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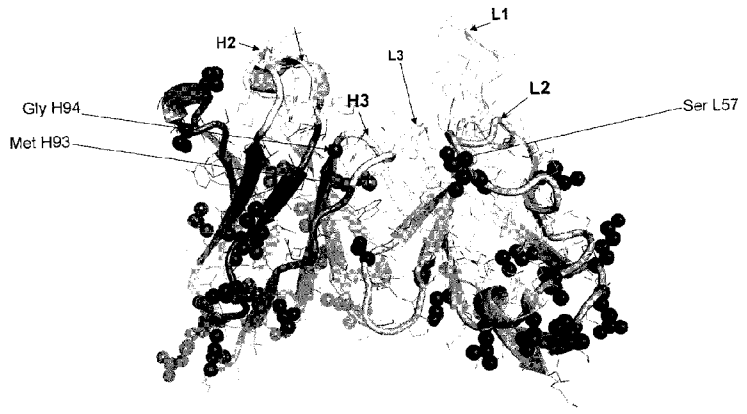
(54) **Title**: ANTIBODIES THAT SPECIFICALLY BLOCK THE BIOLOGICAL ACTIVITY OF A TUMOR ANTIGEN

FIGURE 18A



(57) **Abstract**: Novel monoclonal antibodies that specifically bind to KAAG1 are described. In some embodiments, the antibodies block the biological activity of KAAG1 and are useful in composition in certain cancers, more particularly in cancers that have increased cell surface expression of KAAG1, such as ovarian, renal, lung, colorectal, breast, brain, and prostate cancer, as well as melanoma. The invention also relates to cells expressing the monoclonal antibodies and antigen binding fragments such as humanized and chimeric antibodies. Additionally, methods of detecting and treating cancer using the antibodies and fragments are also disclosed.

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ANTIBODIES THAT SPECIFICALLY BLOCK THE BIOLOGICAL ACTIVITY OF A TUMOR ANTIGEN

FIELD OF THE INVENTION

The present invention relates to monoclonal antibodies and antigen binding fragments thereof that specifically binds to KAAG1 and their use for treating certain diseases including diagnosing, preventing and treating malignant tumors related to ovarian cancer. The present invention also relates to the use of these antibodies for diagnosis, prevention and treatment of various other cancer types.

BACKGROUND OF THE INVENTION

Among gynecologic malignancies, ovarian cancer accounts for the highest tumor-related mortality in women in the United States (Jemal et al., 2005). It is the fourth leading cause of cancer-related death in women in the U.S (Menon et al., 2005). The American Cancer Society estimated a total of 22,220 new cases in 2005 and attributed 16,210 deaths to the disease (Bonome et al., 2005). For the past 30 years, the statistics have remained largely the same - the majority of women who develop ovarian cancer will die of this disease (Chambers and Vanderhyden, 2006). The disease carries a 1:70 lifetime risk and a mortality rate of >60% (Chambers and Vanderhyden, 2006). The high mortality rate is due to the difficulties with the early detection of ovarian cancer when the malignancy has already spread beyond the ovary. Indeed, >80% of patients are diagnosed with advanced staged disease (stage III or IV) (Bonome et al., 2005). These patients have a poor prognosis that is reflected in <45% 5-year survival rate, although 80% to 90% will initially respond to chemotherapy (Berek et al., 2000). This increased success compared to 20% 5-year survival rate years earlier is, at least in part, due to the ability to optimally debulk tumor tissue when it is confined to the ovaries, which is a significant prognostic factor for ovarian cancer (Bristow R. E., 2000; Brown et al., 2004). In patients who are diagnosed with early disease (stage I), the 5-yr survival ranges from >90 (Chambers and Vanderhyden, 2006).

Ovarian cancer comprises a heterogeneous group of tumors that are derived from the surface epithelium of the ovary or from surface inclusions. They are classified into serous, mucinous, endometrioid, clear cell, and Brenner (transitional) types corresponding to the different types of epithelia in the organs of the female reproductive tract (Shih and Kurman, 2005). Of these, serous tumors account for ~60% of the ovarian

cancer cases diagnosed. Each histologic subcategory is further divided into three groups: benign, intermediate (borderline tumor or low malignancy potential (LMP)), and malignant, reflecting their clinical behavior (Seidman et al., 2002). LMP represents 10% to 15% of tumors diagnosed as serous and is a conundrum as they display atypical nuclear structure and metastatic behavior, yet they are considerably less aggressive than high-grade serous tumors. The 5-year survival for patients with LMP tumors is 95% in contrast to a <45% survival for advanced high-grade disease over the same period (Berek et al., 2000).

Presently, the diagnosis of ovarian cancer is accomplished, in part, through routine analysis of the medical history of patients and by performing physical, ultrasound and x-ray examinations, and hematological screening. Two alternative strategies have been reported for early hematological detection of serum biomarkers. One approach is the analysis of serum samples by mass spectrometry to find proteins or protein fragments of unknown identity that detect the presence or absence of cancer (Mor et al., 2005; Kozak et al., 2003). However, this strategy is expensive and not broadly available. Alternatively, the presence or absence of known proteins/peptides in the serum is being detected using antibody microarrays, ELISA, or other similar approaches. Serum testing for a protein biomarker called CA-125 (cancer antigen-125) has long been widely performed as a marker for ovarian cancer. However, although ovarian cancer cells may produce an excess of these protein molecules, there are some other cancers, including cancer of the fallopian tube or endometrial cancer (cancer of the lining of the uterus), 60% of people with pancreatic cancer, and 20%-25% of people with other malignancies with elevated levels of CA-125. The CA-125 test only returns a true positive result for about 50% of Stage I ovarian cancer patients and has a 80% chance of returning true positive results from stage II, III, and IV ovarian cancer patients. The other 20% of ovarian cancer patients do not show any increase in CA-125 concentrations. In addition, an elevated CA-125 test may indicate other benign activity not associated with cancer, such as menstruation, pregnancy, or endometriosis. Consequently, this test has very limited clinical application for the detection of early stage disease when it is still treatable, exhibiting a positive predictive value (PPV) of <10%. Even with the addition of ultrasound screening to CA-125, the PPV only improves to around 20% (Kozak et al., 2003). Thus, this test is not an effective screening test.

Despite improved knowledge of the etiology of the disease, aggressive cytoreductive surgery, and modern combination chemotherapy, there has been only little change in mortality. Poor outcomes have been attributed to (1) lack of adequate screening tests for early disease detection in combination with only subtle presentation of symptoms at this stage - diagnosis is frequently being made only after progression to later stages, at which point the peritoneal dissemination of the cancer limits effective treatment and (2) the frequent development of resistance to standard chemotherapeutic strategies limiting improvement in the 5-year survival rate of patients. The initial chemotherapy regimen for ovarian cancer includes the combination of carboplatin (Paraplatin) and paclitaxel (taxol). Years of clinical trials have proved this combination to be most effective after effective surgery - reduces tumor volume in about 80% of the women with newly diagnosed ovarian cancer and 40% to 50% will have complete regression - but studies continue to look for ways to improve it. Recent abdominal infusion of chemotherapeutics to target hard-to-reach cells in combination with intravenous delivery has increased the effectiveness. However, severe side effects often lead to an incomplete course of treatment. Some other chemotherapeutic agents include doxorubicin, cisplatin, cyclophosphamide, bleomycin, etoposide, vinblastine, topotecan hydrochloride, ifosfamide, 5-fluorouracil and melphalan. More recently, clinical trials have demonstrated that intraperitoneal administration of cisplatin confers a survival advantage compared to systemic intravenous chemotherapy (Cannistra and McGuire, 2007). The excellent survival rates for women with early stage disease receiving chemotherapy provide a strong rationale for research efforts to develop strategies to improve the detection of ovarian cancer. Furthermore, the discovery of new ovarian cancer-related biomarkers will lead to the development of more effective therapeutic strategies with minimal side effects for the future treatment of ovarian cancer.

Notwithstanding these recent advances in the understanding and the treatment for ovarian cancer, the use of chemotherapy is invariably associated with severe adverse reactions, which limit their use. Consequently, the need for more specific strategies such as combining antigen tissue specificity with the selectivity of monoclonal antibodies should permit a significant reduction in off-target-associated side effects. The use of monoclonal antibodies for the therapy of ovarian cancer is beginning to emerge with an increasing number of ongoing clinical trials (Oei et al., 2008; Nicodemus and berek, 2005). Most of these trials have examined the use of monoclonal antibodies conjugated

to radioisotopes, such as yttrium-90, or antibodies that target tumor antigens already identified in other cancer types An example of this is the use of bevacizumab, which targets vascular endothelial growth factor (Burger, 2007). There are very few ovarian cancer specific antigens that are currently under investigation as therapeutic targets for monoclonal antibodies. Some examples include the use of a protein termed B7-H4 (Simon et al., 2006) and more recently folate receptor-alpha (Ebel et al., 2007), the latter of which has recently entered Phase II clinical trials.

Kidney associated antigen 1 (KAAG1) was originally cloned from a cDNA library derived from a histocompatibility leukocyte antigen-B7 renal carcinoma cell line as an antigenic peptide presented to cytotoxic T lymphocytes (Van den Eynde et al., 1999, Genebank accession no Q9UBP8) The locus containing *KAAG1* was found to encode two genes transcribed in both directions on opposite strands. The sense strand was found to encode a transcript that encodes a protein termed DCDC2. Expression studies by these authors found that the *KAAG1* antisense transcript was tumor specific and exhibited very little expression in normal tissues whereas the *DCDC2* sense transcript was ubiquitously expressed (Van den Eynde et al., 1999). The expression of the *KAAG1* transcript in cancer, and in particular ovarian cancer, renal cancer, lung cancer, colon cancer, breast cancer and melanoma was disclosed in the published patent application No PCT/CA2007/001134. Van den Eynde et al., also observed RNA expression in renal carcinomas, colorectal carcinomas, melanomas, sarcomas, leukemias, brain tumors, thyroid tumors, mammary carcinomas, prostatic carcinomas, oesophageal carcinomas, bladder tumors, lung carcinomas and head and neck tumors. Recently, strong genetic evidence obtained through linkage disequilibrium studies found that the *VMP/DCDC2/KAAG1* locus was associated with dyslexia (Schumacher et al., 2006, Cope et al., 2005). One of these reports pointed to the DCDC2 marker as the culprit in dyslexic patients since the function of this protein in cortical neuron migration was in accordance with symptoms of these patients who often display abnormal neuronal migration and maturation (Schumacher et al., 2006).

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 relevant to the present disclosure as it existed before the priority date of each claim of this application.

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.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides an isolated antibody or an antigen binding fragment thereof, wherein said antibody or antigen binding fragment thereof is capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or is capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2.

