830
Thr Ser Met Thr Tyr Thr Glu Lys Ser Glu Val Ser Ser Ser Ile
1835 1840 1845
His Pro Arg Pro Glu Thr Ser Ala Pro Gly Ala Glu Thr Thr Leu
1850 1855 1860
Thr Ser Thr Pro Gly Asn Arg Ala Ile Ser Leu Thr Leu Pro Phe
1865 1870 1875
Ser Ser Ile Pro Val Glu Glu Val Ile Ser Thr Gly Ile Thr Ser
1880 1885 1890
Gly Pro Asp Ile Asn Ser Ala Pro Met Thr His Ser Pro Ile Thr
1895 1900 1905
Pro Pro Thr Ile Val Trp Thr Ser Thr Gly Thr Ile Glu Gln Ser
1910 1915 1920
Thr Gln Pro Leu His Ala Val Ser Ser Glu Lys Val Ser Val Gln
1925 1930 1935
Thr Gln Ser Thr Pro Tyr Val Asn Ser Val Ala Val Ser Ala Ser
1940 1945 1950
Pro Thr His Glu Asn Ser Val Ser Ser Gly Ser Ser Thr Ser Ser
1955 1960 1965
Pro Tyr Ser Ser Ala Ser Leu Glu Ser Leu Asp Ser Thr Ile Ser
1970 1975 1980
Arg Arg Asn Ala Ile Thr Ser Trp Leu Trp Asp Leu Thr Thr Ser
1985 1990 1995
Leu Pro Thr Thr Thr Trp Pro Ser Thr Ser Leu Ser Glu Ala Leu
2000 2005 2010
Ser Ser Gly His Ser Gly Val Ser Asn Pro Ser Ser Thr Thr Thr
2015 2020 2025
Glu Phe Pro Leu Phe Ser Ala Ala Ser Thr Ser Ala Ala Lys Gln
2030 2035 2040
Arg Asn Pro Glu Thr Glu Thr His Gly Pro Gln Asn Thr Ala Ala
2045 2050 2055
Ser Thr Leu Asn Thr Asp Ala Ser Ser Val Thr Gly Leu Ser Glu
2060 2065 2070
Thr Pro Val Gly Ala Ser Ile Ser Ser Glu Val Pro Leu Pro Met
2075 2080 2085
Ala Ile Thr Ser Arg Ser Asp Val Ser Gly Leu Thr Ser Glu Ser
2090 2095 2100
Thr Ala Asn Pro Ser Leu Gly Thr Ala Ser Ser Ala Gly Thr Lys
2105 2110 2115
Leu Thr Arg Thr Ile Ser Leu Pro Thr Ser Glu Ser Leu Val Ser
2120 2125 2130
Phe Arg Met Asn Lys Asp Pro Trp Thr Val Ser Ile Pro Leu Gly
2135 2140 2145
Ser His Pro Thr Thr Asn Thr Glu Thr Ser Ile Pro Val Asn Ser
2150 2155 2160
Ala Gly Pro Pro Gly Leu Ser Thr Val Ala Ser Asp Val Ile Asp
2165 2170 2175

Thr Pro Ser Asp Gly Ala Glu Ser Ile Pro Thr Val Ser Phe Ser
2180 2185 2190
Pro Ser Pro Asp Thr Glu Val Thr Thr Ile Ser His Phe Pro Glu
2195 2200 2205
Lys Thr Thr His Ser Phe Arg Thr Ile Ser Ser Leu Thr His Glu
2210 2215 2220
Leu Thr Ser Arg Val Thr Pro Ile Pro Gly Asp Trp Met Ser Ser
2225 2230 2235
Ala Met Ser Thr Lys Pro Thr Gly Ala Ser Pro Ser Ile Thr Leu
2240 2245 2250
Gly Glu Arg Arg Thr Ile Thr Ser Ala Ala Pro Thr Thr Ser Pro
2255 2260 2265
Ile Val Leu Thr Ala Ser Phe Thr Glu Thr Ser Thr Val Ser Leu
2270 2275 2280
Asp Asn Glu Thr Thr Val Lys Thr Ser Asp Ile Leu Asp Ala Arg
2285 2290 2295
Lys Thr Asn Glu Leu Pro Ser Asp Ser Ser Ser Ser Ser Asp Leu
2300 2305 2310
Ile Asn Thr Ser Ile Ala Ser Ser Thr Met Asp Val Thr Lys Thr
2315 2320 2325
Ala Ser Ile Ser Pro Thr Ser Ile Ser Gly Met Thr Ala Ser Ser
2330 2335 2340
Ser Pro Ser Leu Phe Ser Ser Asp Arg Pro Gln Val Pro Thr Ser
2345 2350 2355
Thr Thr Glu Thr Asn Thr Ala Thr Ser Pro Ser Val Ser Ser Asn
2360 2365 2370
Thr Tyr Ser Leu Asp Gly Gly Ser Asn Val Gly Gly Thr Pro Ser
2375 2380 2385
Thr Leu Pro Pro Phe Thr Ile Thr His Pro Val Glu Thr Ser Ser
2390 2395 2400
Ala Leu Leu Ala Trp Ser Arg Pro Val Arg Thr Phe Ser Thr Met
2405 2410 2415
Val Ser Thr Asp Thr Ala Ser Gly Glu Asn Pro Thr Ser Ser Asn
2420 2425 2430
Ser Val Val Thr Ser Val Pro Ala Pro Gly Thr Trp Thr Ser Val
2435 2440 2445
Gly Ser Thr Thr Asp Leu Pro Ala Met Gly Phe Leu Lys Thr Ser
2450 2455 2460
Pro Ala Gly Glu Ala His Ser Leu Leu Ala Ser Thr Ile Glu Pro
2465 2470 2475
Ala Thr Ala Phe Thr Pro His Leu Ser Ala Ala Val Val Thr Gly
2480 2485 2490
Ser Ser Ala Thr Ser Glu Ala Ser Leu Leu Thr Thr Ser Glu Ser
2495 2500 2505
Lys Ala Ile His Ser Ser Pro Gln Thr Pro Thr Thr Pro Thr Ser
2510 2515 2520
Gly Ala Asn Trp Glu Thr Ser Ala Thr Pro Glu Ser Leu Leu Val
2525 2530 2535
Val Thr Glu Thr Ser Asp Thr Thr Leu Thr Ser Lys Ile Leu Val
2540 2545 2550

Thr Asp Thr Ile Leu Phe Ser Thr Val Ser Thr Pro Pro Ser Lys
2555 2560 2565
Phe Pro Ser Thr Gly Thr Leu Ser Gly Ala Ser Phe Pro Thr Leu
2570 2575 2580
Leu Pro Asp Thr Pro Ala Ile Pro Leu Thr Ala Thr Glu Pro Thr
2585 2590 2595
Ser Ser Leu Ala Thr Ser Phe Asp Ser Thr Pro Leu Val Thr Ile
2600 2605 2610
Ala Ser Asp Ser Leu Gly Thr Val Pro Glu Thr Thr Leu Thr Met
2615 2620 2625
Ser Glu Thr Ser Asn Gly Asp Ala Leu Val Leu Lys Thr Val Ser
2630 2635 2640
Asn Pro Asp Arg Ser Ile Pro Gly Ile Thr Ile Gln Gly Val Thr
2645 2650 2655
Glu Ser Pro Leu His Pro Ser Ser Thr Ser Pro Ser Lys Ile Val
2660 2665 2670
Ala Pro Arg Asn Thr Thr Tyr Glu Gly Ser Ile Thr Val Ala Leu
2675 2680 2685
Ser Thr Leu Pro Ala Gly Thr Thr Gly Ser Leu Val Phe Ser Gln
2690 2695 2700
Ser Ser Glu Asn Ser Glu Thr Thr Ala Leu Val Asp Ser Ser Ala
2705 2710 2715
Gly Leu Glu Arg Ala Ser Val Met Pro Leu Thr Thr Gly Ser Gln
2720 2725 2730
Gly Met Ala Ser Ser Gly Gly Ile Arg Ser Gly Ser Thr His Ser
2735 2740 2745
Thr Gly Thr Lys Thr Phe Ser Ser Leu Pro Leu Thr Met Asn Pro
2750 2755 2760
Gly Glu Val Thr Ala Met Ser Glu Ile Thr Thr Asn Arg Leu Thr
2765 2770 2775
Ala Thr Gln Ser Thr Ala Pro Lys Gly Ile Pro Val Lys Pro Thr
2780 2785 2790
Ser Ala Glu Ser Gly Leu Leu Thr Pro Val Ser Ala Ser Ser Ser
2795 2800 2805
Pro Ser Lys Ala Phe Ala Ser Leu Thr Thr Ala Pro Pro Thr Trp
2810 2815 2820
Gly Ile Pro Gln Ser Thr Leu Thr Phe Glu Phe Ser Glu Val Pro
2825 2830 2835
Ser Leu Asp Thr Lys Ser Ala Ser Leu Pro Thr Pro Gly Gln Ser
2840 2845 2850
Leu Asn Thr Ile Pro Asp Ser Asp Ala Ser Thr Ala Ser Ser Ser
2855 2860 2865
Leu Ser Lys Ser Pro Glu Lys Asn Pro Arg Ala Arg Met Met Thr
2870 2875 2880
Ser Thr Lys Ala Ile Ser Ala Ser Ser Phe Gln Ser Thr Gly Phe
2885 2890 2895
Thr Glu Thr Pro Glu Gly Ser Ala Ser Pro Ser Met Ala Gly His
2900 2905 2910
Glu Pro Arg Val Pro Thr Ser Gly Thr Gly Asp Pro Arg Tyr Ala
2915 2920 2925

Ser Glu Ser Met Ser Tyr Pro Asp Pro Ser Lys Ala Ser Ser Ala
2930 2935 2940
Met Thr Ser Thr Ser Leu Ala Ser Lys Leu Thr Thr Leu Phe Ser
2945 2950 2955
Thr Gly Gln Ala Ala Arg Ser Gly Ser Ser Ser Ser Pro Ile Ser
2960 2965 2970
Leu Ser Thr Glu Lys Glu Thr Ser Phe Leu Ser Pro Thr Ala Ser
2975 2980 2985
Thr Ser Arg Lys Thr Ser Leu Phe Leu Gly Pro Ser Met Ala Arg
2990 2995 3000
Gln Pro Asn Ile Leu Val His Leu Gln Thr Ser Ala Leu Thr Leu
3005 3010 3015
Ser Pro Thr Ser Thr Leu Asn Met Ser Gln Glu Glu Pro Pro Glu
3020 3025 3030
Leu Thr Ser Ser Gln Thr Ile Ala Glu Glu Glu Gly Thr Thr Ala
3035 3040 3045
Glu Thr Gln Thr Leu Thr Phe Thr Pro Ser Glu Thr Pro Thr Ser
3050 3055 3060
Leu Leu Pro Val Ser Ser Pro Thr Glu Pro Thr Ala Arg Arg Lys
3065 3070 3075
Ser Ser Pro Glu Thr Trp Ala Ser Ser Ile Ser Val Pro Ala Lys
3080 3085 3090
Thr Ser Leu Val Glu Thr Thr Asp Gly Thr Leu Val Thr Thr Ile
3095 3100 3105
Lys Met Ser Ser Gln Ala Ala Gln Gly Asn Ser Thr Trp Pro Ala
3110 3115 3120
Pro Ala Glu Glu Thr Gly Ser Ser Pro Ala Gly Thr Ser Pro Gly
3125 3130 3135
Ser Pro Glu Met Ser Thr Thr Leu Lys Ile Met Ser Ser Lys Glu
3140 3145 3150
Pro Ser Ile Ser Pro Glu Ile Arg Ser Thr Val Arg Asn Ser Pro
3155 3160 3165
Trp Lys Thr Pro Glu Thr Thr Val Pro Met Glu Thr Thr Val Glu
3170 3175 3180
Pro Val Thr Leu Gln Ser Thr Ala Leu Gly Ser Gly Ser Thr Ser
3185 3190 3195
Ile Ser His Leu Pro Thr Gly Thr Thr Ser Pro Thr Lys Ser Pro
3200 3205 3210
Thr Glu Asn Met Leu Ala Thr Glu Arg Val Ser Leu Ser Pro Ser
3215 3220 3225
Pro Pro Glu Ala Trp Thr Asn Leu Tyr Ser Gly Thr Pro Gly Gly
3230 3235 3240
Thr Arg Gln Ser Leu Ala Thr Met Ser Ser Val Ser Leu Glu Ser
3245 3250 3255
Pro Thr Ala Arg Ser Ile Thr Gly Thr Gly Gln Gln Ser Ser Pro
3260 3265 3270
Glu Leu Val Ser Lys Thr Thr Gly Met Glu Phe Ser Met Trp His
3275 3280 3285
Gly Ser Thr Gly Gly Thr Thr Gly Asp Thr His Val Ser Leu Ser
3290 3295 3300