In a further aspect, the present invention provides an isolated antibody or an antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1; SEQ ID NO.:2), selected from the group consisting of an antibody or antigen binding fragment thereof comprising:

a. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16; and

i. a CDRL1 of formula $X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\ is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of formula $FX_{1c}STX_{2c}X_{3c}S$ (SEQ ID NO.:76) wherein X_{1c} is A or G; X_{2c} is R or T, and; X_{3c} is E, K or A; and

iii. a CDRL3 of formula $X_{1f}QX_{2f}X_{3f}X_{4f}X_{5f}PLT$ (SEQ ID NO.:79) wherein X_{1f} is Q or L; X_{2f} is Y or H; X_{3f} is D, F or Y; X_{4f} is E, A, N or S, and; X_{5f} is I, F or T; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.: 18; and

i. a CDRH1 of formula $GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82) wherein X_{1i} is T, I or K; X_{2i} is T or S; X_{3i} is D or E; X_{4i} is E, N or D, and; X_{5i} is M, I or V;

ii. a CDRH2 of formula $X_{1j}X_{2j}DPX_{3j}TGX_{4j}TX_{5j}$ (SEQ ID NO.:83) wherein X_{1j} is V or G; X_{2j} is I or L; X_{3j} is A, G or E; X_{4j} is R, G, D, A, S, N or V, and; X_{5j} is A or V; and

iii. a CDRH3 of formula $MX_{1o}X_{2o}X_{3o}DY$ (SEQ ID NO.:88) wherein X_{1o} is G or S; X_{2o} is Y or H, and; X_{3o} is A or S or a CDRH3 of formula $IX_{1p}YAX_{2p}DY$ (SEQ ID NO.:89) wherein;X_{1p} may be G or S and; X_{2p} may be absent or M;

b. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:20; and

i. a CDRL1 of formula a CDRL1 of formula $X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\ is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of formula $X_{1d}VSX_{2d}X_{3d}X_{4d}S$ (SEQ ID NO.:77) wherein X_{1d} is L or K; X_{2d} is K or N; X_{3d} is L or R and; X_{4d} is D or F; and

iii. a CDRL3 of formula $X_{1h}QGX_{2h}HX_{3h}PX_{4h}T$ (SEQ ID NO.:81) wherein X_{1h} is W or F; X_{2h} is S or T; X_{3h} is F or V, and;X_{4h} is R or L; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:22; and

iv. a CDRH1 of SEQ ID NO.:36;

v. a CDRH2 of formula $DINPX_{1n}YGX_{2n}X_{3n}T$ (SEQ ID NO.:87) Wherein X_{1n} is N or Y, X_{2n} is G or T and; X_{3n} is I or T; and

vi. a CDRH3 of SEQ ID NO.:38;

c. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24; and

i. a CDRL1 of formula $KASQDX_{1b}X_{2b}X_{3b}X_{4b}X_{5b}X_{6b}$ (SEQ ID NO.:75), wherein X_{1b} is V or I; X_{2b} is G or H; X_{3b} is T, N or R; X_{4b} is F, Y or A; X_{5b} is V or L, and; X_{6b} is N or A;

ii. a CDRL2 of formula $X_{1e}ANRLVX_{2e}$ (SEQ ID NO.:78), wherein X_{1e} is R or H and; X_{2e} is D or A; and

iii. a CDRL3 of formula $X_{1f}QX_{2f}X_{3f}X_{4f}X_{5f}PLT$ (SEQ ID NO.:79) wherein X_{1f} is Q or L; X_{2f} is Y or H; X_{3f} is D, F or Y; X_{4f} is E, A, N or S, and; X_{5f} is I, F or T; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:26; and

iv. a CDRH1 of SEQ ID NO.:42;

v. a CDRH2 of formula $YIX_{1l}X_{2l}X_{3l}GX_{4l}X_{5l}X_{6l}$ (SEQ ID NO.:85) wherein X_{1l} is S or N; X_{2l} is F or Y; X_{3l} is D, E or N; X_{4l} is D or H; X_{5l} is Y, S or N; and X_{6l} is D, E or N; and

vi. a CDRH3 of SEQ ID NO.:44;

d. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:105; and

i. a CDRL1 of formula $X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\ is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of formula $X_{1d}VSX_{2d}X_{3d}X_{4d}S$ (SEQ ID NO.:77) wherein X_{1d} is L or K; X_{2d} is K or N; X_{3d} is L or R and; X_{4d} is D or F; and

iii. a CDRL3 of formula $X_{1h}QGX_{2h}HX_{3h}PX_{4h}T$ (SEQ ID NO.:81) Wherein X_{1h} is W or F; X_{2h} is S or T; X_{3h} is F or V, and; X_{4h} is R or L ; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132; and

iv. a CDRH1 of formula $GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82) wherein X_{1i} is T, I or K; X_{2i} is T or S; X_{3i} is D or E; X_{4i} is E, N or D, and; X_{5i} is M, I or V;

v. a CDRH2 of formula X_{1m}INPYNX_{2m}VTE (SEQ ID NO.:86) wherein X_{1m} is N or Y, and; X_{2m} is E, D or N; and

vi. a CDRH3 of formula A$X_{1q}X_{2q}$GLRX_{3q} (SEQ ID NO.:90) wherein X_{1q} is R or W; X_{2q} is W or F and; X_{3q} is Q or N;

e. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:109; and

i. a CDRL1 of formula X_{1a}SSX_{2a}SLL$X_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\ is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of SEQ ID NO.:165; and

iii. a CDRL3 of SEQ ID NO.:166; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:153; and

iv. a CDRH1 of SEQ ID NO.:167;

v. a CDRH2 of formula DINPX_{1n}YG$X_{2n}X_{3n}$T (SEQ ID NO.:87) wherein X_{1n} is N or Y, X_{2n} is G or T and; X_{3n} is I or T ; and

vi. a CDRH3 of SEQ ID NO.:169; and

f. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:126; and

i. a CDRL1 of formula KASQD$X_{1b}X_{2b}X_{3b}X_{4b}X_{5b}X_{6b}$ (SEQ ID NO.:75) wherein X_{1b} is V or I; X_{2b} is G or H; X_{3b} is T, N or R; X_{4b} is F, Y or A; X_{5b} is V or L, and; X_{6b} is N or A;

ii. a CDRL2 of SEQ ID NO.:171; and

iii. a CDRL3 of formula X_{1f}Q$X_{2f}X_{3f}X_{4f}X_{5f}$PLT (SEQ ID NO.:79) wherein X_{1f} is Q or L; X_{2f} is Y or H; X_{3f} is D, F or Y; X_{4f} is E, A, N or S, and; X_{5f} is I, F or T; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:145; and

iv. a CDRH1 of formula $GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82) wherein X_{1i} is T, I or K; X_{2i} is T or S; X_{3i} is D or E; X_{4i} is E, N or D, and; X_{5i} is M, I or V;

v. a CDRH2 of formula $X_{1j}X_{2j}DPX_{3j}TGX_{4j}TX_{5j}$ (SEQ ID NO.:83) wherein X_{1j} is V or G; X_{2j} is I or L; X_{3j} is A, G or E; X_{4j} is R, G, D, A, S, N or V, and; X_{5j} is A or V; and

vi. a CDRH3 of formula $MX_{1o}X_{2o}X_{3o}DY$ (SEQ ID NO.:88) wherein X_{1o} is G or S; X_{2o} is Y or H, and; X_{3o} is A or S.

In a further aspect, the present invention provides an isolated antibody or an antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1) and comprising:

a. three CDRs of a light chain variable domain defined in SEQ ID NO.:16 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:18;

b. three CDRs of a light chain variable domain defined in SEQ ID NO.:20 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:22;

c. three CDRs of a light chain variable domain defined in SEQ ID NO.:24 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:26;

d. three CDRs of a light chain variable domain defined in SEQ ID NO.:105 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:132;

e. three CDRs of a light chain variable domain defined in SEQ ID NO.:106 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:133;

f. three CDRs of a light chain variable domain defined in SEQ ID NO.:107 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:134;

g. three CDRs of a light chain variable domain defined in SEQ ID NO.:108 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:154;

h. three CDRs of a light chain variable domain defined in SEQ ID NO.:109 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:153;

i. three CDRs of a light chain variable domain defined in SEQ ID NO.:110 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:135;

j. three CDRs of a light chain variable domain defined in SEQ ID NO.:111 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:136;

k. three CDRs of a light chain variable domain defined in SEQ ID NO.:112 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:149;

l. three CDRs of a light chain variable domain defined in SEQ ID NO.:113 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:137;

m. three CDRs of a light chain variable domain defined in SEQ ID NO.:114 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:140;

n. three CDRs of a light chain variable domain defined in SEQ ID NO.:115 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:141;

o. three CDRs of a light chain variable domain defined in SEQ ID NO.:116 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:142;

p. three CDRs of a light chain variable domain defined in SEQ ID NO.:117 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:139;

q. three CDRs of a light chain variable domain defined in SEQ ID NO.:118 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:147;

r. three CDRs of a light chain variable domain defined in SEQ ID NO.:119 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:143;

s. three CDRs of a light chain variable domain defined in SEQ ID NO.:120 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:152;

t. three CDRs of a light chain variable domain defined in SEQ ID NO.:121 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:146;

u. three CDRs of a light chain variable domain defined in SEQ ID NO.:122 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:138;

v. three CDRs of a light chain variable domain defined in SEQ ID NO.:123 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:150;

w. three CDRs of a light chain variable domain defined in SEQ ID NO.:124 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:144;

x. three CDRs of a light chain variable domain defined in SEQ ID NO.:126 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:145;

y. three CDRs of a light chain variable domain defined in SEQ ID NO.:127 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:157;

z. three CDRs of a light chain variable domain defined in SEQ ID NO.:128 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:155;

aa. three CDRs of a light chain variable domain defined in SEQ ID NO.:129 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:156;

bb. three CDRs of a light chain variable domain defined in SEQ ID NO.:130 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:151;

cc. a light chain variable domain defined in SEQ ID NO.:16 and a heavy chain variable domain defined in SEQ ID NO.:18;

dd. a light chain variable domain defined in SEQ ID NO.:20 and a heavy chain variable domain defined in SEQ ID NO.:22;

ee. a light chain variable domain defined in SEQ ID NO.:24 and a heavy chain variable domain defined in SEQ ID NO.:26;

ff. a light chain variable domain defined in SEQ ID NO.:105 and a heavy chain variable domain defined in SEQ ID NO.:132;

gg. a light chain variable domain defined in SEQ ID NO.:106 and a heavy chain variable domain defined in SEQ ID NO.:133;

hh. a light chain variable domain defined in SEQ ID NO.:107 and a heavy chain variable domain defined in SEQ ID NO.:134;

ii. a light chain variable domain defined in SEQ ID NO.:108 and a heavy chain variable domain defined in SEQ ID NO.:154;

jj. a light chain variable domain defined in SEQ ID NO.:109 and a heavy chain variable domain defined in SEQ ID NO.:153;

kk. a light chain variable domain defined in SEQ ID NO.:110 and a heavy chain variable domain defined in SEQ ID NO.:135;

ll. a light chain variable domain defined in SEQ ID NO.:111 and a heavy chain variable domain defined in SEQ ID NO.:136;

mm. a light chain variable domain defined in SEQ ID NO.:112 and a heavy chain variable domain defined in SEQ ID NO.:149;

nn. a light chain variable domain defined in SEQ ID NO.:113 and a heavy chain variable domain defined in SEQ ID NO.:137;

oo. a light chain variable domain defined in SEQ ID NO.:114 and a heavy chain variable domain defined in SEQ ID NO.:140;

pp. a light chain variable domain defined in SEQ ID NO.:115 and a heavy chain variable domain defined in SEQ ID NO.:141;

qq. a light chain variable domain defined in SEQ ID NO.:116 and a heavy chain variable domain defined in SEQ ID NO.:142;

rr. a light chain variable domain defined in SEQ ID NO.:117 and a heavy chain variable domain defined in SEQ ID NO.:139;

ss. a light chain variable domain defined in SEQ ID NO.:118 and a heavy chain variable domain defined in SEQ ID NO.:147;

tt. a light chain variable domain defined in SEQ ID NO.:119 and a heavy chain variable domain defined in SEQ ID NO.:143;

uu. a light chain variable domain defined in SEQ ID NO.:120 and a heavy chain variable domain defined in SEQ ID NO.:152;

vv. a light chain variable domain defined in SEQ ID NO.:121 and a heavy chain variable domain defined in SEQ ID NO.:146;

ww. a light chain variable domain defined in SEQ ID NO.:122 and a heavy chain variable domain defined in SEQ ID NO.:138;

xx. a light chain variable domain defined in SEQ ID NO.:123 and a heavy chain variable domain defined in SEQ ID NO.:150;

yy. a light chain variable domain defined in SEQ ID NO.:124 and a heavy chain variable domain defined in SEQ ID NO.:144;

zz. a light chain variable domain defined in SEQ ID NO.:126 and a heavy chain variable domain defined in SEQ ID NO.:145;

aaa. a light chain variable domain defined in SEQ ID NO.:127 and a heavy chain variable domain defined in SEQ ID NO.:157;

bbb. a light chain variable domain defined in SEQ ID NO.:128 and a heavy chain variable domain defined in SEQ ID NO.:155;

ccc. a light chain variable domain defined in SEQ ID NO.:129 and a heavy chain variable domain defined in SEQ ID NO.:156;

ddd. a light chain variable domain defined in SEQ ID NO.:130 and a heavy chain variable domain defined in SEQ ID NO.:151;

eee. a light chain variable domain as set forth in SEQ ID NO.:178 and a heavy chain variable domain as set forth in SEQ ID NO.:179; or

fff. a light chain variable domain as set forth in SEQ ID NO.:182 and a heavy chain variable domain as set forth in SEQ ID NO.:183.

In a further aspect, the present invention provides an isolated antibody or an antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1:SEQ ID NO.:2) comprising:

a. a heavy chain variable domain comprising three complementarity determining regions of SEQ ID NO.:18 and a light chain variable domain comprising three complementarity determining regions of SEQ ID NO.:16;

b. A heavy chain variable domain comprising a CDRH3 having a sequence of SEQ ID NO.: 32, a CDRH1 having a sequence of SEQ

ID NO.: 30 and a CDRH2 having a sequence of SEQ ID NO.:31 and a light chain variable domain comprising a CDRL3 having a sequence of SEQ ID NO.:29, a CDRL1 having a sequence of SEQ ID NO.:27 and a CDRL2 having a sequence of SEQ ID NO.:28;

c. a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16;

d. a heavy chain variable domain as defined in SEQ ID NO.:18 and a light chain variable domain as defined in SEQ ID NO.:16;

e. a heavy chain comprising a sequence at least 80% identical to SEQ ID NO.:6 and a light chain comprising a sequence at least 80% identical to SEQ ID NO.:4;

f. a heavy chain variable domain comprising a sequence as set forth in SEQ ID NO.:179 and a light chain variable domain comprising a sequence as set forth in SEQ ID NO.:178;

g. a heavy chain comprising a sequence as set forth in SEQ ID NO.:177 and a light chain comprising a sequence as set forth in SEQ ID NO.:176;

h. a heavy chain variable domain comprising three complementary determining regions of SEQ ID NO.:22 and a light chain variable domain comprising three complementary determining regions of SEQ ID NO.:20;

i. a heavy chain variable domain comprising a CDRH3 having a sequence of SEQ ID NO.: 38, a CDRH1 having a sequence of SEQ ID NO.: 36 and a CDRH2 having a sequence of SEQ ID NO.:37 and a light chain variable domain comprising a CDRL3 having a sequence of SEQ ID NO.:35, a CDRL1 having a sequence of SEQ ID NO.:33 and a CDRL2 having a sequence of SEQ ID NO.:34;

j. a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:22 and a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:20;

k. a heavy chain as defined in SEQ ID NO.:22 and a light chain as defined in SEQ ID NO.:20, or

l. a heavy chain comprising a sequence at least 80% identical to SEQ ID NO.:10 and a light chain comprising a sequence at least 80% identical to SEQ ID NO.:8.

In a further aspect, the present invention provides an isolated antibody or antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1) and comprising:

a. a light chain variable domain having the sequence: DIVMTQSPXSLAVS+G++XT+NCKSSQSLLNSNFQKNFLAWY QQKPGQXPKLLIYFASTRESS+PDRFXGSGSGTDFTLTISS+Q AED+AXY+CQQHYSTPLTFGXGTKLE+K, wherein + is a conservative substitution of a corresponding amino acid of SEQ ID NO. :16 and wherein X is an amino acid found at a corresponding position in SEQ ID NO.:16 or SEQ ID NO.:178; and

b. a heavy chain variable domain having the sequence: EVQLXQSXAE+X+PGASVX+SCKASGYIFTDYEIHWV+QXPX XGLEW+GVIDPETGNTAFNQKFKG+XT+TADXS+STAYMEL SSLTSED+AVYYCMGYSDYWGQGTX+TVSS, wherein + is a conservative substitution of a corresponding amino acid of SEQ ID NO.:18 and wherein X is an amino acid found at a corresponding position in SEQ ID NO.:18 or SEQ ID NO.:179.

In a further aspect, the present invention provides an isolated antibody or an antigen binding fragment thereof capable of competing with the antibody or antigen binding fragment thereof of the invention.

In a further aspect, the present invention provides an isolated nucleic acid encoding a light chain variable domain and/or a heavy chain variable domain of the antibody or antigen binding fragment thereof of the invention.

In a further aspect, the present invention provides a vector comprising the nucleic acid of the invention.

In a further aspect, the present invention provides an isolated cell comprising the nucleic acid of the invention or comprising or expressing the antibody or antigen binding fragment thereof of the invention.

In a further aspect, the present invention provides a pharmaceutical composition comprising the antibody or antigen binding fragment thereof of the invention, and a pharmaceutically acceptable carrier.

In a further aspect, the present invention provides a composition comprising the antibody or antigen binding fragment thereof of the invention, and a carrier.

In a further aspect, the present invention provides a method of reducing tumor spread, metastasis of tumor cells, tumor invasion, tumor formation or for inducing tumor lysis or of treating cancer, the method comprising administering an isolated antibody or antigen binding fragment thereof capable of binding to KAAG1 (SEQ ID NO.:2) or to the variant to a subject in need, wherein the cancer, tumor or tumor cells comprises cells expressing KAAG1 or a variant thereof and wherein said antibody or antigen binding fragment thereof is an antibody or antigen binding fragment thereof of the invention.

In a further aspect, the present invention provides a method of detecting a tumor comprising cells expressing KAAG1 or a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2, the method comprising administering the antibody or antigen binding fragment thereof of the invention, to a subject in need.

In a further aspect, the present invention provides a method for detecting KAAG1 (SEQ ID NO.:2) or a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2, the method comprising contacting a cell expressing KAAG1 or the KAAG1 variant or a sample comprising or suspected of comprising KAAG1 or the KAAG1 variant with the antibody of the invention and measuring binding.

In a further aspect, the present invention provides a kit comprising the antibody of the invention.

In a further aspect, the present invention provides the use of an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or comprising at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2 to generate antibodies or antigen binding fragments thereof capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2, which antibodies or antigen binding fragments thereof are for treating cancer, detecting

cancer, reducing tumor spread, reducing metastasis, tumor invasion, tumor formation or for inducing tumor lysis.

In a further aspect, the present invention provides a composition for generating antibodies or antigen binding fragments thereof capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2, the composition comprising a polypeptide comprising an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or comprising at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2 wherein said polypeptide lacks amino acids 1-25 of SEQ ID NO. :2, and a carrier.

In a further aspect, the present invention provides a method for generating antibodies or antigen binding fragments thereof capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2 for treating cancer, detecting cancer, reducing tumor spread, metastasis, tumor invasion, tumor formation or inducing tumor lysis, the method comprising administering a polypeptide comprising an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or comprising at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2.

In a further aspect, the present invention provides the use of an antibody or antigen binding fragment thereof capable of binding to KAAG1 (SEQ ID NO.:2) or to a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2, wherein the antibody or antigen binding fragment thereof binds to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2 in the manufacture of a medicament for:

a. treatment of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof, wherein said antibody or antigen binding fragment thereof induces lysis of tumor cells, reduces spreading of tumor cells, decreases formation of tumor or decreases metastasis of tumor cells, wherein the tumor or tumor cells expresses KAAG1 or the KAAG1 variant thereof;

b. treatment of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof, wherein the antibody or antigen binding fragment thereof is as defined in the invention;

c. treatment of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof wherein the antibody or antigen binding fragment thereof is as defined in the invention and comprises framework amino acids of a human antibody;

d. reducing tumor spread, wherein the tumor comprises cells expressing KAAG1 or the KAAG1 variant thereof;

e. reducing metastasis of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

f. reducing invasion of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

g. reducing formation of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

h. inducing tumor lysis of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

i. reducing spread of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

j. diagnosis of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof; or

k. detection of tumor cells expressing KAAG1 or the KAAG1 variant thereof.

In a further aspect, the present invention provides the use of an antibody or an antigen binding fragment thereof capable of binding to KAAG1 (SEQ ID NO.:2) or to a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2 in the diagnosis of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof or in the detection of tumor cells expressing KAAG1 or the KAAG1 variant thereof, wherein the antibody or antigen binding fragment thereof binds to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2.

In a further aspect, the present invention provides a kit comprising a first vector encoding the light chain variable domain of the antibody or antigen binding fragment thereof of the invention and a second vector encoding the heavy chain variable domain of the antibody or antigen binding fragment thereof of the invention.

In a further aspect, the present invention provides a method of making an antibody or an antigen binding fragment thereof comprising culturing an isolated cell so that the antibody or antigen binding fragment thereof of the invention is produced.

This invention relates to the expression of KAAG1 in tumor cells. The invention also relates to specific anti-KAAG1 antibodies and antigen binding fragments as well as kits useful for the treatment, detection and diagnosis of cancer. The antibodies and antigen

binding fragments may more particularly be useful for the treatment, detection and diagnosis of cancer where tumor cells expresses KAAG1, such as ovarian cancer, skin cancer, renal cancer, colorectal cancer, sarcoma, leukemia, brain cancer, cancer of the thyroid, breast cancer, prostate cancer, cancer of the oesophagus, bladder cancer, lung cancer and head and neck cancer.

The present invention provides in one aspect thereof, an isolated or substantially purified antibody or antigen binding fragment which may be capable of specific binding to Kidney associated antigen 1 (KAAG1 defined in SEQ ID NO.:2) or to a KAAG1 variant.

More specifically and in accordance with an embodiment of the invention, the antibody or antigen binding fragment may bind to a domain located between amino acid 30 and amino acid 84 of KAAG1.

In accordance with another embodiment of the invention, the antibody or antigen binding fragment may be capable of binding to an epitope comprised within amino acid 1 to 35 of KAAG1.

In accordance with a further embodiment of the invention, the antibody or antigen binding fragment may be capable of binding to an epitope comprised within amino acid 36 to 60 of KAAG1.

In accordance with yet a further embodiment of the invention, the antibody or antigen binding fragment may be capable of binding to an epitope comprised within amino acid 61 to 84 of KAAG1.

The antibody or antigen binding fragment of the present invention is especially capable of specific binding to a secreted form of KAAG1, i.e., a form of KAAG1 where the signal peptide has been cleaved.

The antibody or antigen binding fragment of the present invention is especially capable of binding to the extracellular region of KAAG1.

As such, the present invention encompasses diagnostic and/or therapeutic antibodies or antigen binding fragments having specificity for a secreted form of KAAG1 or for an extracellular region of KAAG1. Also encompassed by the present invention are antibodies or antigen binding fragments having the same epitope specificity as the

antibody of the present invention. A candidate antibody may be identified by determining whether it will bind to the epitope to which the antibodies described herein binds and/or by performing competition assays with antibodies or antigen binding fragments known to bind to the epitope.

Therefore another aspect the present invention provides an isolated antibody or antigen binding fragment capable of competing with the antibody or antigen binding fragment described herein.

Isolated antibodies or antigen binding fragments of the present invention include those which may be capable of inducing killing (elimination, destruction, lysis) of KAAG1-expressing tumor cells or KAAG1 variant-expressing tumor cells (e.g., in an ADCC-dependent manner).

Isolated antibodies or antigen binding fragments of the present invention also include those which are characterized by their ability to reduce spreading of KAAG1- expressing tumor cells and also those which are characterized by their ability to decrease or impair formation of KAAG1- expressing tumors.

The antibodies or antigen binding fragments may be particularly effective when KAAG1 is expressed at the surface of the KAAG1-expressing tumor cells and may be particularly useful in targeting KAAG1- expressing tumor cells characterized by anchorage-independent growth.

The invention relates to monoclonal antibodies, polyclonal antibodies, chimeric antibodies, humanized antibodies and human antibodies (isolated) as well as antigen binding fragments having the characteristics described herein. Antibodies or antigen binding fragments encompassing permutations of the light and/or heavy chains between a monoclonal, chimeric, humanized or human antibody are also encompassed herewith.

The antibodies or antigen binding fragments of the present invention may thus comprise amino acids of a human constant region and/or framework amino acids of a human antibody.

The term "antibody" refers to intact antibody, monoclonal or polyclonal antibodies. The term "antibody" also encompasses multispecific antibodies such as bispecific antibodies. Human antibodies are usually made of two light chains and two heavy chains each

comprising variable regions and constant regions. The light chain variable region comprises 3 CDRs, identified herein as CDRL1, CDRL2 and CDRL3 flanked by framework regions. The heavy chain variable region comprises 3 CDRs, identified herein as CDRH1, CDRH2 and CDRH3 flanked by framework regions.