Thr Ser Ser Asn Ile Leu Glu Asp Pro Val Thr Ser Pro Asn Ser
3305 3310 3315
Val Ser Ser Leu Thr Asp Lys Ser Lys His Lys Thr Glu Thr Trp
3320 3325 3330
Val Ser Thr Thr Ala Ile Pro Ser Thr Val Leu Asn Asn Lys Ile
3335 3340 3345
Met Ala Ala Glu Gln Gln Thr Ser Arg Ser Val Asp Glu Ala Tyr
3350 3355 3360
Ser Ser Thr Ser Ser Trp Ser Asp Gln Thr Ser Gly Ser Asp Ile
3365 3370 3375
Thr Leu Gly Ala Ser Pro Asp Val Thr Asn Thr Leu Tyr Ile Thr
3380 3385 3390
Ser Thr Ala Gln Thr Thr Ser Leu Val Ser Leu Pro Ser Gly Asp
3395 3400 3405
Gln Gly Ile Thr Ser Leu Thr Asn Pro Ser Gly Gly Lys Thr Ser
3410 3415 3420
Ser Ala Ser Ser Val Thr Ser Pro Ser Ile Gly Leu Glu Thr Leu
3425 3430 3435
Arg Ala Asn Val Ser Ala Val Lys Ser Asp Ile Ala Pro Thr Ala
3440 3445 3450
Gly His Leu Ser Gln Thr Ser Ser Pro Ala Glu Val Ser Ile Leu
3455 3460 3465
Asp Val Thr Thr Ala Pro Thr Pro Gly Ile Ser Thr Thr Ile Thr
3470 3475 3480
Thr Met Gly Thr Asn Ser Ile Ser Thr Thr Thr Pro Asn Pro Glu
3485 3490 3495
Val Gly Met Ser Thr Met Asp Ser Thr Pro Ala Thr Glu Arg Arg
3500 3505 3510
Thr Thr Ser Thr Glu His Pro Ser Thr Trp Ser Ser Thr Ala Ala
3515 3520 3525
Ser Asp Ser Trp Thr Val Thr Asp Met Thr Ser Asn Leu Lys Val
3530 3535 3540
Ala Arg Ser Pro Gly Thr Ile Ser Thr Met His Thr Thr Ser Phe
3545 3550 3555
Leu Ala Ser Ser Thr Glu Leu Asp Ser Met Ser Thr Pro His Gly
3560 3565 3570
Arg Ile Thr Val Ile Gly Thr Ser Leu Val Thr Pro Ser Ser Asp
3575 3580 3585
Ala Ser Ala Val Lys Thr Glu Thr Ser Thr Ser Glu Arg Thr Leu
3590 3595 3600
Ser Pro Ser Asp Thr Thr Ala Ser Thr Pro Ile Ser Thr Phe Ser
3605 3610 3615
Arg Val Gln Arg Met Ser Ile Ser Val Pro Asp Ile Leu Ser Thr
3620 3625 3630
Ser Trp Thr Pro Ser Ser Thr Glu Ala Glu Asp Val Pro Val Ser
3635 3640 3645
Met Val Ser Thr Asp His Ala Ser Thr Lys Thr Asp Pro Asn Thr
3650 3655 3660
Pro Leu Ser Thr Phe Leu Phe Asp Ser Leu Ser Thr Leu Asp Trp
3665 3670 3675

Asp Thr Gly Arg Ser Leu Ser Ser Ala Thr Ala Thr Thr Ser Ala
3680 3685 3690
Pro Gln Gly Ala Thr Thr Pro Gln Glu Leu Thr Leu Glu Thr Met
3695 3700 3705
Ile Ser Pro Ala Thr Ser Gln Leu Pro Phe Ser Ile Gly His Ile
3710 3715 3720
Thr Ser Ala Val Thr Pro Ala Ala Met Ala Arg Ser Ser Gly Val
3725 3730 3735
Thr Phe Ser Arg Pro Asp Pro Thr Ser Lys Lys Ala Glu Gln Thr
3740 3745 3750
Ser Thr Gln Leu Pro Thr Thr Thr Ser Ala His Pro Gly Gln Val
3755 3760 3765
Pro Arg Ser Ala Ala Thr Thr Leu Asp Val Ile Pro His Thr Ala
3770 3775 3780
Lys Thr Pro Asp Ala Thr Phe Gln Arg Gln Gly Gln Thr Ala Leu
3785 3790 3795
Thr Thr Glu Ala Arg Ala Thr Ser Asp Ser Trp Asn Glu Lys Glu
3800 3805 3810
Lys Ser Thr Pro Ser Ala Pro Trp Ile Thr Glu Met Met Asn Ser
3815 3820 3825
Val Ser Glu Asp Thr Ile Lys Glu Val Thr Ser Ser Ser Ser Val
3830 3835 3840
Leu Arg Thr Leu Asn Thr Leu Asp Ile Asn Leu Glu Ser Gly Thr
3845 3850 3855
Thr Ser Ser Pro Ser Trp Lys Ser Ser Pro Tyr Glu Arg Ile Ala
3860 3865 3870
Pro Ser Glu Ser Thr Thr Asp Lys Glu Ala Ile His Pro Ser Thr
3875 3880 3885
Asn Thr Val Glu Thr Thr Gly Trp Val Thr Ser Ser Glu His Ala
3890 3895 3900
Ser His Ser Thr Ile Pro Ala His Ser Ala Ser Ser Lys Leu Thr
3905 3910 3915
Ser Pro Val Val Thr Thr Ser Thr Arg Glu Gln Ala Ile Val Ser
3920 3925 3930
Met Ser Thr Thr Thr Trp Pro Glu Ser Thr Arg Ala Arg Thr Glu
3935 3940 3945
Pro Asn Ser Phe Leu Thr Ile Glu Leu Arg Asp Val Ser Pro Tyr
3950 3955 3960
Met Asp Thr Ser Ser Thr Thr Gln Thr Ser Ile Ile Ser Ser Pro
3965 3970 3975
Gly Ser Thr Ala Ile Thr Lys Gly Pro Arg Thr Glu Ile Thr Ser
3980 3985 3990
Ser Lys Arg Ile Ser Ser Ser Phe Leu Ala Gln Ser Met Arg Ser
3995 4000 4005
Ser Asp Ser Pro Ser Glu Ala Ile Thr Arg Leu Ser Asn Phe Pro
4010 4015 4020
Ala Met Thr Glu Ser Gly Gly Met Ile Leu Ala Met Gln Thr Ser
4025 4030 4035
Pro Pro Gly Ala Thr Ser Leu Ser Ala Pro Thr Leu Asp Thr Ser
4040 4045 4050

Ala Thr Ala Ser Trp Thr Gly Thr Pro Leu Ala Thr Thr Gln Arg
4055 4060 4065
Phe Thr Tyr Ser Glu Lys Thr Thr Leu Phe Ser Lys Gly Pro Glu
4070 4075 4080
Asp Thr Ser Gln Pro Ser Pro Pro Ser Val Glu Glu Thr Ser Ser
4085 4090 4095
Ser Ser Ser Leu Val Pro Ile His Ala Thr Thr Ser Pro Ser Asn
4100 4105 4110
Ile Leu Leu Thr Ser Gln Gly His Ser Pro Ser Ser Thr Pro Pro
4115 4120 4125
Val Thr Ser Val Phe Leu Ser Glu Thr Ser Gly Leu Gly Lys Thr
4130 4135 4140
Thr Asp Met Ser Arg Ile Ser Leu Glu Pro Gly Thr Ser Leu Pro
4145 4150 4155
Pro Asn Leu Ser Ser Thr Ala Gly Glu Ala Leu Ser Thr Tyr Glu
4160 4165 4170
Ala Ser Arg Asp Thr Lys Ala Ile His His Ser Ala Asp Thr Ala
4175 4180 4185
Val Thr Asn Met Glu Ala Thr Ser Ser Glu Tyr Ser Pro Ile Pro
4190 4195 4200
Gly His Thr Lys Pro Ser Lys Ala Thr Ser Pro Leu Val Thr Ser
4205 4210 4215
His Ile Met Gly Asp Ile Thr Ser Ser Thr Ser Val Phe Gly Ser
4220 4225 4230
Ser Glu Thr Thr Glu Ile Glu Thr Val Ser Ser Val Asn Gln Gly
4235 4240 4245
Leu Gln Glu Arg Ser Thr Ser Gln Val Ala Ser Ser Ala Thr Glu
4250 4255 4260
Thr Ser Thr Val Ile Thr His Val Ser Ser Gly Asp Ala Thr Thr
4265 4270 4275
His Val Thr Lys Thr Gln Ala Thr Phe Ser Ser Gly Thr Ser Ile
4280 4285 4290
Ser Ser Pro His Gln Phe Ile Thr Ser Thr Asn Thr Phe Thr Asp
4295 4300 4305
Val Ser Thr Asn Pro Ser Thr Ser Leu Ile Met Thr Glu Ser Ser
4310 4315 4320
Gly Val Thr Ile Thr Thr Gln Thr Gly Pro Thr Gly Ala Ala Thr
4325 4330 4335
Gln Gly Pro Tyr Leu Leu Asp Thr Ser Thr Met Pro Tyr Leu Thr
4340 4345 4350
Glu Thr Pro Leu Ala Val Thr Pro Asp Phe Met Gln Ser Glu Lys
4355 4360 4365
Thr Thr Leu Ile Ser Lys Gly Pro Lys Asp Val Ser Trp Thr Ser
4370 4375 4380
Pro Pro Ser Val Ala Glu Thr Ser Tyr Pro Ser Ser Leu Thr Pro
4385 4390 4395
Phe Leu Val Thr Thr Ile Pro Pro Ala Thr Ser Thr Leu Gln Gly
4400 4405 4410
Gln His Thr Ser Ser Pro Val Ser Ala Thr Ser Val Leu Thr Ser
4415 4420 4425

Gly Leu Val Lys Thr Thr Asp Met Leu Asn Thr Ser Met Glu Pro
4430 4435 4440
Val Thr Asn Ser Pro Gln Asn Leu Asn Asn Pro Ser Asn Glu Ile
4445 4450 4455
Leu Ala Thr Leu Ala Ala Thr Thr Asp Ile Glu Thr Ile His Pro
4460 4465 4470
Ser Ile Asn Lys Ala Val Thr Asn Met Gly Thr Ala Ser Ser Ala
4475 4480 4485
His Val Leu His Ser Thr Leu Pro Val Ser Ser Glu Pro Ser Thr
4490 4495 4500
Ala Thr Ser Pro Met Val Pro Ala Ser Ser Met Gly Asp Ala Leu
4505 4510 4515
Ala Ser Ile Ser Ile Pro Gly Ser Glu Thr Thr Asp Ile Glu Gly
4520 4525 4530
Glu Pro Thr Ser Ser Leu Thr Ala Gly Arg Lys Glu Asn Ser Thr
4535 4540 4545
Leu Gln Glu Met Asn Ser Thr Thr Glu Ser Asn Ile Ile Leu Ser
4550 4555 4560
Asn Val Ser Val Gly Ala Ile Thr Glu Ala Thr Lys Met Glu Val
4565 4570 4575
Pro Ser Phe Asp Ala Thr Phe Ile Pro Thr Pro Ala Gln Ser Thr
4580 4585 4590
Lys Phe Pro Asp Ile Phe Ser Val Ala Ser Ser Arg Leu Ser Asn
4595 4600 4605
Ser Pro Pro Met Thr Ile Ser Thr His Met Thr Thr Thr Gln Thr
4610 4615 4620
Gly Ser Ser Gly Ala Thr Ser Lys Ile Pro Leu Ala Leu Asp Thr
4625 4630 4635
Ser Thr Leu Glu Thr Ser Ala Gly Thr Pro Ser Val Val Thr Glu
4640 4645 4650
Gly Phe Ala His Ser Lys Ile Thr Thr Ala Met Asn Asn Asp Val
4655 4660 4665
Lys Asp Val Ser Gln Thr Asn Pro Pro Phe Gln Asp Glu Ala Ser
4670 4675 4680
Ser Pro Ser Ser Gln Ala Pro Val Leu Val Thr Thr Leu Pro Ser
4685 4690 4695
Ser Val Ala Phe Thr Pro Gln Trp His Ser Thr Ser Ser Pro Val
4700 4705 4710
Ser Met Ser Ser Val Leu Thr Ser Ser Leu Val Lys Thr Ala Gly
4715 4720 4725
Lys Val Asp Thr Ser Leu Glu Thr Val Thr Ser Ser Pro Gln Ser
4730 4735 4740
Met Ser Asn Thr Leu Asp Asp Ile Ser Val Thr Ser Ala Ala Thr
4745 4750 4755
Thr Asp Ile Glu Thr Thr His Pro Ser Ile Asn Thr Val Val Thr
4760 4765 4770
Asn Val Gly Thr Thr Gly Ser Ala Phe Glu Ser His Ser Thr Val
4775 4780 4785
Ser Ala Tyr Pro Glu Pro Ser Lys Val Thr Ser Pro Asn Val Thr
4790 4795 4800