The term "antigen-binding fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to bind to an antigen (e.g., KAAG1, secreted form of KAAG1 or variants thereof). It has been shown that the antigen-binding function of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen-binding fragment" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and C_{H1} domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and C_{H1} domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a V_H domain; and (vi) an isolated complementarity determining region (CDR), e.g., V_H CDR3. Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single polypeptide chain in which the V_L and V_H regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding fragment" of an antibody. Furthermore, the antigen-binding fragments include binding-domain immunoglobulin fusion proteins comprising (i) a binding domain polypeptide (such as a heavy chain variable region, a light chain variable region, or a heavy chain variable region fused to a light chain variable region via a linker peptide) that is fused to an immunoglobulin hinge region polypeptide, (ii) an immunoglobulin heavy chain CH2 constant region fused to the hinge region, and (iii) an immunoglobulin heavy chain CH3 constant region fused to the CH2 constant region. The hinge region may be modified by replacing one or more cysteine residues with serine residues so as to prevent dimerization. Such binding-domain immunoglobulin fusion proteins are further disclosed in US 2003/0118592 and US 2003/0133939. These antibody fragments are obtained using conventional techniques known to those with skill

in the art, and the fragments are screened for utility in the same manner as are intact antibodies.

A typical antigen binding site is comprised of the variable regions formed by the pairing of a light chain immunoglobulin and a heavy chain immunoglobulin. The structure of the antibody variable regions is very consistent and exhibits very similar structures. These variable regions are typically comprised of relatively homologous framework regions (FR) interspaced with three hypervariable regions termed Complementarity Determining Regions (CDRs). The overall binding activity of the antigen binding fragment is often dictated by the sequence of the CDRs. The FRs often play a role in the proper positioning and alignment in three dimensions of the CDRs for optimal antigen binding.

Antibodies and/or antigen binding fragments of the present invention may originate, for example, from a mouse, a rat or any other mammal or from other sources such as through recombinant DNA technologies.

Further scope, applicability and advantages of the present invention will become apparent from the non-restrictive detailed description given hereinafter. It should be understood, however, that this detailed description, while indicating exemplary embodiments of the invention, is given by way of example only, with reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows the expression profiling analyses using semi-quantitative RT-PCR reactions carried out to measure the level of KAAG1 mRNA expression in RNA samples derived from greater than 20 ovarian tumors, benign (low malignancy potential) tumors, ovarian cancer cell lines, and 30 normal tissues. The control panels show GAPDH expression, a house-keeping gene used to compare the amount of starting material in each RT-PCR reaction.

Figure 1B shows semi-quantitative RT-PCR experiments demonstrating that KAAG1 mRNA is expressed in ovarian cancer cell lines, in particular those that are derived from ascites.

Figure 1C shows a diagram illustrating the ability of ovarian cancer cell lines to form 3D structures called spheroids. The left panels show the cells grown in medium lacking serum whereas 5% serum stimulated the formation of the spheroid structures.

Figure 1D shows semi-quantitative RT-PCR experiments demonstrating that the KAAG1 mRNA is highly induced during the formation of spheroids in ovarian cancer cell lines.

Figure 2A shows a diagram illustrating the wound or scratch assay, a cell-based assay that is a measurement of a cell line's ability to migrate into a denuded area over a pre-determined period of time. TOV-21G cells harboring KAAG1 shRNAs display a reduced capacity to fill in the denuded area.

Figure 2B shows an illustration of the clonogenic assay, also known as a colony survival assay. It measured the survival of diluted cells over a period of several days. TOV-21G cells harboring KAAG1 shRNAs display reduced survival.

Figure 3A shows a polyacrylamide gel that was stained with Coomassie Blue and contains a sample (10 μg) of purified Fc-KAAG1 fusion protein that was produced in transiently transfected 293E cells.

Figure 3B shows the results of an ELISA of one of the 96-well plates containing individual monoclonal antibodies selected from Omniclonal library #3 containing anti-KAAG1 Fabs. The results showed that 48 (highlighted in grey) of the Fabs interacted very efficiently with KAAG1. The wells indicated by bold numbers contained the exemplary monoclonals 3D3, 3G10, and 3C4.

Figure 4A shows a polyacrylamide gel that was stained with Coomassie Blue and contains a sample (10 μg) of purified Fc-KAAG1 fusion protein (lane 1), a truncated mutant of KAAG1 spanning amino acids 1-60 (lane 2), and another truncated mutant of KAAG1 spanning amino acids 1-35 (lane 3) that were produced in transiently transfected 293E cells. All proteins were Fc fusion proteins.

Figure 4B is a scheme that illustrates the truncated mutants of KAAG1 that were generated for the epitope mapping studies.

Figure 4C shows a drawing that describes the results from ELISA analyses to map the epitopes that are bound by the anti-KAAG1 antibodies contained in Omniclonal library

#3. The results showed that the majority of monoclonals interact with central region of KAAG1 and that certain antibodies bound to the amino- or carboxyl-termini of KAAG1.

Figure 5 presents a scheme that illustrates the steps involved to convert the mouse Fabs into IgG1 mouse-human chimeric mAbs.

Figure 6 shows drawings that compare the binding of the mouse anti-KAAG1 Fabs with the binding of the corresponding IgG1 chimeric monoclonal antibodies for exemplary antibodies 3D3, 3G10, and 3C4. The results indicate that the relative binding of the Fab variable regions was maintained when transferred to a full human IgG1 scaffold.

Figure 7 shows depictions of spheroid formation experiments using TOV-21G and OV-90 ovarian cancer cell lines in the presence of chimeric IgG1 anti-KAAG1 monoclonal antibodies. Loosely packed structures are indicative of less invasive cancer cell lines. The results show spheroids treated with the exemplary anti-KAAG1 antibodies 3D3, 3G10, or 3C4.

Figure 8A shows a scan of a tissue microarray containing approximately 70 biopsy samples obtained from ovarian tumor patients. The samples were blotted with the 3D3 anti-KAAG1 antibody and showed that the vast majority of ovarian tumors expressed very high level of KAAG1 antigen.

Figure 8B a higher magnification picture from the tissue microarray experiment. The arrows show the membrane localization of KAAG1 at the apical surface of the epithelial layer of cells in serous ovarian tumors.

Figure 8C illustrates other immunohistochemical studies that demonstrate that KAAG1 is highly expressed in all ovarian cancer types. The histotypes shown are serous, mucinous and endometroid.

Figure 9A, 9B and 9C is a summary of alignment results obtained for selected CDRL1, CDRL2 or CDRL3 sequences using the ClustalW2 program; where " * " means that the residues in that column are identical in all sequences in the alignment, " : " means that conserved substitutions have been observed and " . " means that semi-conserved substitutions are observed. Consensus CDRs were generated using the ClustalW program (Larkin M.A., et al., (2007) ClustalW and ClustalX version 2. *Bioinformatics 2007 23(21): 2947-2948*).

Figure 10A, 10B and 10C is a summary of alignment results obtained for selected CDRH1, CDRH2 or CDRH3 sequences using the ClustalW2 program; where " * " means that the residues in that column are identical in all sequences in the alignment, " : " means that conserved substitutions have been observed and " . " means that semi-conserved substitutions are observed. Consensus CDRs were generated using the ClustalW program (Larkin M.A., et al., (2007) ClustalW and ClustalX version 2. *Bioinformatics 2007 23(21): 2947-2948*).

Figure 11 represents sequence comparison between each of the light chain variable regions generated and representative light chain variable regions identified in SEQ ID NOs:16, 20, 24 or 105. Percent sequence identity and percent sequence similarity has been determined unsing Blast2 sequence program as indicated herein.

Figure 12 represents sequence comparison between each of the heavy chain variable regions generated and representative heavy chain variable regions identified in SEQ ID NOs:18, 22, 26 or 132. Percent sequence identity and percent sequence similarity has been determined unsing Blast2 sequence program as indicated herein.

Figure 13 An IgG_1 antibody that targets KAAG1 can efficiently mediate ADCC activity *in vitro*. PBMNCs (AllCells, LLC, Emoryville, CA) were incubated with 3D3 for 30 min and mixed with either OVCAR-3 or WIL2-S cells at a ratio of 1:25. The cells were incubated for 4 h at 37 C and cell lysis was determined by measuring LDH levels in the medium. Cell cytotoxicity was calculated as follows: % cytotoxicity = (experimental – effector spontaneous – target spontaneous) x 100 / (target maximum – target spontaneous).

Figure 14 Anti-KAAG1 mAbs prevent the spread of TOV-112D ovarian tumors *in vivo*. 1 x 10^6 cells were implanted in the peritoneal cavity of SCID mice in a volume of 200 μL. Treatment with either PBS or antibodies diluted in PBS was performed 2 days later at a dose of 25 mg/kg qwk. The mice were sacrificed as soon as the tumors were detected by palpation of the abdomen. The number of tumors were scored visually (B) and the data in panel A is expressed as the average number of tumors/mouse ± SE.

Figure 15 shows immunohistochemistry performed with an anti-KAAG1 antibody on human skin tumor tissue microarrays (Pantomics Inc., Richmond, CA) of several sections isolated from squamous cell carcinomas and melanomas.

Figure 16 illustrates spheroid formation of melanoma cell lines (A375 and SK-MEL5) and of renal cell carcinoma cell lines (A498 and 786-O) in the presence or absence of the chimeric 3D3 antibody.

Figure 17A represents graphs illustrating the binding of increasing concentrations of the 3C4, 3D3 and 3G10 antibodies to cell lines (OV-90, TOV-21G and SKOV-3) fixed under condition that do not permeate the cells.

Figure 17B is a graph illustrating the results of flow cytometry performed on SKOV-3 cell line with the 3D3 antibody.

Figure 18A is a schematic illustrating the structure of the 3D3 antibody model.

Figure 18B is a schematic illustrating the structure of the 3C4 antibody model.

Figure 19A is a graph illustrating the binding of increasing concentration of the humanized 3D3 antibody in comparison with the chimeric 3D3 antibody to recombinant KAAG1.

Figure 19B is a table summarizing the kinetics parameters of the humanized 3D3 antibody, the chimeric 3D3 antibody as well as hybrid antibodies encompassing permutations of the light and heavy chains of the chimeric or humanized antibody.

Figure 19C illustrates spheroid formation of SKOV-3 ovarian cancer cells in the presence of the humanized 3D3 antibody, chimeric 3D3 antibody or in the presence of a buffer or a control IgG.

Figure 20A represents sequence alignment of the monoclonal 3D3 light chain variable region (SEQ ID NO.:16) and the humanized 3D3 light chain variable region (SEQ ID NO.:178). The humanized 3D3 light chain variable region is 86% identical (94% sequence similarity) to the monoclonal 3D3 light chain variable region and their three CDRs are 100% (indicated in bold).

Figure 20B represents sequence alignment of the monoclonal 3D3 heavy chain variable region (SEQ ID NO.:18) and the humanized 3D3 heavy chain variable region (SEQ ID NO.:179). The humanized 3D3 heavy chain variable region is 82% identical (91% sequence similarity) to the monoclonal 3D3 heavy chain variable region and their three CDRs are 100% (indicated in bold).

Figure 21A represents sequence alignment of the monoclonal 3C4 light chain variable region (SEQ ID NO.:24) and the humanized 3C4 light chain variable region (SEQ ID

NO.:182). The humanized 3C4 light chain variable region is 85% identical (93% sequence similarity) to the monoclonal 3C4 light chain variable region and their three CDRs are 100% (indicated in bold).

Figure 21B represents sequence alignment of the monoclonal 3C4 heavy chain variable region (SEQ ID NO.:26) and the humanized 3C4 heavy chain variable region (SEQ ID NO.:183). The humanized 3C4 heavy chain variable region is 86% identical (93% sequence similarity) to the monoclonal 3C4 heavy chain variable region and their three CDRs are 100% (indicated in bold).

DETAILED DESCRIPTION OF THE INVENTION

The expression and biological activity of KAAG1 in cancer cells

The present invention relates to the use of antibodies to target tumors found in various cancer types, in particular ovarian cancer. In order to direct the antibodies to the tumors, the identification of tumor-specific antigens that are expressed at the cell surface of the cancer cells must be carried out. There are several technologies that are available to identify tumor-specific antigens and the method that was used to identify KAAG1 in ovarian tumors, an innovative discovery platform called Subtractive Transcription-based Amplification of mRNA (STAR), is described in the published patent application No. PCT/CA2007/001134.

Analysis of the ovarian cancer STAR libraries yielded many genes that encode secreted and cell surface proteins. One of these, termed AB-0447, contained an open reading frame that encoded a polypeptide of 84 amino acids, corresponding to SEQ ID NO.:2 that was encoded by a cDNA of 885 base pairs with the nucleotide sequence shown in SEQ ID NO.:1. A search of publicly available databases revealed that the AB-0447 nucleotide sequence was identical to that of a gene called KAAG1. Bioinformatic analysis predicted a membrane-anchored protein that presents its functional domain to the extracellular compartment. KAAG1 was originally cloned from a kidney cancer library as a cell surface antigen, a result that confirms its membrane localization. Additionally, our studies showed that the protein was processed at its amino-terminus, a result that was consistent with cleavage of a functional signal peptide at or between amino acids 30 and 34. Furthermore, transient expression of the full-length cDNA resulted in detection of cleaved KAAG1 in the culture medium. This last finding indicated that this membrane-

anchored protein could be shed from the cells when expressed at high levels. In contrast, expression of an amino-truncated mutant of KAAG1 resulted in intra-cellular retention of the protein. There are currently no published reports that shed any light on its function and the over-expression of KAAG1 in ovarian cancer, as disclosed by this invention, has never been previously documented.

We have thus investigated whether KAAG1 could be used for antibody-based diagnostics and therapeutics.

Several ovarian cancer cell-based models have been established, such as TOV-21G, TOV-112D, OV-90, and others, and are familiar to those skilled in the art. These cells are part of a collection of human ovarian cancer cell lines derived from patients with ovarian tumors or ascites fluid. These cell lines have undergone an in-depth analysis, including global gene expression patterns on microarrays that make them excellent cell-based models for human ovarian cancer. The growth properties, gene expression patterns, and response to chemotherapeutic drugs indicated that these cell lines are very representative of ovarian tumor behavior *in vivo* (Benoît et al., 2007). RT-PCR analysis of total RNA isolated from these ovarian cancer cell lines showed that the KAAG1 transcript was weakly expressed in the cell lines derived from primary tumors. In contrast, cell lines derived from ascitic fluid contained high levels of KAAG1 expression. The increased expression of KAAG1 in cells from the ascitic fluid suggested that the environment of the cells influences the regulation of the *KAAG1* gene. Ascitic cells are associated with advanced disease and this pattern of expression implies that increased KAAG1 levels are associated with anchorage-independent growth. In concordance with this latter suggestion, KAAG1 expression was found to significantly increase in cell lines derived from primary tumors when these cells were cultured as spheroids in 3D cultures. These spheroids have been extensively characterized and were found to display many properties associated with tumors *in vivo* (Cody et al., 2008). Thus, expression of KAAG1 was found to be significantly increased in models that mimic tumor progression, in particular during the evolution of ovarian cancer.

With the demonstration that KAAG1 expression is regulated in ovarian cancer cells, the function of this gene in ovarian cancer cell behavior was examined in cell-based assays. To that effect, RNA interference (RNAi) was used to knock down the expression of the endogenous KAAG1 gene in the ovarian cancer cell lines and it was found that

decreased expression of KAAG1 resulted in a significant reduction in the migration of the cells as determined in a standard cell motility assay, as exemplified by a wound healing (or scratch) assay. This type of assay measures the speed at which cells fill a denuded area in a confluent monolayer. Decreased expression of KAAG1 resulted in a reduction in the survival of ovarian cancer cell lines as measured by a clonogenic assay, such as a colony survival assay. Those skilled in the art may use other methods to evaluate the requirement of KAAG1 in the behavior of cancer cells, in particular ovarian cancer cells.

Based on the expression of KAAG1 in a large proportion of ovarian tumors, its limited expression in normal tissues, and a concordance between expression levels and increased malignancy, and a putative biological role for KAAG1 in the behavior of ovarian cancer cell lines, KAAG1 was chosen as a therapeutic target for the development of antibodies for the detection, prevention, and treatment of ovarian cancer. Expression of KAAG1 in cancer, other than ovarian cancer also lead the Applicant to the evaluation of therapeutic or diagnostic antibodies for other cancer indications.

Therefore, a variety of anti-KAAG1 antibodies and antigen binding fragments thereof, such as monoclonal antibodies, polyclonal antibodies, chimeric and humanized antibodies (including humanized monoclonal antibodies), antibody fragments, single chain antibodies, domain antibodies, and polypeptides with an antigen binding region, useful for targeting KAAG1 are provided.

KAAG1 as antigen and epitopes derived from KAAG1

The Applicant has come to the unexpected discovery that KAAG1 is expressed in several tumor types and is also found in blood and in ascitic fluid of patients. This antigen may thus be useful for targeting tumor cells expressing the antigen *in vivo* and in the development of detection assays for measuring the tumor associated antigen *in vitro* or *in vivo*. The KAAG1 antigen circulating in blood lacks the signal peptide.

The present invention therefore provides a KAAG1 antigen useful for generating antibodies specific for the circulating form of KAAG1 and/or specific for tumor-expressed KAAG1. The KAAG1 antigen (i.e., epitope) may comprise a fragment of at least 10 amino acids (and up to 84 amino acids) of KAAG1 and may especially bind to the extracellular region of KAAG1.

An exemplary antigen is the whole KAAG1 protein or a variant form having at least 80% sequence identity with SEQ ID NO.:2 or a fragment thereof.

Another exemplary antigen derived from KAAG1 is the secreted or circulating form of KAAG1 which lacks the signal peptide or the extracellular region of KAAG1. This antigen may more particularly lack amino acids 1 to 25, 1 to 26, 1 to 27, 1 to 28, 1 to 29, 1 to 30, 1 to 31, 1 to 32, 1 to 33, 1 to 34, 1 to 35 or 1 to 36 of KAAG1.

The antigen or the epitope described herein may be fused with a carrier such as keyhole limpet (KHL), bovine serum albumin (BSA), ovalbumin (OVA) or else in order to generate antibodies and antigen binding fragments.

The present invention also provides an epitope comprised within amino acid 1 to 35 of SEQ ID NO.:2, within amino acid 36 to 60 of SEQ ID NO.:2 or within amino acid 61 to 84 of SEQ ID NO.:2 to generate antibodies and antigen binding fragments described herein.The present invention further provides a composition for generating antibodies to a secreted or circulating form of KAAG1 or to an extracellular region of KAAG1, the composition may comprise an epitope of KAAG1 comprised within amino acids 30 to 84 of SEQ ID NO.:2 and a carrier. The epitope may especially comprise at least 10 amino acids of KAAG1.

Exemplary embodiments of compositions are pharmaceutical composition for generating antibodies to a secreted or circulating form of KAAG1 or to the extracellular region of KAAG1. The pharmaceutical composition may comprise an epitope of KAAG1 comprised within amino acids 30 to 84 of SEQ ID NO.:2 and a pharmaceutically acceptable carrier.

In yet a further aspect the invention provides a method for generating antibodies to a secreted or circulating form of KAAG1. The method may comprise administering a polypeptide comprising an epitope of KAAG1 comprised within amino acids 30 to 84 of SEQ ID NO.:2 wherein the epitope lacks a KAAG1 signal peptide.

Alternatively, the method may comprise administering an epitope which comprises the signal peptide and selecting antibodies which only binds to the secreted form or the extracellular region of the protein.

In an additional aspect, the present invention provides the use of an epitope of KAAG1 comprised within amino acids 30 to 84 of SEQ ID NO.:2 for generating antibodies to a secreted or circulating form of KAAG1.

Antibodies and antigen binding fragments that binds to KAAG1

Antibodies were initially isolated from Fab librairies for their specificity towards the antigen of interest. Comparison of the amino acid sequences of the light chain variable domains or the heavy chain variable domains of antibodies showing the greatest characteristics allowed us to derive consensus sequences within the CDRs and within the variable regions. The consensus for CDRs are provided in SEQ ID Nos: 74 to 90.

The variable regions described herein may be fused with constant regions of a desired species thereby allowing recognition of the antibody by effector cells of the desired species. The constant region may originate, for example, from an IgG1, IgG2, IgG3, or IgG4 subtype. Cloning or synthesizing a constant region in frame with a variable region is well within the scope of a person of skill in the art and may be performed, for example, by recombinant DNA technology.

In certain embodiments of the present invention, antibodies that bind to KAAG1 may be of the IgG1, IgG2, IgG3, or IgG4 subtype. More specific embodiments of the invention relates to an antibody of the IgG1 subtype. The antibody may be a humanized antibody of the IgG1 subtype that is biologically active in mediating antibody-dependent cellular cytotoxicity (ADCC), complement-mediated cytotoxicity (CMC), or associated with immune complexes. The typical ADCC involves activation of natural killer (NK) cells and is reliant on the recognition of antibody-coated cells by Fc receptors on the surface of the NK cells. The Fc receptors recognize the Fc domain of antibodies such as is present on IgG1, which bind to the surface of a target cell, in particular a cancerous cell that expresses an antigen, such as KAAG1. Once bound to the Fc receptor of IgG the NK cell releases cytokines and cytotoxic granules that enter the target cell and promote cell death by triggering apoptosis.

In some instances, anti-KAAG1 antibodies with substantially identical light and heavy chain variable regions to antibody 3D3, will interact with an epitope spanned by amino acids 36 – 60, inclusively, of KAAG1. In other instances, anti-KAAG1 antibodies with substantially identical light and heavy chain variable regions to antibody 3G10, will interact with an epitope spanned by amino acids 61 – 84, inclusively, of KAAG1. In yet

another instance, anti-KAAG1 antibodies with substantially identical light and heavy chain variable regions to antibody 3C4 will interact with an epitope spanned by amino acids 1 – 35, inclusively, of KAAG1.

The present invention described a collection of antibodies that bind to KAAG1. In certain embodiments, the antibodies may be selected from the group consisting of polyclonal antibodies, monoclonal antibodies such as chimeric or humanized antibodies, antibody fragments such as antigen binding fragments, single chain antibodies, domain antibodies, and polypeptides with an antigen binding region.

In an aspect of the invention, the isolated antibody or antigen binding fragment of the present invention may be capable of inducing killing (elimination, destruction, lysis) of KAAG1-expressing tumor cells or KAAG1 variant-expressing tumor cells (e.g., in an ADCC-dependent manner).

In a further aspect of the invention, the isolated antibody or antigen binding fragment of the present invention may especially be characterized by its capacity of reducing spreading of KAAG1- expressing tumor cells.

In an additional aspect of the invention, the isolated antibody or antigen binding fragment of the present invention may be characterized by its capacity of decreasing or impairing formation of KAAG1- expressing tumors.

In accordance with an embodiment of the invention, the antibody or antigen binding fragment may be more particularly effective when KAAG1 is expressed at the surface of the KAAG1-expressing tumor cells.

Also in accordance with the present invention, the antibody or antigen binding fragment may be especially useful in targeting KAAG1- expressing tumor cells which are characterized by anchorage-independent growth.

In a further aspect, the present invention relates to an isolated antibody or antigen binding fragment for use in the treatment of cancer comprising tumor cells expressing KAAG1.

In yet a further aspect, the present invention relates to an isolated antibody or antigen binding fragment for use in the detection of cancer comprising tumor cells expressing KAAG1.

In an exemplary embodiment of the invention, the isolated antibody or antigen binding fragment may comprise amino acids of a constant region, which may originate, for example, from a human antibody.

In another exemplary embodiment of the invention, the isolated antibody or antigen binding fragment may comprise framework amino acids of a human antibody.