Thr Ser Thr Met Glu Asp Thr Thr Ile Ser Arg Ser Ile Pro Lys
4805 4810 4815
Ser Ser Lys Thr Thr Arg Thr Glu Thr Glu Thr Thr Ser Ser Leu
4820 4825 4830
Thr Pro Lys Leu Arg Glu Thr Ser Ile Ser Gln Glu Ile Thr Ser
4835 4840 4845
Ser Thr Glu Thr Ser Thr Val Pro Tyr Lys Glu Leu Thr Gly Ala
4850 4855 4860
Thr Thr Glu Val Ser Arg Thr Asp Val Thr Ser Ser Ser Ser Thr
4865 4870 4875
Ser Phe Pro Gly Pro Asp Gln Ser Thr Val Ser Leu Asp Ile Ser
4880 4885 4890
Thr Glu Thr Asn Thr Arg Leu Ser Thr Ser Pro Ile Met Thr Glu
4895 4900 4905
Ser Ala Glu Ile Thr Ile Thr Thr Gln Thr Gly Pro His Gly Ala
4910 4915 4920
Thr Ser Gln Asp Thr Phe Thr Met Asp Pro Ser Asn Thr Thr Pro
4925 4930 4935
Gln Ala Gly Ile His Ser Ala Met Thr His Gly Phe Ser Gln Leu
4940 4945 4950
Asp Val Thr Thr Leu Met Ser Arg Ile Pro Gln Asp Val Ser Trp
4955 4960 4965
Thr Ser Pro Pro Ser Val Asp Lys Thr Ser Ser Pro Ser Ser Phe
4970 4975 4980
Leu Ser Ser Pro Ala Met Thr Thr Pro Ser Leu Ile Ser Ser Thr
4985 4990 4995
Leu Pro Glu Asp Lys Leu Ser Ser Pro Met Thr Ser Leu Leu Thr
5000 5005 5010
Ser Gly Leu Val Lys Ile Thr Asp Ile Leu Arg Thr Arg Leu Glu
5015 5020 5025
Pro Val Thr Ser Ser Leu Pro Asn Phe Ser Ser Thr Ser Asp Lys
5030 5035 5040
Ile Leu Ala Thr Ser Lys Asp Ser Lys Asp Thr Lys Glu Ile Phe
5045 5050 5055
Pro Ser Ile Asn Thr Glu Glu Thr Asn Val Lys Ala Asn Asn Ser
5060 5065 5070
Gly His Glu Ser His Ser Pro Ala Leu Ala Asp Ser Glu Thr Pro
5075 5080 5085
Lys Ala Thr Thr Gln Met Val Ile Thr Thr Thr Val Gly Asp Pro
5090 5095 5100
Ala Pro Ser Thr Ser Met Pro Val His Gly Ser Ser Glu Thr Thr
5105 5110 5115
Asn Ile Lys Arg Glu Pro Thr Tyr Phe Leu Thr Pro Arg Leu Arg
5120 5125 5130
Glu Thr Ser Thr Ser Gln Glu Ser Ser Phe Pro Thr Asp Thr Ser
5135 5140 5145
Phe Leu Leu Ser Lys Val Pro Thr Gly Thr Ile Thr Glu Val Ser
5150 5155 5160
Ser Thr Gly Val Asn Ser Ser Ser Lys Ile Ser Thr Pro Asp His
5165 5170 5175

Asp Lys Ser Thr Val Pro Pro Asp Thr Phe Thr Gly Glu Ile Pro
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Arg Val Phe Thr Ser Ser Ile Lys Thr Lys Ser Ala Glu Met Thr
5195 5200 5205
Ile Thr Thr Gln Ala Ser Pro Pro Glu Ser Ala Ser His Ser Thr
5210 5215 5220
Leu Pro Leu Asp Thr Ser Thr Thr Leu Ser Gln Gly Gly Thr His
5225 5230 5235
Ser Thr Val Thr Gln Gly Phe Pro Tyr Ser Glu Val Thr Thr Leu
5240 5245 5250
Met Gly Met Gly Pro Gly Asn Val Ser Trp Met Thr Thr Pro Pro
5255 5260 5265
Val Glu Glu Thr Ser Ser Val Ser Ser Leu Met Ser Ser Pro Ala
5270 5275 5280
Met Thr Ser Pro Ser Pro Val Ser Ser Thr Ser Pro Gln Ser Ile
5285 5290 5295
Pro Ser Ser Pro Leu Pro Val Thr Ala Leu Pro Thr Ser Val Leu
5300 5305 5310
Val Thr Thr Thr Asp Val Leu Gly Thr Thr Ser Pro Glu Ser Val
5315 5320 5325
Thr Ser Ser Pro Pro Asn Leu Ser Ser Ile Thr His Glu Arg Pro
5330 5335 5340
Ala Thr Tyr Lys Asp Thr Ala His Thr Glu Ala Ala Met His His
5345 5350 5355
Ser Thr Asn Thr Ala Val Thr Asn Val Gly Thr Ser Gly Ser Gly
5360 5365 5370
His Lys Ser Gln Ser Ser Val Leu Ala Asp Ser Glu Thr Ser Lys
5375 5380 5385
Ala Thr Pro Leu Met Ser Thr Thr Ser Thr Leu Gly Asp Thr Ser
5390 5395 5400
Val Ser Thr Ser Thr Pro Asn Ile Ser Gln Thr Asn Gln Ile Gln
5405 5410 5415
Thr Glu Pro Thr Ala Ser Leu Ser Pro Arg Leu Arg Glu Ser Ser
5420 5425 5430
Thr Ser Glu Lys Thr Ser Ser Thr Thr Glu Thr Asn Thr Ala Phe
5435 5440 5445
Ser Tyr Val Pro Thr Gly Ala Ile Thr Gln Ala Ser Arg Thr Glu
5450 5455 5460
Ile Ser Ser Ser Arg Thr Ser Ile Ser Asp Leu Asp Arg Pro Thr
5465 5470 5475
Ile Ala Pro Asp Ile Ser Thr Gly Met Ile Thr Arg Leu Phe Thr
5480 5485 5490
Ser Pro Ile Met Thr Lys Ser Ala Glu Met Thr Val Thr Thr Gln
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Thr Thr Thr Pro Gly Ala Thr Ser Gln Gly Ile Leu Pro Trp Asp
5510 5515 5520
Thr Ser Thr Thr Leu Phe Gln Gly Gly Thr His Ser Thr Val Ser
5525 5530 5535
Gln Gly Phe Pro His Ser Glu Ile Thr Thr Leu Arg Ser Arg Thr
5540 5545 5550

Pro Gly Asp Val Ser Trp Met Thr Thr Pro Pro Val Glu Glu Thr
5555 5560 5565
Ser Ser Gly Phe Ser Leu Met Ser Pro Ser Met Thr Ser Pro Ser
5570 5575 5580
Pro Val Ser Ser Thr Ser Pro Glu Ser Ile Pro Ser Ser Pro Leu
5585 5590 5595
Pro Val Thr Ala Leu Leu Thr Ser Val Leu Val Thr Thr Thr Asn
5600 5605 5610
Val Leu Gly Thr Thr Ser Pro Glu Pro Val Thr Ser Ser Pro Pro
5615 5620 5625
Asn Leu Ser Ser Pro Thr Gln Glu Arg Leu Thr Thr Tyr Lys Asp
5630 5635 5640
Thr Ala His Thr Glu Ala Met His Ala Ser Met His Thr Asn Thr
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Ala Val Ala Asn Val Gly Thr Ser Ile Ser Gly His Glu Ser Gln
5660 5665 5670
Ser Ser Val Pro Ala Asp Ser His Thr Ser Lys Ala Thr Ser Pro
5675 5680 5685
Met Gly Ile Thr Phe Ala Met Gly Asp Thr Ser Val Ser Thr Ser
5690 5695 5700
Thr Pro Ala Phe Phe Glu Thr Arg Ile Gln Thr Glu Ser Thr Ser
5705 5710 5715
Ser Leu Ile Pro Gly Leu Arg Asp Thr Arg Thr Ser Glu Glu Ile
5720 5725 5730
Asn Thr Val Thr Glu Thr Ser Thr Val Leu Ser Glu Val Pro Thr
5735 5740 5745
Thr Thr Thr Thr Glu Val Ser Arg Thr Glu Val Ile Thr Ser Ser
5750 5755 5760
Arg Thr Thr Ile Ser Gly Pro Asp His Ser Lys Met Ser Pro Tyr
5765 5770 5775
Ile Ser Thr Glu Thr Ile Thr Arg Leu Ser Thr Phe Pro Phe Val
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Thr Gly Ser Thr Glu Met Ala Ile Thr Asn Gln Thr Gly Pro Ile
5795 5800 5805
Gly Thr Ile Ser Gln Ala Thr Leu Thr Leu Asp Thr Ser Ser Thr
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Ala Ser Trp Glu Gly Thr His Ser Pro Val Thr Gln Arg Phe Pro
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His Ser Glu Glu Thr Thr Thr Met Ser Arg Ser Thr Lys Gly Val
5840 5845 5850
Ser Trp Gln Ser Pro Pro Ser Val Glu Glu Thr Ser Ser Pro Ser
5855 5860 5865
Ser Pro Val Pro Leu Pro Ala Ile Thr Ser His Ser Ser Leu Tyr
5870 5875 5880
Ser Ala Val Ser Gly Ser Ser Pro Thr Ser Ala Leu Pro Val Thr
5885 5890 5895
Ser Leu Leu Thr Ser Gly Arg Arg Lys Thr Ile Asp Met Leu Asp
5900 5905 5910
Thr His Ser Glu Leu Val Thr Ser Ser Leu Pro Ser Ala Ser Ser
5915 5920 5925