Without being limited to the exemplary embodiments presented herein, the Applicant as generated specific antibodies and antigen binding fragments which may be useful for the purposes described herein.

The present invention therefore provides in an exemplary embodiment, an isolated antibody or antigen binding fragment comprising a light chain variable domain having;

a. a CDRL1 sequence selected from the group consisting of SEQ ID NO.:74 and SEQ ID NO.:75;
b. a CDRL2 sequence selected from the group consisting of SEQ ID NO.:76, SEQ ID NO.: 77 and SEQ ID NO.:78, or;
c. a CDRL3 sequence selected from the group consisting of SEQ ID NO.:79, SEQ ID NO.:80 and SEQ ID NO.:81.

The isolated antibody or antigen binding fragment may also comprise a heavy chain variable domain having;

a. a CDRH1 sequence comprising SEQ ID NO.:82;
b. a CDRH2 sequence selected from the group consisting of SEQ ID NO.:83, SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:86 and SEQ ID NO.:87, or;
c. a CDRH3 sequence selected from the group consisting of SEQ ID NO.:88, SEQ ID NO.:89 and SEQ ID NO.:90.

In an exemplary embodiment, the antibody or antigen binding fragment may comprise any individual CDR or a combination of CDR1, CDR2 and/or CDR3 of the light chain variable region. The CDR3 may more particularly be selected. Combination may include

for example, CDRL1 and CDRL3; CDRL1 and CDRL2; CDRL2 and CDRL3 and; CDRL1, CDRL2 and CDRL3.

In another exemplary embodiment, the antibody or antigen binding fragment may comprise any individual CDR or a combination of CDR1, CDR2 and/or CDR3 of the heavy chain variable region. The CDR3 may more particularly be selected. Combination may include for example, CDRH1 and CDRH3; CDRH1 and CDRH2; CDRH2 and CDRH3 and; CDRH1, CDRH2 and CDRH3.

In accordance with the present invention, the antibody or antigen binding fragment may comprise at least two CDRs of a CDRL1, a CDRL2 or a CDRL3.

Also in accordance with the present invention, the antibody or antigen binding fragment may comprise one CDRL1, one CDRL2 and one CDRL3.

Further in accordance with the present invention, the antibody or antigen binding fragment may comprise:

a. At least two CDRs of a CDRL1, CDRL2 or CDRL3 and;
b. At least two CDRs of a CDRH1, one CDRH2 or one CDRH3.

The antibody or antigen binding fragment may more preferably comprise one CDRL1, one CDRL2 and one CDRL3.

The antibody or antigen binding fragment may also more preferably comprise one CDRH1, one CDRH2 and one CDRH3.

Other exemplary embodiments of the invention relates to an isolated antibody or antigen binding fragment comprising a heavy chain variable domain having;

a. a CDRH1 sequence comprising SEQ ID NO.:82;
b. a CDRH2 sequence selected from the group consisting of SEQ ID NO.:83, SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:86 and SEQ ID NO.:87, or;
c. a CDRH3 sequence selected from the group consisting of SEQ ID NO.:88, SEQ ID NO.:89 and SEQ ID NO.:90.

In accordance witht the present invention, the antibody or antigen binding fragment may comprise one CDRH1, one CDRH2 or one CDRH3.

In accordance witht the present invention, the antibody or antigen binding fragment may also comprise one CDRH1, one CDRH2 and one CDRH3.

When only one of the light chain variable domain or the heavy chain variable domain is available, an antibody or antigen-binding fragment may be reconstituted by screening a library of complementary variable domains using methods known in the art (Portolano et al. The Journal of Immunology (1993) 150:880-887, Clarkson et al., Nature (1991) 352:624-628).

Also encompassed by the present invention are polypeptides or antibodies comprising variable chains having at least one conservative amino acid substitution in at least one of the CDRs described herein (in comparison with the original CDR).

The present invention also encompasses polypeptides or antibodies comprising variable chains having at least one conservative amino acid substitution in at least two of the CDRs (in comparison with the original CDRs).

The present invention also encompasses polypeptides or antibodies comprising variable chains having at least one conservative amino acid substitution in the 3 CDRs (in comparison with the original CDRs).

The present invention also encompasses polypeptides or antibodies comprising variable chains having at least two conservative amino acid substitutions in at least one of the CDRs (in comparison with the original CDRs).

The present invention also encompasses polypeptides or antibodies comprising variable chains having at least two conservative amino acid substitutions in at least two of the CDRs (in comparison with the original CDRs).

The present invention also encompasses polypeptides or antibodies comprising variable chains having at least two conservative amino acid substitutions in the 3 CDRs (in comparison with the original CDRs).

In another aspect, the present invention relates to a polypeptide, antibody or antigen binding fragment comprising (on a single polypeptide chain or on separate polypeptide chains) at least one complementarity-determining region of a light chain variable domain

and at least one complementarity-determining region of a heavy chain variable domain of one of the antibodies or antigen binding fragment described herein.

The present invention relates in another aspect thereof to anti-KAAG1 antibodies that may comprise (on a single polypeptide chain or on separate polypeptide chains) all six complementarity-determining regions (CDRs) of the antibody or antigen binding fragment described herein.

The antibodies or antigen binding fragment of the present invention may further comprise additional amino acids flanking the amino and/or carboxy region of the CDR(s). Those additional amino acids may be as illustrated in Table A or Table B or may include, for example, conservative amino acid substitution.

In accordance with the present invention, the antibody may comprise a CDRL1 sequence comprising or consisting of formula:

$X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74)

wherein X_{1a} may be a basic amino acid;
wherein X_{2a} may be a basic amino acid;
wherein X_{3a} may be H, Y or N;
wherein X_{4a} may be S, T, N or R;
wherein X_{5a} may be absent, S or N;
wherein X_{6a} may be D, F or N;
wherein X_{7a} may be G or Q;
wherein X_{8a} may be K, L or N;
wherein X_{9a} may be T or N;
wherein X_{10a} may be an aromatic amino acid, and;
wherein X_{11a} may be A, N, E or Y.

In an exemplary embodiment of the invention X_{1a} may be K or R.

In a further embodiment of the invention X_{2a} may be Q or K.

In yet a further embodiment of the invention X_{3a} may be N or H.

In an additional embodiment of the invention X_{10a} may be Y or F.

More specific embodiments of the invention include CDRL1 of SEQ ID NO.:74 where: X_{1a} is K; X_{2a} is Q; X_{3a} is N; X_{3a} is H; X_{4a} is S; X_{4a} is T; X_{5a} is S; X_{5a} is absent; X_{6a} is N; X_{7a} is Q; X_{7a} is G; X_{8a} is K; X_{9a} is N; X_{9a} is T; X_{10a} is Y; or X_{11a} is A.

In accordance with the present invention, the antibody may comprise a CDRL1 sequence comprising or consisting of formula:
$KASQDX_{1b}X_{2b}X_{3b}X_{4b}X_{5b}X_{6b}$ (SEQ ID NO.:75)
wherein X_{1b} may be an hydrophobic amino acid;
wherein X_{2b} may be G or H;
wherein X_{3b} may be T, N or R;
wherein X_{4b} may be F, Y or A;
wherein X_{5b} may be an hydrophobic amino acid, and;
wherein X_{6b} may be N or A.

In an exemplary embodiment of the invention X_{1b} may be V or I.

In another exemplary embodiment of the invention X_{5b} may be V or L.

More specific embodiments of the invention include CDRL1 of SEQ ID NO.:75 where X_{1b} is I; X_{2b} is H; X_{3b} is T; X_{3b} is N; X_{4b} is Y; X_{4b} is F; X_{5b} is L or X_{6b} is N.

In accordance with the present invention, the antibody may comprise a CDRL2 sequence comprising or consisting of formula:
$FX_{1c}STX_{2c}X_{3c}S$ (SEQ ID NO.:76)
Wherein X_{1c} is A or G;
Wherein X_{2c} is R or T, and;
Wherein X_{3c} is E, K or A.

In an exemplary embodiment of the invention X_{1c} may be A and X_{2c} may be T.

In another exemplary embodiment of the invention X_{1c} may be A and X_{2c} may be R.

Other specific embodiments of the invention include CDRL2 of SEQ ID NO.:76 where

X_{1c} is A; X_{2c} is R or X_{3c} is E.

In accordance with the present invention, the antibody may comprise a CDRL2 sequence comprising or consisting of formula:

$X_{1d}VSX_{2d}X_{3d}X_{4d}S$ (SEQ ID NO.:77)
Wherein X_{1d} may be L or K;
Wherein X_{2d} may be a basic amino acid;
Wherein X_{3d} may be L or R and;
Wherein X_{4d} may be D or F.

In an exemplary embodiment of the invention X_{2d} may be K or N.

Other specific embodiments of the invention include CDRL2 of SEQ ID NO.:77 where X_{1d} is L; X_{2d} is K; X_{3d} is L or X_{4d} is D.

In accordance with the present invention, the antibody may comprise a CDRL2 sequence comprising or consisting of formula:
$X_{1e}ANRLVX_{2e}$ (SEQ ID NO.:78)
Wherein X_{1e} may be a basic amino acid, and;
Wherein X_{2e} may be D or A.

In an exemplary embodiment of the invention X_{1e} may be R or H.

Other specific embodiments of the invention include CDRL2 of SEQ ID NO.:78 where X_{1e} is R or X_{2e} is D.

In accordance with the present invention, the antibody may comprise a CDRL3 sequence comprising or consisting of formula:
$X_{1f}QX_{2f}X_{3f}X_{4f}X_{5f}PLT$ (SEQ ID NO.:79)
Wherein X_{1f} may be Q or L;
Wherein X_{2f} may be an aromatic amino acid;
Wherein X_{3f} may be D, F or Y;
Wherein X_{4f} may be E, A, N or S, and;
Wherein X_{5f} may be I, F or T.

In an exemplary embodiment of the invention X_{2f} may be Y or H.

In another exemplary embodiment of the invention X_{3f} may be Y or D.

In yet another exemplary embodiment of the invention X_{5f} may be I or T.

Other specific embodiments of the invention include CDRL3 of SEQ ID NO.:79 where X_{1f} is Q; X_{2f} is H; X_{3f} is D; X_{3f} is Y; X_{4f} is S; X_{4f} is E; X_{4f} is A; X_{5f} is T, or X_{5f} is I.

In accordance with the present invention, the antibody may comprise a CDRL3 sequence comprising or consisting of formula:

$QQHX_{1g}X_{2g}X_{3g}PLT$ (SEQ ID NO.:80)

Wherein X_{1g} may be an aromatic amino acid;

Wherein X_{2g} may be N or S, and;

Wherein X_{3g} may be I or T.

In an exemplary embodiment of the invention X_{1g} may be F or Y

Other specific embodiments of the invention include CDRL3 of SEQ ID NO.:80 where X_{2g} is S or X_{3g} is T.

In accordance with the present invention, the antibody may comprise a CDRL3 sequence comprising or consisting of formula:

$X_{1h}QGX_{2h}HX_{3h}PX_{4h}T$ (SEQ ID NO.:81)

Wherein X_{1h} may be an aromatic amino acid;

Wherein X_{2h} may be a neutral hydrophilic amino acid;

Wherein X_{3h} may be F or V, and;

Wherein X_{4h} may be R or L.

In an exemplary embodiment of the invention X_{1h} may be W or F.

In another exemplary embodiment of the invention X_{2h} may be S or T.

Other specific embodiments of the invention include CDRL3 of SEQ ID NO.:81 where X_{1h} is W; X_{2h} is T; X_{3h} is F, or X_{4h} is R.

In accordance with the present invention, the antibody may comprise a CDRH1 sequence comprising or consisting of formula:

$GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82)

Wherein X_{1i} may be T, I or K;

Wherein X_{2i} may be a neutral hydrophilic amino acid;

Wherein X_{3i} may be an acidic amino acid;

Wherein X_{4i} may be E, N or D, and;

Wherein X_{5i} may be hydrophobic amino acid.

In an exemplary embodiment of the invention X_{2i} may be T or S.

In another exemplary embodiment of the invention X_{3i} may be D or E.

In yet another exemplary embodiment of the invention X_{4i} may be N or E.

In a further exemplary embodiment of the invention X_{5i} may be M, I or v.

Other specific embodiments of the invention include CDRH1 of SEQ ID NO.:82 where X_{2i} is T; X_{3i} is D; X_{4i} is E; X_{5i} is I or X_{5i} is M.

In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

$X_{1j}X_{2j}DPX_{3j}TGX_{4j}TX_{5j}$ (SEQ ID NO.:83)

Wherein X_{1j} may be V or G

Wherein X_{2j} may be a hydrophobic amino acid;

Wherein X_{3j} may be A, G or E;

Wherein X_{4j} may be R, G, D, A, S, N or V, and;

Wherein X_{5j} may be a hydrophobic amino acid.

In an exemplary embodiment of the invention X_{2j} may be I or L.

In another exemplary embodiment of the invention X_{5j} may be A or V.

Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:83 where X_{1j} is V; X_{2j} is I; X_{3j} is E; X_{4j} is D or X_{5j} is A.

In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

$VX_{1k}DPX_{2k}TGX_{3k}TA$ (SEQ ID NO.:84)

Wherein X_{1k} may be an hydrophobic amino acid;

Wherein X_{2k} may be A, E or G;

Wherein X_{3k} may be R, G, A, S, N V or D.

In an exemplary embodiment of the invention X_{1k} may be L or I.

Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:84 where X_{1k} is I; X_{2k} is E, or X_{3k} is D.

In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

$YIX_{1l}X_{2l}X_{3l}GX_{4l}X_{5l}X_{6l}$ (SEQ ID NO.:85)

Wherein $X1_l$ may be S or N;

Wherein X_{2l} may be an aromatic amino acid

Wherein X_{3l} may be D, E or N;

Wherein $X4_l$ may be a D or H;

Wherein X_{5l} may be Y, S or N;

Wherein X_{6l} may be D, E or N.

In an exemplary embodiment of the invention X_{3l} may be D or N.

In another exemplary embodiment of the invention X_{6l} may be D or N.

Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:85 where X_{2l} is F or Y, X_{3l} is N, X_{4l} is D or X_{6l} is N.

In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

$X_{1m}INPYNX_{2m}VTE$ (SEQ ID NO.:86)

wherein X_{1m} may be N or Y, and;

wherein X_{2m} may be E, D or N.

In an exemplary embodiment of the invention X_{2m} may be D or N.

Other specific embodiments of the invention include CDRH2 of SEQ ID NO.:86 where X_{1m} is N or X_{2m} is D.

In accordance with the present invention, the antibody may comprise a CDRH2 sequence comprising or consisting of formula:

$DINPX_{1n}YGX_{2n}X_{3n}T$ (SEQ ID NO.:87)

Wherein X_{1n} may be N or Y,

Wherein X_{2n} may be G or T and;

wherein X_{3n} may be I or T.

In accordance with the present invention, the antibody may comprise a CDRH3 sequence comprising or consisting of formula:

$MX_{1o}X_{2o}X_{3o}DY$ (SEQ ID NO.:88)

Wherein X_{1o} may be G or S;

Wherein X_{2o} may be Y or H, and;

wherein X_{3o} may be A or S.

Other specific embodiments of the invention include CDRH3 of SEQ ID NO.:88 where X_{1o} is G; X_{2o} is Y or X_{3o} is S.

In accordance with the present invention, the antibody may comprise a CDRH3 sequence comprising or consisting of formula:

$IX_{1p}YAX_{2p}DY$ (SEQ ID NO.:89)

Wherein X_{1p} may be G or S and;

Wherein X_{2p} may be absent or M.

Other specific embodiments of the invention include CDRH3 of SEQ ID NO.:89 where X_{1p} is S or X_{2p} is M.

In accordance with the present invention, the antibody may comprise a CDRH3 sequence comprising or consisting of formula:

$AX_{1q}X_{2q}GLRX_{3q}$ (SEQ ID NO.:90)

Wherein X_{1q} may be R or W;

Wherein X_{2q} may be an aromatic amino acid and;

wherein X_{3q} may be a basic amino acid.

In an exemplary embodiment of the invention X_{2q} may be W or F.

In another exemplary embodiment of the invention X_{3q} may be Q or N.

Other specific embodiments of the invention include CDRH3 of SEQ ID NO.:90 where X_{1q} is R; X_{2q} is W or X_{3q} is N.

The framework region of the heavy and/or light chains described herein may be derived from one or more of the framework regions illustrated in Tables A and B. The antibody or antigen binding fragments may thus comprise one or more of the CDRs described herein (e.g., selected from the specific CDRs or consensus CDRs of SEQ ID NO.:74 to 90) and

framework regions originating from those illustrated in Tables A and B. In Tables A and B, the expected CDRs are shown in bold, while the framework regions are not.

Table 2 describes the sequences of the nucleotides and the amino acids corresponding to the complete light and heavy chain immunoglobulins of specific examples of anti-KAAG1 antibodies.

TABLE 2 – complete sequences of light and heavy chain immunoglobulins that bind to KAAG1

Antibody designation	**Chain type**	**Nucleotide sequence (SEQ ID NO.:)**	**Amino acid sequence (SEQ ID NO.:)**
3D3	Light (L)	3	4
3D3	Heavy (H)	5	6
3G10	Light	7	8
3G10	Heavy	9	10
3C4	Light	11	12
3C4	Heavy	13	14

An antibody or antigen binding fragment that can bind KAAG1 may comprise any one L chain with any one H chain immunoglobulin that is listed in Table 2. In certain embodiments, the light chain of antibody 3D3 may be combined with the heavy chain of 3D3 or the heavy chain of 3G10 to form a complete antibody with KAAG1-binding activity. In an exemplary embodiment of the present invention, the 3D3 L chain may be combined with the 3D3 H chain, the 3G10 L chain may be combined with the 3G10 H chain, or the 3C4 L chain may be combined with the 3C4 H chain. Additionally, some examples of antibodies or antigen binding fragment may consist of any combination of two L chains and any two H chains from the list of antibodies listed in Table 2.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 3D3 are shown in SEQ ID NOS:3 and 5, respectively, and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 3D3 are shown in SEQ ID NOS:4 and 6, respectively. Thus, in an exemplary embodiment, an antibody that binds to KAAG1 may comprise the light chain amino acid shown in SEQ ID

NO.:4 combined with the heavy chain amino acid sequence shown in SEQ ID NO.:6. In another embodiment, the antibody may comprise two identical 3D3 light chains comprising of SEQ ID NO.:4 and two identical 3D3 heavy chains comprising SEQ ID NO.:6.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 3G10 are shown in SEQ ID NOS:7 and 9, respectively, and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 3G10 are shown in SEQ ID NOS:8 and 10, respectively. Thus, in an exemplary embodiment, an antibody that binds to KAAG1 may comprise the light chain amino acid shown in SEQ ID NO.:8 combined with the heavy chain amino acid sequence shown in SEQ ID NO.:10. In another embodiment, the antibody may comprise two identical 3G10 light chains comprising SEQ ID NO.:8 and two identical 3G10 heavy chains comprising SEQ ID NO.:10.

The complete nucleotide sequences of the light and heavy immunoglobulin chains of antibody 3C4 are shown in SEQ ID NOS:11 and 13, respectively and the corresponding amino acid sequences of the light and heavy immunoglobulin chains of antibody 3C4 are shown in SEQ ID NOS:12 and 14, respectively. Thus, in an exemplary embodiment, an antibody that binds to KAAG1 may comprise the light chain amino acid shown in SEQ ID NO.:12 combined with the heavy chain amino acid sequence shown in SEQ ID NO.:14. In another embodiment, the antibody may comprise two identical 3C4 light chains comprising SEQ ID NO.:12 and two identical 3C4 heavy chains comprising SEQ ID NO.:14.

Variants of other anti-KAAG1 antibodies or antigen binding fragments formed by the combination of light and/or heavy immunoglobulin chains may each independently have at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identity to the amino acid sequences listed in Table 2 are also provided. In certain embodiments, the antibody variants may comprise at least one light chain and one heavy chain. In other instances, the antibody variants may comprise two identical light chains and two identical heavy chains. In accordance with the present invention, the region of variation may be located in the constant region or in the variable region. Also in accordance with the present invention, the region of variation may be located in the framework region.

Also encompassed by the present invention are antibodies comprising a light chain comprising one of the variable region illustrated in Table A and a heavy chain comprising one of the variable region illustrated in Table B. The light chain and heavy chain may comprise a constant domain. Combinations of light chains and heavy chains of Table 2, Table A and Table B are also encompassed by the present invention.

Antibodies or antigen binding fragments that contain the light chain and heavy chain variable regions are also provided in the present invention. Additionally, certain embodiments include antigen binding fragments, variants, and derivatives of these light and heavy chain variable regions.

Yet other exemplary embodiments of the invention includes an isolated antibody or antigen binding fragment capable of specific binding to SEQ ID NO.:2, to an extracellular portion of SEQ ID NO.:2, or to a secreted form of SEQ ID NO.:2 or to a variant thereof, the antibody comprising:

a. the light chain variable domain defined in SEQ ID NO.:16 and the heavy chain variable domain defined in SEQ ID NO.:18,
b. the light chain variable domain defined in SEQ ID NO.:20 and the heavy chain variable domain defined in SEQ ID NO.:22;
c. the light chain variable domain defined in SEQ ID NO.:24 and the heavy chain variable domain defined in SEQ ID NO.:26;
d. the light chain variable domain defined in SEQ ID NO.:105 and the heavy chain variable domain defined in SEQ ID NO.:132,
e. the light chain variable domain defined in SEQ ID NO.:106 and the heavy chain variable domain defined in SEQ ID NO.:133,
f. the light chain variable domain defined in SEQ ID NO.:107 and the heavy chain variable domain defined in SEQ ID NO.:134,
g. the light chain variable domain defined in SEQ ID NO.:108 and the heavy chain variable domain defined in SEQ ID NO.:154,
h. the light chain variable domain defined in SEQ ID NO.:109 and the heavy chain variable domain defined in SEQ ID NO.:153,
i. the light chain variable domain defined in SEQ ID NO.:110 and the heavy chain variable domain defined in SEQ ID NO.:135,
j. the light chain variable domain defined in SEQ ID NO.:111 and the heavy chain variable domain defined in SEQ ID NO.:136,

k. the light chain variable domain defined in SEQ ID NO.:112 and the heavy chain variable domain defined in SEQ ID NO.:149,

l. the light chain variable domain defined in SEQ ID NO.:113 and the heavy chain variable domain defined in SEQ ID NO.:137,

m. the light chain variable domain defined in SEQ ID NO.:114 and the heavy chain variable domain defined in SEQ ID NO.:140,

n. the light chain variable domain defined in SEQ ID NO.:115 and the heavy chain variable domain defined in SEQ ID NO.:141,

o. the light chain variable domain defined in SEQ ID NO.:116 and the heavy chain variable domain defined in SEQ ID NO.:142,

p. the light chain variable domain defined in SEQ ID NO.:117 and the heavy chain variable domain defined in SEQ ID NO.:139,

q. the light chain variable domain defined in SEQ ID NO.:119 and the heavy chain variable domain defined in SEQ ID NO.:143,

r. the light chain variable domain defined in SEQ ID NO.:120 and the heavy chain variable domain defined in SEQ ID NO.:152,

s. the light chain variable domain defined in SEQ ID NO.:121 and the heavy chain variable domain defined in SEQ ID NO.:146,

t. the light chain variable domain defined in SEQ ID NO.:122 and the heavy chain variable domain defined in SEQ ID NO.:138,

u. the light chain variable domain defined in SEQ ID NO.:123 and the heavy chain variable domain defined in SEQ ID NO.:150,

v. the light chain variable domain defined in SEQ ID NO.:124 and the heavy chain variable domain defined in SEQ ID NO.:144,

w. the light chain variable domain defined in SEQ ID NO.:126 and the heavy chain variable domain defined in SEQ ID NO.:145,

x. the light chain variable domain defined in SEQ ID NO.:127 and the heavy chain variable domain defined in SEQ ID NO.:157,

y. the light chain variable domain defined in SEQ ID NO.:128 and the heavy chain variable domain defined in SEQ ID NO.:155,

z. the light chain variable domain defined in SEQ ID NO.:129 and the heavy chain variable domain defined in SEQ ID NO.:156, or;

aa. the light chain variable domain defined in SEQ ID NO.:130 and the heavy chain variable domain defined in SEQ ID NO.:151.