Phe Ser Gly Glu Ile Leu Thr Ser Glu Ala Ser Thr Asn Thr Glu
5930 5935 5940
Thr Ile His Phe Ser Glu Asn Thr Ala Glu Thr Asn Met Gly Thr
5945 5950 5955
Thr Asn Ser Met His Lys Leu His Ser Ser Val Ser Ile His Ser
5960 5965 5970
Gln Pro Ser Gly His Thr Pro Pro Lys Val Thr Gly Ser Met Met
5975 5980 5985
Glu Asp Ala Ile Val Ser Thr Ser Thr Pro Gly Ser Pro Glu Thr
5990 5995 6000
Lys Asn Val Asp Arg Asp Ser Thr Ser Pro Leu Thr Pro Glu Leu
6005 6010 6015
Lys Glu Asp Ser Thr Ala Leu Val Met Asn Ser Thr Thr Glu Ser
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Asn Thr Val Phe Ser Ser Val Ser Leu Asp Ala Ala Thr Glu Val
6035 6040 6045
Ser Arg Ala Glu Val Thr Tyr Tyr Asp Pro Thr Phe Met Pro Ala
6050 6055 6060
Ser Ala Gln Ser Thr Lys Ser Pro Asp Ile Ser Pro Glu Ala Ser
6065 6070 6075
Ser Ser His Ser Asn Ser Pro Pro Leu Thr Ile Ser Thr His Lys
6080 6085 6090
Thr Ile Ala Thr Gln Thr Gly Pro Ser Gly Val Thr Ser Leu Gly
6095 6100 6105
Gln Leu Thr Leu Asp Thr Ser Thr Ile Ala Thr Ser Ala Gly Thr
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Pro Ser Ala Arg Thr Gln Asp Phe Val Asp Ser Glu Thr Thr Ser
6125 6130 6135
Val Met Asn Asn Asp Leu Asn Asp Val Leu Lys Thr Ser Pro Phe
6140 6145 6150
Ser Ala Glu Glu Ala Asn Ser Leu Ser Ser Gln Ala Pro Leu Leu
6155 6160 6165
Val Thr Thr Ser Pro Ser Pro Val Thr Ser Thr Leu Gln Glu His
6170 6175 6180
Ser Thr Ser Ser Leu Val Ser Val Thr Ser Val Pro Thr Pro Thr
6185 6190 6195
Leu Ala Lys Ile Thr Asp Met Asp Thr Asn Leu Glu Pro Val Thr
6200 6205 6210
Arg Ser Pro Gln Asn Leu Arg Asn Thr Leu Ala Thr Ser Glu Ala
6215 6220 6225
Thr Thr Asp Thr His Thr Met His Pro Ser Ile Asn Thr Ala Val
6230 6235 6240
Ala Asn Val Gly Thr Thr Ser Ser Pro Asn Glu Phe Tyr Phe Thr
6245 6250 6255
Val Ser Pro Asp Ser Asp Pro Tyr Lys Ala Thr Ser Ala Val Val
6260 6265 6270
Ile Thr Ser Thr Ser Gly Asp Ser Ile Val Ser Thr Ser Met Pro
6275 6280 6285
Arg Ser Ser Ala Met Lys Lys Ile Glu Ser Glu Thr Thr Phe Ser
6290 6295 6300

Leu Ile Phe Arg Leu Arg Glu Thr Ser Thr Ser Gln Lys Ile Gly
6305 6310 6315
Ser Ser Ser Asp Thr Ser Thr Val Phe Asp Lys Ala Phe Thr Ala
6320 6325 6330
Ala Thr Thr Glu Val Ser Arg Thr Glu Leu Thr Ser Ser Ser Arg
6335 6340 6345
Thr Ser Ile Gln Gly Thr Glu Lys Pro Thr Met Ser Pro Asp Thr
6350 6355 6360
Ser Thr Arg Ser Val Thr Met Leu Ser Thr Phe Ala Gly Leu Thr
6365 6370 6375
Lys Ser Glu Glu Arg Thr Ile Ala Thr Gln Thr Gly Pro His Arg
6380 6385 6390
Ala Thr Ser Gln Gly Thr Leu Thr Trp Asp Thr Ser Ile Thr Thr
6395 6400 6405
Ser Gln Ala Gly Thr His Ser Ala Met Thr His Gly Phe Ser Gln
6410 6415 6420
Leu Asp Leu Ser Thr Leu Thr Ser Arg Val Pro Glu Tyr Ile Ser
6425 6430 6435
Gly Thr Ser Pro Pro Ser Val Glu Lys Thr Ser Ser Ser Ser Ser
6440 6445 6450
Leu Leu Ser Leu Pro Ala Ile Thr Ser Pro Ser Pro Val Pro Thr
6455 6460 6465
Thr Leu Pro Glu Ser Arg Pro Ser Ser Pro Val His Leu Thr Ser
6470 6475 6480
Leu Pro Thr Ser Gly Leu Val Lys Thr Thr Asp Met Leu Ala Ser
6485 6490 6495
Val Ala Ser Leu Pro Pro Asn Leu Gly Ser Thr Ser His Lys Ile
6500 6505 6510
Pro Thr Thr Ser Glu Asp Ile Lys Asp Thr Glu Lys Met Tyr Pro
6515 6520 6525
Ser Thr Asn Ile Ala Val Thr Asn Val Gly Thr Thr Thr Ser Glu
6530 6535 6540
Lys Glu Ser Tyr Ser Ser Val Pro Ala Tyr Ser Glu Pro Pro Lys
6545 6550 6555
Val Thr Ser Pro Met Val Thr Ser Phe Asn Ile Arg Asp Thr Ile
6560 6565 6570
Val Ser Thr Ser Met Pro Gly Ser Ser Glu Ile Thr Arg Ile Glu
6575 6580 6585
Met Glu Ser Thr Phe Ser Leu Ala His Gly Leu Lys Gly Thr Ser
6590 6595 6600
Thr Ser Gln Asp Pro Ile Val Ser Thr Glu Lys Ser Ala Val Leu
6605 6610 6615
His Lys Leu Thr Thr Gly Ala Thr Glu Thr Ser Arg Thr Glu Val
6620 6625 6630
Ala Ser Ser Arg Arg Thr Ser Ile Pro Gly Pro Asp His Ser Thr
6635 6640 6645
Glu Ser Pro Asp Ile Ser Thr Glu Val Ile Pro Ser Leu Pro Ile
6650 6655 6660
Ser Leu Gly Ile Thr Glu Ser Ser Asn Met Thr Ile Ile Thr Arg
6665 6670 6675

Thr Gly Pro Pro Leu Gly Ser Thr Ser Gln Gly Thr Phe Thr Leu
6680 6685 6690
Asp Thr Pro Thr Thr Ser Ser Arg Ala Gly Thr His Ser Met Ala
6695 6700 6705
Thr Gln Glu Phe Pro His Ser Glu Met Thr Thr Val Met Asn Lys
6710 6715 6720
Asp Pro Glu Ile Leu Ser Trp Thr Ile Pro Pro Ser Ile Glu Lys
6725 6730 6735
Thr Ser Phe Ser Ser Ser Leu Met Pro Ser Pro Ala Met Thr Ser
6740 6745 6750
Pro Pro Val Ser Ser Thr Leu Pro Lys Thr Ile His Thr Thr Pro
6755 6760 6765
Ser Pro Met Thr Ser Leu Leu Thr Pro Ser Leu Val Met Thr Thr
6770 6775 6780
Asp Thr Leu Gly Thr Ser Pro Glu Pro Thr Thr Ser Ser Pro Pro
6785 6790 6795
Asn Leu Ser Ser Thr Ser His Glu Ile Leu Thr Thr Asp Glu Asp
6800 6805 6810
Thr Thr Ala Ile Glu Ala Met His Pro Ser Thr Ser Thr Ala Ala
6815 6820 6825
Thr Asn Val Glu Thr Thr Ser Ser Gly His Gly Ser Gln Ser Ser
6830 6835 6840
Val Leu Ala Asp Ser Glu Lys Thr Lys Ala Thr Ala Pro Met Asp
6845 6850 6855
Thr Thr Ser Thr Met Gly His Thr Thr Val Ser Thr Ser Met Ser
6860 6865 6870
Val Ser Ser Glu Thr Thr Lys Ile Lys Arg Glu Ser Thr Tyr Ser
6875 6880 6885
Leu Thr Pro Gly Leu Arg Glu Thr Ser Ile Ser Gln Asn Ala Ser
6890 6895 6900
Phe Ser Thr Asp Thr Ser Ile Val Leu Ser Glu Val Pro Thr Gly
6905 6910 6915
Thr Thr Ala Glu Val Ser Arg Thr Glu Val Thr Ser Ser Gly Arg
6920 6925 6930
Thr Ser Ile Pro Gly Pro Ser Gln Ser Thr Val Leu Pro Glu Ile
6935 6940 6945
Ser Thr Arg Thr Met Thr Arg Leu Phe Ala Ser Pro Thr Met Thr
6950 6955 6960
Glu Ser Ala Glu Met Thr Ile Pro Thr Gln Thr Gly Pro Ser Gly
6965 6970 6975
Ser Thr Ser Gln Asp Thr Leu Thr Leu Asp Thr Ser Thr Thr Lys
6980 6985 6990
Ser Gln Ala Lys Thr His Ser Thr Leu Thr Gln Arg Phe Pro His
6995 7000 7005
Ser Glu Met Thr Thr Leu Met Ser Arg Gly Pro Gly Asp Met Ser
7010 7015 7020
Trp Gln Ser Ser Pro Ser Leu Glu Asn Pro Ser Ser Leu Pro Ser
7025 7030 7035
Leu Leu Ser Leu Pro Ala Thr Thr Ser Pro Pro Pro Ile Ser Ser
7040 7045 7050

Thr Leu Pro Val Thr Ile Ser Ser Ser Pro Leu Pro Val Thr Ser
7055 7060 7065
Leu Leu Thr Ser Ser Pro Val Thr Thr Thr Asp Met Leu His Thr
7070 7075 7080
Ser Pro Glu Leu Val Thr Ser Ser Pro Pro Lys Leu Ser His Thr
7085 7090 7095
Ser Asp Glu Arg Leu Thr Thr Gly Lys Asp Thr Thr Asn Thr Glu
7100 7105 7110
Ala Val His Pro Ser Thr Asn Thr Ala Ala Ser Asn Val Glu Ile
7115 7120 7125
Pro Ser Ser Gly His Glu Ser Pro Ser Ser Ala Leu Ala Asp Ser
7130 7135 7140
Glu Thr Ser Lys Ala Thr Ser Pro Met Phe Ile Thr Ser Thr Gln
7145 7150 7155
Glu Asp Thr Thr Val Ala Ile Ser Thr Pro His Phe Leu Glu Thr
7160 7165 7170
Ser Arg Ile Gln Lys Glu Ser Ile Ser Ser Leu Ser Pro Lys Leu
7175 7180 7185
Arg Glu Thr Gly Ser Ser Val Glu Thr Ser Ser Ala Ile Glu Thr
7190 7195 7200
Ser Ala Val Leu Ser Glu Val Ser Ile Gly Ala Thr Thr Glu Ile
7205 7210 7215
Ser Arg Thr Glu Val Thr Ser Ser Ser Arg Thr Ser Ile Ser Gly
7220 7225 7230
Ser Ala Glu Ser Thr Met Leu Pro Glu Ile Ser Thr Thr Arg Lys
7235 7240 7245
Ile Ile Lys Phe Pro Thr Ser Pro Ile Leu Ala Glu Ser Ser Glu
7250 7255 7260
Met Thr Ile Lys Thr Gln Thr Ser Pro Pro Gly Ser Thr Ser Glu
7265 7270 7275
Ser Thr Phe Thr Leu Asp Thr Ser Thr Thr Pro Ser Leu Val Ile
7280 7285 7290
Thr His Ser Thr Met Thr Gln Arg Leu Pro His Ser Glu Ile Thr
7295 7300 7305
Thr Leu Val Ser Arg Gly Ala Gly Asp Val Pro Arg Pro Ser Ser
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Leu Pro Val Glu Glu Thr Ser Pro Pro Ser Ser Gln Leu Ser Leu
7325 7330 7335
Ser Ala Met Ile Ser Pro Ser Pro Val Ser Ser Thr Leu Pro Ala
7340 7345 7350
Ser Ser His Ser Ser Ser Ala Ser Val Thr Ser Leu Leu Thr Pro
7355 7360 7365
Gly Gln Val Lys Thr Thr Glu Val Leu Asp Ala Ser Ala Glu Pro
7370 7375 7380
Glu Thr Ser Ser Pro Pro Ser Leu Ser Ser Thr Ser Val Glu Ile
7385 7390 7395
Leu Ala Thr Ser Glu Val Thr Thr Asp Thr Glu Lys Ile His Pro
7400 7405 7410
Phe Ser Asn Thr Ala Val Thr Lys Val Gly Thr Ser Ser Ser Gly
7415 7420 7425

His Glu Ser Pro Ser Ser Val Leu Pro Asp Ser Glu Thr Thr Lys
7430 7435 7440
Ala Thr Ser Ala Met Gly Thr Ile Ser Ile Met Gly Asp Thr Ser
7445 7450 7455
Val Ser Thr Leu Thr Pro Ala Leu Ser Asn Thr Arg Lys Ile Gln
7460 7465 7470
Ser Glu Pro Ala Ser Ser Leu Thr Thr Arg Leu Arg Glu Thr Ser
7475 7480 7485
Thr Ser Glu Glu Thr Ser Leu Ala Thr Glu Ala Asn Thr Val Leu
7490 7495 7500
Ser Lys Val Ser Thr Gly Ala Thr Thr Glu Val Ser Arg Thr Glu
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Ala Ile Ser Phe Ser Arg Thr Ser Met Ser Gly Pro Glu Gln Ser
7520 7525 7530
Thr Met Ser Gln Asp Ile Ser Ile Gly Thr Ile Pro Arg Ile Ser
7535 7540 7545
Ala Ser Ser Val Leu Thr Glu Ser Ala Lys Met Thr Ile Thr Thr
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Gln Thr Gly Pro Ser Glu Ser Thr Leu Glu Ser Thr Leu Asn Leu
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Asn Thr Ala Thr Thr Pro Ser Trp Val Glu Thr His Ser Ile Val
7580 7585 7590
Ile Gln Gly Phe Pro His Pro Glu Met Thr Thr Ser Met Gly Arg
7595 7600 7605
Gly Pro Gly Gly Val Ser Trp Pro Ser Pro Pro Phe Val Lys Glu
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Pro His Pro Val Ser Thr Thr Phe Leu Ala His Ile Pro Pro Ser
7640 7645 7650
Pro Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Pro Ala Thr Thr
7655 7660 7665
Thr Asp Ile Leu Gly Thr Ser Thr Glu Pro Gly Thr Ser Ser Ser
7670 7675 7680
Ser Ser Leu Ser Thr Thr Ser His Glu Arg Leu Thr Thr Tyr Lys
7685 7690 7695
Asp Thr Ala His Thr Glu Ala Val His Pro Ser Thr Asn Thr Gly
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Gly Thr Asn Val Ala Thr Thr Ser Ser Gly Tyr Lys Ser Gln Ser
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Gly Asp Thr Ser Val Leu Thr Ser Thr Pro Ala Phe Leu Glu Thr
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Arg Arg Ile Gln Thr Glu Leu Ala Ser Ser Leu Thr Pro Gly Leu
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Arg Glu Ser Ser Gly Ser Glu Gly Thr Ser Ser Gly Thr Lys Met
7775 7780 7785
Ser Thr Val Leu Ser Lys Val Pro Thr Gly Ala Thr Thr Glu Ile
7790 7795 7800

Ser Lys Glu Asp Val Thr Ser Ile Pro Gly Pro Ala Gln Ser Thr
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Ile Ser Pro Asp Ile Ser Thr Arg Thr Val Ser Trp Phe Ser Thr
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Ser Pro Val Met Thr Glu Ser Ala Glu Ile Thr Met Asn Thr His
7835 7840 7845
Thr Ser Pro Leu Gly Ala Thr Thr Gln Gly Thr Ser Thr Leu Asp
7850 7855 7860
Thr Ser Ser Thr Thr Ser Leu Thr Met Thr His Ser Thr Ile Ser
7865 7870 7875
Gln Gly Phe Ser His Ser Gln Met Ser Thr Leu Met Arg Arg Gly
7880 7885 7890
Pro Glu Asp Val Ser Trp Met Ser Pro Pro Leu Leu Glu Lys Thr
7895 7900 7905
Arg Pro Ser Phe Ser Leu Met Ser Ser Pro Ala Thr Thr Ser Pro
7910 7915 7920
Ser Pro Val Ser Ser Thr Leu Pro Glu Ser Ile Ser Ser Ser Pro
7925 7930 7935
Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Leu Ala Lys Thr Thr
7940 7945 7950
Asp Met Leu His Lys Ser Ser Glu Pro Val Thr Asn Ser Pro Ala
7955 7960 7965
Asn Leu Ser Ser Thr Ser Val Glu Ile Leu Ala Thr Ser Glu Val
7970 7975 7980
Thr Thr Asp Thr Glu Lys Thr His Pro Ser Ser Asn Arg Thr Val
7985 7990 7995
Thr Asp Val Gly Thr Ser Ser Ser Gly His Glu Ser Thr Ser Phe
8000 8005 8010
Val Leu Ala Asp Ser Gln Thr Ser Lys Val Thr Ser Pro Met Val
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Ile Thr Ser Thr Met Glu Asp Thr Ser Val Ser Thr Ser Thr Pro
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Gly Phe Phe Glu Thr Ser Arg Ile Gln Thr Glu Pro Thr Ser Ser
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Leu Thr Leu Gly Leu Arg Lys Thr Ser Ser Ser Glu Gly Thr Ser
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Leu Ala Thr Glu Met Ser Thr Val Leu Ser Gly Val Pro Thr Gly
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Ala Thr Ala Glu Val Ser Arg Thr Glu Val Thr Ser Ser Ser Arg
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Thr Ser Ile Ser Gly Phe Ala Gln Leu Thr Val Ser Pro Glu Thr
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Ser Thr Pro Glu Ser Thr His Thr Val Asp Ile Ser Thr Thr Pro
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Asn Trp Val Glu Thr His Ser Thr Val Thr Gln Arg Phe Ser His
8165 8170 8175

Ser Glu Met Thr Thr Leu Val Ser Arg Ser Pro Gly Asp Met Leu
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Trp Pro Ser Gln Ser Ser Val Glu Glu Thr Ser Ser Ala Ser Ser
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Leu Leu Ser Leu Pro Ala Thr Thr Ser Pro Ser Pro Val Ser Ser
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Leu Leu Asn Pro Gly Leu Val Ile Thr Thr Asp Arg Met Gly Ile
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Ser His Glu Arg Leu Thr Thr Leu Glu Asp Thr Val Asp Thr Glu
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Asp Met Gln Pro Ser Thr His Thr Ala Val Thr Asn Val Arg Thr
8285 8290 8295
Ser Ile Ser Gly His Glu Ser Gln Ser Ser Val Leu Ser Asp Ser
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Glu Thr Pro Lys Ala Thr Ser Pro Met Gly Thr Thr Tyr Thr Met
8315 8320 8325
Gly Glu Thr Ser Val Ser Ile Ser Thr Ser Asp Phe Phe Glu Thr
8330 8335 8340
Ser Arg Ile Gln Ile Glu Pro Thr Ser Ser Leu Thr Ser Gly Leu
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Arg Glu Thr Ser Ser Ser Glu Arg Ile Ser Ser Ala Thr Glu Gly
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Pro Asp Gln Phe Thr Ile Ser Pro Asp Ile Ser Thr Glu Ala Ile
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Thr Arg Leu Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ser
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Ala Ile Thr Ile Glu Thr Gly Ser Pro Gly Ala Thr Ser Glu Gly
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Thr Leu Thr Leu Asp Thr Ser Thr Thr Thr Phe Trp Ser Gly Thr
8450 8455 8460
His Ser Thr Ala Ser Pro Gly Phe Ser His Ser Glu Met Thr Thr
8465 8470 8475
Leu Met Ser Arg Thr Pro Gly Asp Val Pro Trp Pro Ser Leu Pro
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Ser Val Glu Glu Ala Ser Ser Val Ser Ser Ser Leu Ser Ser Pro
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Ala Met Thr Ser Thr Ser Phe Phe Ser Thr Leu Pro Glu Ser Ile
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Ser Ser Ser Pro His Pro Val Thr Ala Leu Leu Thr Leu Gly Pro
8525 8530 8535
Val Lys Thr Thr Asp Met Leu Arg Thr Ser Ser Glu Pro Glu Thr
8540 8545 8550

Ser Ser Pro Pro Asn Leu Ser Ser Thr Ser Ala Glu Ile Leu Ala
8555 8560 8565
Thr Ser Glu Val Thr Lys Asp Arg Glu Lys Ile His Pro Ser Ser
8570 8575 8580
Asn Thr Pro Val Val Asn Val Gly Thr Val Ile Tyr Lys His Leu
8585 8590 8595
Ser Pro Ser Ser Val Leu Ala Asp Leu Val Thr Thr Lys Pro Thr
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Ser Pro Met Ala Thr Thr Ser Thr Leu Gly Asn Thr Ser Val Ser
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Thr Gly Ala Thr Thr Lys Val Ser Arg Thr Glu Ala Leu Ser Leu
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Gly Arg Thr Ser Thr Pro Gly Pro Ala Gln Ser Thr Ile Ser Pro
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Glu Ile Ser Thr Glu Thr Ile Thr Arg Ile Ser Thr Pro Leu Thr
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Thr Thr Gly Ser Ala Glu Met Thr Ile Thr Pro Lys Thr Gly His
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Ser Gly Ala Ser Ser Gln Gly Thr Phe Thr Leu Asp Thr Ser Ser
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Arg Ala Ser Trp Pro Gly Thr His Ser Ala Ala Thr His Arg Ser
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Pro His Ser Gly Met Thr Thr Pro Met Ser Arg Gly Pro Glu Asp
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Val Ser Trp Pro Ser Arg Pro Ser Val Glu Lys Thr Ser Pro Pro
8780 8785 8790
Ser Ser Leu Val Ser Leu Ser Ala Val Thr Ser Pro Ser Pro Leu
8795 8800 8805
Tyr Ser Thr Pro Ser Glu Ser Ser His Ser Ser Pro Leu Arg Val
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Thr Ser Leu Phe Thr Pro Val Met Met Lys Thr Thr Asp Met Leu
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Asp Thr Ser Leu Glu Pro Val Thr Thr Ser Pro Pro Ser Met Asn
8840 8845 8850
Ile Thr Ser Asp Glu Ser Leu Ala Thr Ser Lys Ala Thr Met Glu
8855 8860 8865
Thr Glu Ala Ile Gln Leu Ser Glu Asn Thr Ala Val Thr Gln Met
8870 8875 8880
Gly Thr Ile Ser Ala Arg Gln Glu Phe Tyr Ser Ser Tyr Pro Gly
8885 8890 8895
Leu Pro Glu Pro Ser Lys Val Thr Ser Pro Val Val Thr Ser Ser
8900 8905 8910
Thr Ile Lys Asp Ile Val Ser Thr Thr Ile Pro Ala Ser Ser Glu
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Ile Thr Arg Ile Glu Met Glu Ser Thr Ser Thr Leu Thr Pro Thr
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Pro Arg Glu Thr Ser Thr Ser Gln Glu Ile His Ser Ala Thr Lys
8945 8950 8955
Pro Ser Thr Val Pro Tyr Lys Ala Leu Thr Ser Ala Thr Ile Glu
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Asp Ser Met Thr Gln Val Met Ser Ser Ser Arg Gly Pro Ser Pro
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Asp Gln Ser Thr Met Ser Gln Asp Ile Ser Thr Glu Val Ile Thr
8990 8995 9000
Arg Leu Ser Thr Ser Pro Ile Lys Thr Glu Ser Thr Glu Met Thr
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Ile Thr Thr Gln Thr Gly Ser Pro Gly Ala Thr Ser Arg Gly Thr
9020 9025 9030
Leu Thr Leu Asp Thr Ser Thr Thr Phe Met Ser Gly Thr His Ser
9035 9040 9045
Thr Ala Ser Gln Gly Phe Ser His Ser Gln Met Thr Ala Leu Met
9050 9055 9060
Ser Arg Thr Pro Gly Asp Val Pro Trp Leu Ser His Pro Ser Val
9065 9070 9075
Glu Glu Ala Ser Ser Ala Ser Phe Ser Leu Ser Ser Pro Val Met
9080 9085 9090
Thr Ser Ser Ser Pro Val Ser Ser Thr Leu Pro Asp Ser Ile His
9095 9100 9105
Ser Ser Ser Leu Pro Val Thr Ser Leu Leu Thr Ser Gly Leu Val
9110 9115 9120
Lys Thr Thr Glu Leu Leu Gly Thr Ser Ser Glu Pro Glu Thr Ser
9125 9130 9135
Ser Pro Pro Asn Leu Ser Ser Thr Ser Ala Glu Ile Leu Ala Ile
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Thr Glu Val Thr Thr Asp Thr Glu Lys Leu Glu Met Thr Asn Val
9155 9160 9165
Val Thr Ser Gly Tyr Thr His Glu Ser Pro Ser Ser Val Leu Ala
9170 9175 9180
Asp Ser Val Thr Thr Lys Ala Thr Ser Ser Met Gly Ile Thr Tyr
9185 9190 9195
Pro Thr Gly Asp Thr Asn Val Leu Thr Ser Thr Pro Ala Phe Ser
9200 9205 9210
Asp Thr Ser Arg Ile Gln Thr Lys Ser Lys Leu Ser Leu Thr Pro
9215 9220 9225
Gly Leu Met Glu Thr Ser Ile Ser Glu Glu Thr Ser Ser Ala Thr
9230 9235 9240
Glu Lys Ser Thr Val Leu Ser Ser Val Pro Thr Gly Ala Thr Thr
9245 9250 9255
Glu Val Ser Arg Thr Glu Ala Ile Ser Ser Ser Arg Thr Ser Ile
9260 9265 9270
Pro Gly Pro Ala Gln Ser Thr Met Ser Ser Asp Thr Ser Met Glu
9275 9280 9285
Thr Ile Thr Arg Ile Ser Thr Pro Leu Thr Arg Lys Glu Ser Thr
9290 9295 9300

Asp Met Ala Ile Thr Pro Lys Thr Gly Pro Ser Gly Ala Thr Ser
9305 9310 9315
Gln Gly Thr Phe Thr Leu Asp Ser Ser Ser Thr Ala Ser Trp Pro
9320 9325 9330
Gly Thr His Ser Ala Thr Thr Gln Arg Phe Pro Gln Ser Val Val
9335 9340 9345
Thr Thr Pro Met Ser Arg Gly Pro Glu Asp Val Ser Trp Pro Ser
9350 9355 9360
Pro Leu Ser Val Glu Lys Asn Ser Pro Pro Ser Ser Leu Val Ser
9365 9370 9375
Ser Ser Ser Val Thr Ser Pro Ser Pro Leu Tyr Ser Thr Pro Ser
9380 9385 9390
Gly Ser Ser His Ser Ser Pro Val Pro Val Thr Ser Leu Phe Thr
9395 9400 9405
Ser Ile Met Met Lys Ala Thr Asp Met Leu Asp Ala Ser Leu Glu
9410 9415 9420
Pro Glu Thr Thr Ser Ala Pro Asn Met Asn Ile Thr Ser Asp Glu
9425 9430 9435
Ser Leu Ala Ala Ser Lys Ala Thr Thr Glu Thr Glu Ala Ile His
9440 9445 9450
Val Phe Glu Asn Thr Ala Ala Ser His Val Glu Thr Thr Ser Ala
9455 9460 9465
Thr Glu Glu Leu Tyr Ser Ser Ser Pro Gly Phe Ser Glu Pro Thr
9470 9475 9480
Lys Val Ile Ser Pro Val Val Thr Ser Ser Ser Ile Arg Asp Asn
9485 9490 9495
Met Val Ser Thr Thr Met Pro Gly Ser Ser Gly Ile Thr Arg Ile
9500 9505 9510
Glu Ile Glu Ser Met Ser Ser Leu Thr Pro Gly Leu Arg Glu Thr
9515 9520 9525
Arg Thr Ser Gln Asp Ile Thr Ser Ser Thr Glu Thr Ser Thr Val
9530 9535 9540
Leu Tyr Lys Met Pro Ser Gly Ala Thr Pro Glu Val Ser Arg Thr
9545 9550 9555
Glu Val Met Pro Ser Ser Arg Thr Ser Ile Pro Gly Pro Ala Gln
9560 9565 9570
Ser Thr Met Ser Leu Asp Ile Ser Asp Glu Val Val Thr Arg Leu
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Ser Thr Ser Pro Ile Met Thr Glu Ser Ala Glu Ile Thr Ile Thr
9590 9595 9600
Thr Gln Thr Gly Tyr Ser Leu Ala Thr Ser Gln Val Thr Leu Pro
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Ser Gln Gly Leu Ser His Ser Glu Met Thr Asn Leu Met Ser Arg
9635 9640 9645
Gly Pro Glu Ser Leu Ser Trp Thr Ser Pro Arg Phe Val Glu Thr
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Thr Arg Ser Ser Ser Ser Leu Thr Ser Leu Pro Leu Thr Thr Ser
9665 9670 9675

Leu Ser Pro Val Ser Ser Thr Leu Leu Asp Ser Ser Pro Ser Ser
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Pro Leu Pro Val Thr Ser Leu Ile Leu Pro Gly Leu Val Lys Thr
9695 9700 9705
Thr Glu Val Leu Asp Thr Ser Ser Glu Pro Lys Thr Ser Ser Ser
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Pro Asn Leu Ser Ser Thr Ser Val Glu Ile Pro Ala Thr Ser Glu
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Ile Met Thr Asp Thr Glu Lys Ile His Pro Ser Ser Asn Thr Ala
9740 9745 9750
Val Ala Lys Val Arg Thr Ser Ser Ser Val His Glu Ser His Ser
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Ser Val Leu Ala Asp Ser Glu Thr Thr Ile Thr Ile Pro Ser Met
9770 9775 9780
Gly Ile Thr Ser Ala Val Asp Asp Thr Thr Val Phe Thr Ser Asn
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Pro Ala Phe Ser Glu Thr Arg Arg Ile Pro Thr Glu Pro Thr Phe
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Ser Leu Thr Pro Gly Phe Arg Glu Thr Ser Thr Ser Glu Glu Thr
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9830 9835 9840
Ser Ala Thr Thr Glu Val Ser Met Thr Glu Ile Met Ser Ser Asn
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Arg Ile His Ile Pro Asp Ser Asp Gln Ser Thr Met Ser Pro Asp
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Ile Ile Thr Glu Val Ile Thr Arg Leu Ser Ser Ser Ser Met Met
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Ser Glu Ser Thr Gln Met Thr Ile Thr Thr Gln Lys Ser Ser Pro
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Gly Ala Thr Ala Gln Ser Thr Leu Thr Leu Ala Thr Thr Thr Ala
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Pro Leu Ala Arg Thr His Ser Thr Val Pro Pro Arg Phe Leu His
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Ser Glu Met Thr Thr Leu Met Ser Arg Ser Pro Glu Asn Pro Ser
9935 9940 9945
Trp Lys Ser Ser Leu Phe Val Glu Lys Thr Ser Ser Ser Ser Ser
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Leu Leu Ser Leu Pro Val Thr Thr Ser Pro Ser Val Ser Ser Thr
9965 9970 9975
Leu Pro Gln Ser Ile Pro Ser Ser Ser Phe Ser Val Thr Ser Leu
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Leu Thr Pro Gly Met Val Lys Thr Thr Asp Thr Ser Thr Glu Pro
9995 10000 10005
Gly Thr Ser Leu Ser Pro Asn Leu Ser Gly Thr Ser Val Glu Ile
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Leu Ala Ala Ser Glu Val Thr Thr Asp Thr Glu Lys Ile His Pro
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Ser Ser Ser Met Ala Val Thr Asn Val Gly Thr Thr Ser Ser Gly
10040 10045 10050

His Glu Leu Tyr Ser Ser Val Ser Ile His Ser Glu Pro Ser Lys
10055 10060 10065
Ala Thr Tyr Pro Val Gly Thr Pro Ser Ser Met Ala Glu Thr Ser
10070 10075 10080
Ile Ser Thr Ser Met Pro Ala Asn Phe Glu Thr Thr Gly Phe Glu
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Ala Glu Pro Phe Ser His Leu Thr Ser Gly Phe Arg Lys Thr Asn
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Gln Tyr Thr Glu Ile Pro Val Asp Ile Ile Thr Pro Phe Asn Ala
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Ser Pro Ser Ile Thr Glu Ser Thr Gly Ile Thr Ser Phe Pro Glu
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Ser Arg Phe Thr Met Ser Val Thr Glu Ser Thr His His Leu Ser
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Glu Ser Gly Pro Gly Asp Ala Thr Leu Ser Thr Ile Ala Glu Ser
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10325 10330 10335
Thr Arg Met Thr Glu Ser Val Glu Leu Gly Thr Val Thr Ser Ala
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Tyr Gln Val Pro Ser Leu Ser Thr Arg Leu Thr Arg Thr Asp Gly
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Thr Thr Thr Thr Ala Leu Lys Thr Thr Thr Thr Ala Leu Lys Thr
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Thr Ser Arg Ala Thr Leu Thr Thr Ser Val Tyr Thr Pro Thr Leu
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Gly Thr Leu Thr Pro Leu Asn Ala Ser Met Gln Met Ala Ser Thr
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Ile Pro Thr Glu Met Met Ile Thr Thr Pro Tyr Val Phe Pro Asp
10460 10465 10470
Val Pro Glu Thr Thr Ser Ser Leu Ala Thr Ser Leu Gly Ala Glu
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Thr Ser Thr Ala Leu Pro Arg Thr Thr Pro Ser Val Phe Asn Arg
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Glu Ser Glu Thr Thr Ala Ser Leu Val Ser Arg Ser Gly Ala Glu
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Arg Ser Pro Val Ile Gln Thr Leu Asp Val Ser Ser Ser Glu Pro
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Asp Thr Thr Ala Ser Trp Val Ile His Pro Ala Glu Thr Ile Pro
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Thr Val Ser Lys Thr Thr Pro Asn Phe Phe His Ser Glu Leu Asp
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Thr Val Ser Ser Thr Ala Thr Ser His Gly Ala Asp Val Ser Ser
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Pro Leu Val Thr Ile Ser Gly Thr Asp Thr Ser Thr Thr Phe Pro
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Leu Thr His Pro Ala Glu Thr Ser Ser Thr Ile Pro Arg Thr Ile
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Pro Asn Phe Ser His His Glu Ser Asp Ala Thr Pro Ser Ile Ala
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Thr Ser Pro Gly Ala Glu Thr Ser Ser Ala Ile Pro Ile Met Thr
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Val Ser Pro Gly Ala Glu Asp Leu Val Thr Ser Gln Val Thr Ser
10670 10675 10680
Ser Gly Thr Asp Arg Asn Met Thr Ile Pro Thr Leu Thr Leu Ser
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Pro Gly Glu Pro Lys Thr Ile Ala Ser Leu Val Thr His Pro Glu
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Ala Gln Thr Ser Ser Ala Ile Pro Thr Ser Thr Ile Ser Pro Ala
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Val Ser Arg Leu Val Thr Ser Met Val Thr Ser Leu Ala Ala Lys
10730 10735 10740
Thr Ser Thr Thr Asn Arg Ala Leu Thr Asn Ser Pro Gly Glu Pro
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Ala Thr Thr Val Ser Leu Val Thr His Pro Ala Gln Thr Ser Pro
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Thr Val Pro Trp Thr Thr Ser Ile Phe Phe His Ser Lys Ser Asp
10775 10780 10785
Thr Thr Pro Ser Met Thr Thr Ser His Gly Ala Glu Ser Ser Ser
10790 10795 10800

Ala Val Pro Thr Pro Thr Val Ser Thr Glu Val Pro Gly Val Val
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Thr Pro Leu Val Thr Ser Ser Arg Ala Val Ile Ser Thr Thr Ile
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Pro Ile Leu Thr Leu Ser Pro Gly Glu Pro Glu Thr Thr Pro Ser
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Met Ala Thr Ser His Gly Glu Glu Ala Ser Ser Ala Ile Pro Thr
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Pro Thr Val Ser Pro Gly Val Pro Gly Val Val Thr Ser Leu Val
10865 10870 10875
Thr Ser Ser Arg Ala Val Thr Ser Thr Thr Ile Pro Ile Leu Thr
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Phe Ser Leu Gly Glu Pro Glu Thr Thr Pro Ser Met Ala Thr Ser
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His Gly Thr Glu Ala Gly Ser Ala Val Pro Thr Val Leu Pro Glu
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Val Pro Gly Met Val Thr Ser Leu Val Ala Ser Ser Arg Ala Val
10925 10930 10935
Thr Ser Thr Thr Leu Pro Thr Leu Thr Leu Ser Pro Gly Glu Pro
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Glu Thr Thr Pro Ser Met Ala Thr Ser His Gly Ala Glu Ala Ser
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Ser Thr Val Pro Thr Val Ser Pro Glu Val Pro Gly Val Val Thr
10970 10975 10980
Ser Leu Val Thr Ser Ser Ser Gly Val Asn Ser Thr Ser Ile Pro
10985 10990 10995
Thr Leu Ile Leu Ser Pro Gly Glu Leu Glu Thr Thr Pro Ser Met
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Ala Thr Ser His Gly Ala Glu Ala Ser Ser Ala Val Pro Thr Pro
11015 11020 11025
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11030 11035 11040
Ser Ser Arg Ala Val Thr Ser Thr Thr Ile Pro Ile Leu Thr Leu
11045 11050 11055
Ser Ser Ser Glu Pro Glu Thr Thr Pro Ser Met Ala Thr Ser His
11060 11065 11070
Gly Val Glu Ala Ser Ser Ala Val Leu Thr Val Ser Pro Glu Val
11075 11080 11085
Pro Gly Met Val Thr Ser Leu Val Thr Ser Ser Arg Ala Val Thr
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Ser Thr Thr Ile Pro Thr Leu Thr Ile Ser Ser Asp Glu Pro Glu
11105 11110 11115
Thr Thr Thr Ser Leu Val Thr His Ser Glu Ala Lys Met Ile Ser
11120 11125 11130
Ala Ile Pro Thr Leu Ala Val Ser Pro Thr Val Gln Gly Leu Val
11135 11140 11145
Thr Ser Leu Val Thr Ser Ser Gly Ser Glu Thr Ser Ala Phe Ser
11150 11155 11160
Asn Leu Thr Val Ala Ser Ser Gln Pro Glu Thr Ile Asp Ser Trp
11165 11170 11175

Val Ala His Pro Gly Thr Glu Ala Ser Ser Val Val Pro Thr Leu
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Thr Val Ser Thr Gly Glu Pro Phe Thr Asn Ile Ser Leu Val Thr
11195 11200 11205
His Pro Ala Glu Ser Ser Ser Thr Leu Pro Arg Thr Thr Ser Arg
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Phe Ser His Ser Glu Leu Asp Thr Met Pro Ser Thr Val Thr Ser
11225 11230 11235
Pro Glu Ala Glu Ser Ser Ser Ala Ile Ser Thr Thr Ile Ser Pro
11240 11245 11250
Gly Ile Pro Gly Val Leu Thr Ser Leu Val Thr Ser Ser Gly Arg
11255 11260 11265
Asp Ile Ser Ala Thr Phe Pro Thr Val Pro Glu Ser Pro His Glu
11270 11275 11280
Ser Glu Ala Thr Ala Ser Trp Val Thr His Pro Ala Val Thr Ser
11285 11290 11295
Thr Thr Val Pro Arg Thr Thr Pro Asn Tyr Ser His Ser Glu Pro
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Asp Thr Thr Pro Ser Ile Ala Thr Ser Pro Gly Ala Glu Ala Thr
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11330 11335 11340
Val Thr Ser Gln Val Thr Ser Ser Gly Thr Asp Thr Ser Ile Thr
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Ile Pro Thr Leu Thr Leu Ser Ser Gly Glu Pro Glu Thr Thr Thr
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Ser Phe Ile Thr Tyr Ser Glu Thr His Thr Ser Ser Ala Ile Pro
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Thr Leu Pro Val Ser Pro Gly Ala Ser Lys Met Leu Thr Ser Leu
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Val Ile Ser Ser Gly Thr Asp Ser Thr Thr Thr Phe Pro Thr Leu
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Thr Glu Thr Pro Tyr Glu Pro Glu Thr Thr Ala Ile Gln Leu Ile
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His Pro Ala Glu Thr Asn Thr Met Val Pro Arg Thr Thr Pro Lys
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Phe Ser His Ser Lys Ser Asp Thr Thr Leu Pro Val Ala Ile Thr
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Ser Pro Gly Pro Glu Ala Ser Ser Ala Val Ser Thr Thr Thr Ile
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Ser Pro Asp Met Ser Asp Leu Val Thr Ser Leu Val Pro Ser Ser
11480 11485 11490
Gly Thr Asp Thr Ser Thr Thr Phe Pro Thr Leu Ser Glu Thr Pro
11495 11500 11505
Tyr Glu Pro Glu Thr Thr Ala Thr Trp Leu Thr His Pro Ala Glu
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Thr Ser Thr Thr Val Ser Gly Thr Ile Pro Asn Phe Ser His Arg
11525 11530 11535
Gly Ser Asp Thr Ala Pro Ser Met Val Thr Ser Pro Gly Val Asp
11540 11545 11550

Thr Arg Ser Gly Val Pro Thr Thr Thr Ile Pro Pro Ser Ile Pro
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Gly Val Val Thr Ser Gln Val Thr Ser Ser Ala Thr Asp Thr Ser
11570 11575 11580
Thr Ala Ile Pro Thr Leu Thr Pro Ser Pro Gly Glu Pro Glu Thr
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Thr Ala Ser Ser Ala Thr His Pro Gly Thr Gln Thr Gly Phe Thr
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Thr Thr Ser Ser Phe Ser His Ser Ser Pro Asp Ala Thr Pro Val
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Met Ala Thr Ser Pro Arg Thr Glu Ala Ser Ser Ala Val Leu Thr
11660 11665 11670
Thr Ile Ser Pro Gly Ala Pro Glu Met Val Thr Ser Gln Ile Thr
11675 11680 11685
Ser Ser Gly Ala Ala Thr Ser Thr Thr Val Pro Thr Leu Thr His
11690 11695 11700
Ser Pro Gly Met Pro Glu Thr Thr Ala Leu Leu Ser Thr His Pro
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Arg Thr Glu Thr Ser Lys Thr Phe Pro Ala Ser Thr Val Phe Pro
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Gln Val Ser Glu Thr Thr Ala Ser Leu Thr Ile Arg Pro Gly Ala
11735 11740 11745
Glu Thr Ser Thr Ala Leu Pro Thr Gln Thr Thr Ser Ser Leu Phe
11750 11755 11760
Thr Leu Leu Val Thr Gly Thr Ser Arg Val Asp Leu Ser Pro Thr
11765 11770 11775
Ala Ser Pro Gly Val Ser Ala Lys Thr Ala Pro Leu Ser Thr His
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Pro Gly Thr Glu Thr Ser Thr Met Ile Pro Thr Ser Thr Leu Ser
11795 11800 11805
Leu Gly Leu Leu Glu Thr Thr Gly Leu Leu Ala Thr Ser Ser Ser
11810 11815 11820
Ala Glu Thr Ser Thr Ser Thr Leu Thr Leu Thr Val Ser Pro Ala
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Val Ser Gly Leu Ser Ser Ala Ser Ile Thr Thr Asp Lys Pro Gln
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11855 11860 11865
Val Gly Pro Pro Glu Phe Ser Arg Thr Val Thr Gly Thr Thr Met
11870 11875 11880
Thr Leu Ile Pro Ser Glu Met Pro Thr Pro Pro Lys Thr Ser His
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Gly Glu Gly Val Ser Pro Thr Thr Ile Leu Arg Thr Thr Met Val
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Glu Ala Thr Asn Leu Ala Thr Thr Gly Ser Ser Pro Thr Val Ala
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Lys Thr Thr Thr Thr Phe Asn Thr Leu Ala Gly Ser Leu Phe Thr
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Pro Leu Thr Thr Pro Gly Met Ser Thr Leu Ala Ser Glu Ser Val
11945 11950 11955
Thr Ser Arg Thr Ser Tyr Asn His Arg Ser Trp Ile Ser Thr Thr
11960 11965 11970
Ser Ser Tyr Asn Arg Arg Tyr Trp Thr Pro Ala Thr Ser Thr Pro
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Val Thr Ser Thr Phe Ser Pro Gly Ile Ser Thr Ser Ser Ile Pro
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Ser Ser Thr Ala Ala Thr Val Pro Phe Met Val Pro Phe Thr Leu
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Pro Gly Ser Arg Lys Phe Asn Ala Thr Glu Arg Glu Leu Gln Gly
12035 12040 12045
Leu Leu Lys Pro Leu Phe Arg Asn Ser Ser Leu Glu Tyr Leu Tyr
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Ser Gly Cys Arg Leu Ala Ser Leu Arg Pro Glu Lys Asp Ser Ser
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Ala Thr Ala Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Glu
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Asp Leu Gly Leu Asp Arg Glu Arg Leu Tyr Trp Glu Leu Ser Asn
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Leu Thr Asn Gly Ile Gln Glu Leu Gly Pro Tyr Thr Leu Asp Arg
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Gly Thr Pro Ser Ser Ser Pro Ser Pro Thr Thr Ala Gly Pro Leu
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Leu Met Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr
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Glu Glu Asp Met Arg Arg Thr Gly Ser Arg Lys Phe Asn Thr Met
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Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg
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Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr
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His Arg Leu Asp Pro Lys Ser Pro Gly Leu Asn Arg Glu Gln Leu
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Tyr Trp Glu Leu Ser Lys Leu Thr Asn Asp Ile Glu Glu Leu Gly
12260 12265 12270
Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr
12275 12280 12285
His Gln Ser Ser Val Ser Thr Thr Ser Thr Pro Gly Thr Ser Thr
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Val Asp Leu Arg Thr Ser Gly Thr Pro Ser Ser Leu Ser Ser Pro
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Thr Ile Met Ala Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn
12320 12325 12330
Phe Thr Ile Thr Asn Leu Gln Tyr Gly Glu Asp Met Gly His Pro
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Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu
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Leu Gly Pro Ile Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser
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Gly Cys Arg Leu Thr Ser Leu Arg Ser Glu Lys Asp Gly Ala Ala
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Thr Gly Val Asp Ala Ile Cys Ile His His Leu Asp Pro Lys Ser
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Pro Gly Leu Asn Arg Glu Arg Leu Tyr Trp Glu Leu Ser Gln Leu
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12425 12430 12435
Ser Leu Tyr Val Asn Gly Phe Thr His Arg Thr Ser Val Pro Thr
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Ser Ser Thr Pro Gly Thr Ser Thr Val Asp Leu Gly Thr Ser Gly
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Val Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Lys Tyr Glu
12485 12490 12495
Glu Asp Met His Arg Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu
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12530 12535 12540
Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Ala Ile Cys Thr His
12545 12550 12555
Arg Leu Asp Pro Lys Ser Pro Gly Val Asp Arg Glu Gln Leu Tyr
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Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe Thr His
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Trp Ile Pro Val Pro Thr Ser Ser Thr Pro Gly Thr Ser Thr Val
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Ala Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe Thr Ile Thr
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Asn Leu Lys Tyr Glu Glu Asp Met His Cys Pro Gly Ser Arg Lys
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Phe Asn Thr Thr Glu Arg Val Leu Gln Ser Leu Leu Gly Pro Met
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Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu
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Ala Ile Cys Thr His Arg Leu Asp Pro Lys Ser Pro Gly Val Asp
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12725 12730 12735
Lys Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val
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Leu Pro Ser Pro Thr Ser Ala Gly Pro Leu Leu Val Pro Phe Thr
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Gln Leu Thr His Gly Ile Lys Glu Leu Gly Pro Tyr Thr Leu Asp
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Tyr Gly Glu Asp Met Arg His Pro Gly Ser Arg Lys Phe Asn Thr
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Thr Glu Arg Val Leu Gln Gly Leu Leu Gly Pro Leu Phe Lys Asn
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13025 13030 13035
Leu Tyr Trp Gln Leu Ser Gln Met Thr Asn Gly Ile Lys Glu Leu
13040 13045 13050

Gly Pro Tyr Thr Leu Asp Arg Asn Ser Leu Tyr Val Asn Gly Phe
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Thr His Arg Ser Ser Gly Leu Thr Thr Ser Thr Pro Trp Thr Ser
13070 13075 13080
Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Ser Pro Val Pro Ser
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Pro Thr Thr Thr Gly Pro Leu Leu Val Pro Phe Thr Leu Asn Phe
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Thr Ile Thr Asn Leu Gln Tyr Glu Glu Asn Met Gly His Pro Gly
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Ser Arg Lys Phe Asn Ile Thr Glu Ser Val Leu Gln Gly Leu Leu
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Lys Pro Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly
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Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Val Ala Thr
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Arg Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Lys Ile Pro
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Gly Leu Asp Arg Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr
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His Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser
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Leu Tyr Val Asn Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr
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Ser Thr Pro Gly Thr Phe Thr Val Gln Pro Glu Thr Ser Glu Thr
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Pro Ser Ser Leu Pro Gly Pro Thr Ala Thr Gly Pro Val Leu Leu
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Pro Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Gln Tyr Glu Glu
13265 13270 13275
Asp Met Arg Arg Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg
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Val Leu Gln Gly Leu Leu Met Pro Leu Phe Lys Asn Thr Ser Val
13295 13300 13305
Ser Ser Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu
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Lys Asp Gly Ala Ala Thr Arg Val Asp Ala Val Cys Thr His Arg
13325 13330 13335
Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Arg Leu Tyr Trp
13340 13345 13350
Lys Leu Ser Gln Leu Thr His Gly Ile Thr Glu Leu Gly Pro Tyr
13355 13360 13365
Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly Phe Thr His Gln
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Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser Thr Met His
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Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro Met Thr
13400 13405 13410
Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile Thr
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Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg Lys
13430 13435 13440
Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val
13445 13450 13455
Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu
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Thr Leu Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp
13475 13480 13485
Ala Ile Cys Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp
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Arg Glu Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile
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Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val
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Asn Gly Phe Thr Gln Arg Ser Ser Val Pro Thr Thr Ser Ile Pro
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Gly Thr Pro Thr Val Asp Leu Gly Thr Ser Gly Thr Pro Val Ser
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Lys Pro Gly Pro Ser Ala Ala Ser Pro Leu Leu Val Leu Phe Thr
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Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn Met Gln
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His Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln
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Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser Val Gly Pro Leu
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Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly
13625 13630 13635
Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro Asp Pro
13640 13645 13650
Lys Ser Pro Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu Ser
13655 13660 13665
Gln Leu Thr His Asn Ile Thr Glu Leu Gly Pro Tyr Ala Leu Asp
13670 13675 13680
Asn Asp Ser Leu Phe Val Asn Gly Phe Thr His Arg Ser Ser Val
13685 13690 13695
Ser Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala
13700 13705 13710
Ser Lys Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His
13715 13720 13725
Leu Leu Ile Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg
13730 13735 13740
Tyr Glu Glu Asn Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr
13745 13750 13755
Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr
13760 13765 13770
Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg
13775 13780 13785
Pro Glu Lys Asp Gly Glu Ala Thr Gly Val Asp Ala Ile Cys Thr
13790 13795 13800

His Arg Pro Asp Pro Thr Gly Pro Gly Leu Asp Arg Glu Gln Leu
13805 13810 13815
Tyr Leu Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly
13820 13825 13830
Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr
13835 13840 13845
His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly Val Val Ser Glu
13850 13855 13860
Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu Arg Tyr Met
13865 13870 13875
Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile Thr Asp
13880 13885 13890
Asn Val Met Gln His Leu Leu Ser Pro Leu Phe Gln Arg Ser Ser
13895 13900 13905
Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser
13910 13915 13920
Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr
13925 13930 13935
Leu Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe
13940 13945 13950
His Glu Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro
13955 13960 13965
Tyr Ser Leu Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu
13970 13975 13980
Pro Gly Pro Asp Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr
13985 13990 13995
Phe Leu Pro Pro Leu Ser Glu Ala Thr Thr Ala Met Gly Tyr His
14000 14005 14010
Leu Lys Thr Leu Thr Leu Asn Phe Thr Ile Ser Asn Leu Gln Tyr
14015 14020 14025
Ser Pro Asp Met Gly Lys Gly Ser Ala Thr Phe Asn Ser Thr Glu
14030 14035 14040
Gly Val Leu Gln His Leu Leu Arg Pro Leu Phe Gln Lys Ser Ser
14045 14050 14055
Met Gly Pro Phe Tyr Leu Gly Cys Gln Leu Ile Ser Leu Arg Pro
14060 14065 14070
Glu Lys Asp Gly Ala Ala Thr Gly Val Asp Thr Thr Cys Thr Tyr
14075 14080 14085
His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile Gln Gln Leu Tyr
14090 14095 14100
Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe
14105 14110 14115
Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro
14120 14125 14130
Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile
14135 14140 14145
Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr
14150 14155 14160
Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr
14165 14170 14175

Lys Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr
14180 14185 14190
Asn Leu Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe
14195 14200 14205
Ser Ser Asn Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp
14210 14215 14220
Lys Thr Leu Asn Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln
14225 14230 14235
Leu Val Asp Ile His Val Thr Glu Met Glu Ser Ser Val Tyr Gln
14240 14245 14250
Pro Thr Ser Ser Ser Ser Thr Gln His Phe Tyr Leu Asn Phe Thr
14255 14260 14265
Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala Gln Pro Gly Thr
14270 14275 14280
Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp Ala Leu Asn
14285 14290 14295
Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser Asp Cys
14300 14305 14310
Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr Gly
14315 14320 14325
Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp
14330 14335 14340
Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly
14345 14350 14355
Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val
14360 14365 14370
Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser
14375 14380 14385
Asp Leu Pro Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu
14390 14395 14400
Leu Gly Val Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr
14405 14410 14415
Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys
14420 14425 14430
Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
14435 14440 14445

<210> 151
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114-N1

<400> 151
Ala Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr

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

<210> 152
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114-N2

<400> 152
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Ala Gly Thr Gln Leu Gln Asn Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
50 55 60
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
65 70 75 80
Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
85 90 95
Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp
100 105 110
Leu Gln

<210> 153
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114-N12

<400> 153
Ala Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Ala Gly Thr Gln Leu Gln Asn Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
50 55 60
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
65 70 75 80
Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
85 90 95
Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp
100 105 110
Leu Gln

<210> 154
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114-N123

<400> 154
Ala Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Ala Gly Thr Gln Leu Gln Ala Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
50 55 60
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
65 70 75 80
Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
85 90 95
Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp
100 105 110
Leu Gln

<210> 155
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c344 N-term of first tandem repeat

<400> 155
Trp Glu Leu Ser Gln Leu
1 5

<210> 156
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c344 C-term of first tandem repeat

<400> 156
Thr Gly Val Asp Ser Leu Cys
1 5

<210> 157
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c344 N-term of ectodomain

<400> 157
Asn Phe Ser Pro Leu Ala Arg
1 5

<210> 158
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c344 C-term of ectodomain

<400> 158
Thr Gly Asn Ser Asp Leu Pro
1 5

<210> 159
<211> 25

<212> PRT
<213> Artificial Sequence

<220>
<223> Transmembrane

<400> 159
Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile
1 5 10 15
Thr Cys Leu Ile Cys Gly Val Leu Val
20 25

<210> 160
<211> 31
<212> PRT
<213> Artificial Sequence

<220>
<223> Cytoplasmic tail

<400> 160
Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln
1 5 10 15
Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
20 25 30

<210> 161
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114 ectodomain

<400> 161
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro
50 55

<210> 162
<211> 24
<212> PRT

<213> Artificial Sequence

<220>
<223> MUC16c80 ectodomain

<400> 162
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Asp Leu Pro
20

<210> 163
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c86 ectodomain

<400> 163
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro
50 55

<210> 164
<211> 22
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c86 transmembrane

<400> 164
Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile
1 5 10 15
Thr Cys Leu Ile Cys Gly
20

<210> 165
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c86 cytoplasmic

<400> 165
Asp Leu Glu Asp Leu Gln
1 5

<210> 166
<211> 58
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16 3(N to A)c114 ectodomain

<400> 166
Ala Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Ala Gly Thr Gln Leu Gln Ala Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro
50 55

<210> 167
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> LGALS3 sugar binding domain

<400> 167
Pro Tyr Asn Leu Pro Leu Pro Gly Gly Val Val Pro Arg Met Leu Ile
1 5 10 15
Thr Ile Leu Gly Thr Val Lys Pro Asn Ala Asn Arg Ile Ala Leu Asp
20 25 30
Phe Gln Arg Gly Asn Asp Val Ala Phe His Phe Asn Pro Arg Phe Asn
35 40 45
Glu Asn Asn Arg Arg Val Ile Val Cys Asn Thr Lys Leu Asp Asn Asn
50 55 60
Trp Gly Arg Glu Glu Arg Gln Ser Val Phe Pro Phe Glu Ser Gly Lys
65 70 75 80
Pro Phe Lys Ile Gln Val Leu Val Glu Pro Asp His Phe Lys Val Ala
85 90 95
Val Asn Asp Ala His Leu Leu Gln Tyr Asn His Arg Val Lys Lys Leu

100 105 110
Asn Glu Ile Ser Lys Leu Gly Ile Ser Gly Asp Ile Asp Leu Thr Ser
115 120 125

<210> 168
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16 nonglycosylated peptide 2

<400> 168
Cys Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn
1 5 10 15
Arg Asn Glu

<210> 169
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16 unrelated peptide 18mer

<400> 169
Gly Ala Val Pro Arg Ser Ala Thr Ile Asn Val Ser Arg Ile Ala Thr
1 5 10 15
Gly Pro

<210> 170
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> 18mer (no C)

<400> 170
Thr Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser
1 5 10 15
Val

<210> 171
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> 15mer (no C)

<400> 171
Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val
1 5 10

<210> 172
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> MUC16c114-N23

<400> 172
Asn Phe Ser Pro Leu Ala Arg Arg Val Asp Arg Val Ala Ile Tyr Glu
1 5 10 15
Glu Phe Leu Arg Met Thr Arg Ala Gly Thr Gln Leu Gln Ala Phe Thr
20 25 30
Leu Asp Arg Ser Ser Val Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn
35 40 45
Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro Phe Trp Ala Val Ile Leu
50 55 60
Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly
65 70 75 80
Val Leu Val Thr Thr Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val
85 90 95
Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp
100 105 110
Leu Gln

<210> 173
<211> 344
<212> PRT
<213> Artificial Sequence

<220>
<223> N24 mut c344

<400> 173
Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr
1 5 10 15

Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn
20 25 30
Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Gln
35 40 45
Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu
50 55 60
Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu
65 70 75 80
His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser
85 90 95
Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser
100 105 110
Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His
115 120 125
Gln Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met
130 135 140
Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His Phe
145 150 155 160
Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala
165 170 175
Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp
180 185 190
Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser
195 200 205
Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr
210 215 220
Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp
225 230 235 240
Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Ala Gly Thr
245 250 255
Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly
260 265 270
Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro
275 280 285
Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile
290 295 300
Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys
305 310 315 320
Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser
325 330 335
His Leu Asp Leu Glu Asp Leu Gln
340

<210> 174
<211> 344
<212> PRT
<213> Artificial Sequence

<220>

<223> N30 mut c344

<400> 174
Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr
1 5 10 15
Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn
20 25 30
Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Gln
35 40 45
Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu
50 55 60
Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu
65 70 75 80
His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser
85 90 95
Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser
100 105 110
Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His
115 120 125
Gln Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met
130 135 140
Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His Phe
145 150 155 160
Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala
165 170 175
Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp
180 185 190
Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser
195 200 205
Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr
210 215 220
Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp
225 230 235 240
Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Asn Gly Thr
245 250 255
Gln Leu Gln Ala Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly
260 265 270
Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro
275 280 285
Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile
290 295 300
Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys
305 310 315 320
Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser
325 330 335
His Leu Asp Leu Glu Asp Leu Gln
340

<210> 175

<211> 344
<212> PRT
<213> Artificial Sequence

<220>
<223> N24-N30 mut c344

<400> 175
Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln Leu Gly Phe Tyr
1 5 10 15
Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr Ala Pro Gln Asn
20 25 30
Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His Ile Val Asn Gln
35 40 45
Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr Ile Thr Leu Leu
50 55 60
Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys Gly Ser Gln Leu
65 70 75 80
His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu Thr Met Asp Ser
85 90 95
Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn Leu Asp Pro Ser
100 105 110
Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn Ala Ser Phe His
115 120 125
Gln Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His Val Thr Glu Met
130 135 140
Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser Thr Gln His Phe
145 150 155 160
Tyr Leu Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser Gln Asp Lys Ala
165 170 175
Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg Asn Ile Glu Asp
180 185 190
Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys Ser Tyr Phe Ser
195 200 205
Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn Arg His His Thr
210 215 220
Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala Arg Arg Val Asp
225 230 235 240
Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr Arg Ala Gly Thr
245 250 255
Gln Leu Gln Ala Phe Thr Leu Asp Arg Ser Ser Val Leu Val Asp Gly
260 265 270
Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn Ser Asp Leu Pro
275 280 285
Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu Leu Gly Leu Ile
290 295 300
Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg Arg Arg Lys Lys
305 310 315 320
Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly Tyr Tyr Gln Ser
325 330 335

His Leu Asp Leu Glu Asp Leu Gln
340