It is to be understood herein, that the light chain variable region of the specific combination provided above may be changed for any other light chain variable region. Similarly, the heavy chain variable region of the specific combination provided above may be changed for any other heavy chain variable region.

Specific examples of sequences present in these light and heavy chain variable regions are disclosed in Table 3.

Table 3 – Sequences of light and heavy chain variable regions that bind to KAAG1

Antibody designation	Variable region type	Nucleotide sequence (SEQ ID NO.:)	Amino acid sequence (SEQ ID NO.:)
3D3	Light (VL)	15	16
3D3	Heavy (VH)	17	18
3G10	Light	19	20
3G10	Heavy	21	22
3C4	Light	23	24
3C4	Heavy	25	26
3z1A02	Light		105
3z1A02	Heavy		132
3z1E10	Light		109
3z1E10	Heavy		153
3z1G12L	Light		126
3z1G12H	Heavy		145

Therefore, antibodies and antigen binding fragments that bind to KAAG1 may comprise one light variable region and one heavy variable region of the same designated antibody or in any combinations. For example, in an exemplary embodiment, an anti-KAAG1 antibody or fragment may comprise the 3D3 light chain variable region (SEQ ID NO.:16) and the 3D3 heavy chain variable region (SEQ ID NO.:18). In an alternate embodiment, an anti-KAAG1 antibody or fragment may comprise the 3D3 light chain variable region (SEQ ID NO.:16) and the 3G10 heavy chain variable region (SEQ ID NO.:22). In another embodiment, the anti-KAAG1 antibodies may comprise two identical light chain variable regions and two identical heavy chain regions. In yet another embodiment, the anti-

KAAG1 antibodies may comprise two different light chain variable regions and two different heavy chain regions.

Variants of other anti-KAAG1 antibodies formed by the combination of light and/or heavy chain variable regions that each have at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% identity to the amino acid sequences listed in Table 3 are also provided. Those skilled in the art will also recognize that the anti-KAAG1 antibody variants may include conservative amino acid changes, amino acid substitutions, deletions, or additions in the amino acid sequences of the light and/or heavy chain variable regions listed in Table 3.

In accordance with the present invention, the region of variation may be located in the framework region of the variable region. Table 4 – Sequences of the light and heavy chain CDRs

Antibody designation	Chain type	CDR	SEQ ID NO.:	Amino acid sequence
3D3	Light (L)	CDR L1	27	KSSQSLLNSNFQKNFLA
3D3	Light	CDR L2	28	FASTRES
3D3	Light	CDR L3	29	QQHYSTPLT
3D3	Heavy (H)	CDR H1	30	GYIFTDYEIH
3D3	Heavy	CDR H2	31	VIDPETGNTA
3D3	Heavy	CDR H3	32	MGYSDY
3G10	Light	CDR L1	33	RSSQSLLHSNGNTYLE
3G10	Light	CDR L2	34	KVSNRFS
3G10	Light	CDR L3	35	FQGSHVPLT
3G10	Heavy	CDR H1	36	GYTFTDNYMN
3G10	Heavy	CDR H2	37	DINPYYGTTT
3G10	Heavy	CDR H3	38	ARDDWFDY
3C4	Light	CDR L1	39	KASQDIHNFLN
3C4	Light	CDR L2	40	RANRLVD
3C4	Light	CDR L3	41	LQYDEIPLT
3C4	Heavy	CDR H1	42	GFSITSGYGWH
3C4	Heavy	CDR H2	43	YINYDGHND
3C4	Heavy	CDR H3	44	ASSYDGLFAY

Antibody designation	Chain type	CDR	SEQ ID NO.:	Amino acid sequence
3z1A02	Light	CDR L1	158	KSSQSLLHSDGKTYLN
3z1A02	Light	CDR L2	159	LVSKLDS
3z1A02	Light	CDR L3	160	WQGTHFPRT
3z1A02	Heavy	CDR H1	161	GYTFTD YNMH
3z1A02	Heavy	CDR H2	162	YINPYNDVTE
3z1A02	Heavy	CDR H3	163	AWFGL RQ
3z1E10	Light	CDR L1	164	RSSKSLLHSNGN TYLY
3z1E10	Light	CDR L2	165	RMSNLAS
3z1E10	Light	CDR L3	166	MQHLEYPYT
3z1E10	Heavy	CDR H1	167	GDTFTD YYMN
3z1E10	Heavy	CDR H2	168	DINPNYGGIT
3z1E10	Heavy	CDR H3	169	QAYYRNS DY
3z1G12L	Light	CDR L1	170	KASQDVGTAVA
3z1G12L	Light	CDR L2	171	WTSTRHT
3z1G12L	Light	CDR L3	172	QQHYSIPLT
3z1G12H	Heavy	CDR H1	173	GYIFTDYEIH
3z1G12H	Heavy	CDR H2	174	VIDPETGNTA
3z1G12H	Heavy	CDR H3	175	MGYSDY

In certain embodiments of the present invention, the anti-KAAG1 antibodies or antigen binding fragments may comprise the CDR sequences shown in Table 4 or have substantial sequence identity to the CDR sequences of Table 4. In an exemplary embodiment, the 3D3 anti-KAAG1 antibody may comprise a light chain variable region containing CDR1, 2, and 3 that are encoded by SEQ ID NOS:27, 28, and 29, respectively, and/or a heavy chain variable region containing CDR1, 2, and 3 that are encoded by SEQ ID NOS:30, 31, and 32, respectively. In other embodiments the CDR3 region may be sufficient to provide antigen binding. As such polypeptides comprising the $CDR3_L$ or the $CDR3_H$ or both the $CDR3_L$ and the $CDR3_H$ are encompassed by the present invention.

Additionally, the anti-KAAG1 antibodies or antigen binding fragments may include any combination of the CDRs listed in Table 4. For example, the antibodies or antigen binding fragments may include the light chain CDR3 and the heavy chain CDR3. It is understood that the CDRs that are contained in the anti-KAAG1 antibodies or antigen binding fragments may be variant CDRs with 80%, 85%, 90%, or 95% sequence identity to the CDR sequences presented in Table 4. Those skilled in the art will also recognize that the variants may include conservative amino acid changes, amino acid substitutions, deletions, or additions in the CDR sequences listed in Table 4.

Other exemplary embodiments of the invention includes an isolated antibody or antigen binding fragment capable of specific binding to SEQ ID NO.:2, to an extracellular portion of SEQ ID NO.:2 or to a secreted form of SEQ ID NO.:2 or to a variant thereof, the antibody comprising:

a. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:16 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:18,
b. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:20 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:22;
c. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:24 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:26;
d. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:105 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:132,
e. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:106 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:133,
f. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:107 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:134,
g. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:108 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:154,

h. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:109 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:153,

i. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:110 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:135,

j. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:111 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:136,

k. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:112 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:149,

l. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:113 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:137,

m. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:114 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:140,

n. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:115 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:141,

o. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:116 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:142,

p. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:117 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:139,

q. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:119 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:143,

r. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:120 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:152,

s. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:121 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:146,

t. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:122 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:138,

u. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:123 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:150,

v. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:124 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:144,

w. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:126 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:145,

x. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:127 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:157,

y. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:128 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:155,

z. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:129 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:156, or;

aa. the 3CDRs of a light chain variable domain defined in SEQ ID NO.:130 and/or the 3CDRs of a heavy chain variable domain defined in SEQ ID NO.:151.

Again, the light chain variable region of the specific combination provided above may be changed for any other light chain variable region described herein. Similarly, the heavy chain variable region of the specific combination provided above may be changed for any other heavy chain variable region described herein.

Variant antibody and antigen binding fragments

The present invention also encompasses variants of the antibodies or antigen binding fragments described herein. Variant antibodies or antigen binding fragments included are those having a variation in the amino acid sequence. For example, variant antibodies or antigen binding fragments included are those having at least one variant CDR (two, three, four, five or six variant CDRs or even twelve variant CDRs), a variant light chain variable domain, a variant heavy chain variable domain, a variant light chain and/or a variant heavy chain. Variant antibodies or antigen binding fragments included in the present invention are those having, for example, similar or improved binding affinity in comparison with the original antibody or antigen binding fragment.

As used herein the term "variant" applies to any of the sequence described herein and includes for example, a variant CDR (either CDRL1, CDRL2, CDRL3, CDRH1, CDRH2 and/or CDRH3), a variant light chain variable domain, a variant heavy chain variable domain, a variant light chain, a variant heavy chain, a variant antibody, a variant antigen binding fragment and a KAAG1 variant.

Variant antibodies or antigen binding fragments encompassed by the present invention are those which may comprise an insertion, a deletion or an amino acid substitution (conservative or non-conservative). These variants may have at least one amino acid residue in its amino acid sequence removed and a different residue inserted in its place.

The sites of greatest interest for substitutional mutagenesis include the hypervariable regions (CDRs), but modifications in the framework region or even in the constant region are also contemplated. Conservative substitutions may be made by exchanging an amino acid (of a CDR, variable chain, antibody, etc.) from one of the groups listed below (group 1 to 6) for another amino acid of the same group.

Other exemplary embodiments of conservative substitutions are shown in Table 1A under the heading of "preferred substitutions". If such substitutions result in a undesired property, then more substantial changes, denominated "exemplary substitutions" in Table 1A, or as further described below in reference to amino acid classes, may be introduced and the products screened.

It is known in the art that variants may be generated by substitutional mutagenesis and retain the biological activity of the polypeptides of the present invention. These variants

have at least one amino acid residue in the amino acid sequence removed and a different residue inserted in its place. For example, one site of interest for substitutional mutagenesis may include a site in which particular residues obtained from various species are identical. Examples of substitutions identified as "conservative substitutions" are shown in Table 1A. If such substitutions result in a change not desired, then other type of substitutions, denominated "exemplary substitutions" in Table 1A, or as further described herein in reference to amino acid classes, are introduced and the products screened.

Substantial modifications in function or immunological identity are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation. (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side chain properties:

(group 1) hydrophobic: norleucine, methionine (Met), Alanine (Ala), Valine (Val), Leucine (Leu), Isoleucine (Ile)

(group 2) neutral hydrophilic: Cysteine (Cys), Serine (Ser), Threonine (Thr)

(group 3) acidic: Aspartic acid (Asp), Glutamic acid (Glu)

(group 4) basic: Asparagine (Asn), Glutamine (Gln), Histidine (His), Lysine (Lys), Arginine (Arg)

(group 5) residues that influence chain orientation: Glycine (Gly), Proline (Pro); and

(group 6) aromatic: Tryptophan (Trp), Tyrosine (Tyr), Phenylalanine (Phe)

Non-conservative substitutions will entail exchanging a member of one of these classes for another.

Table 1A. Amino acid substitution

Original residue	Exemplary substitution	Conservative substitution
Ala (A)	Val, Leu, Ile	Val
Arg (R)	Lys, Gln, Asn	Lys
Asn (N)	Gln, His, Lys, Arg, Asp	Gln
Asp (D)	Glu, Asn	Glu

Original residue	Exemplary substitution	Conservative substitution
Cys (C)	Ser, Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp, Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn, Gln, Lys, Arg,	Arg
Ile (I)	Leu, Val, Met, Ala, Phe, norleucine	Leu
Leu (L)	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys (K)	Arg, Gln, Asn	Arg
Met (M)	Leu, Phe, Ile	Leu
Phe (F)	Leu, Val, Ile, Ala, Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr, Phe	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser	Phe
Val (V)	Ile, Leu, Met, Phe, Ala, norleucine	Leu

Variation in the amino acid sequence of the variant antibody or antigen binding fragment may include an amino acid addition, deletion, insertion, substitution etc., one or more modification in the backbone or side-chain of one or more amino acid, or an addition of a group or another molecule to one or more amino acids (side-chains or backbone).

Variant antibody or antigen binding fragment may have substantial sequence similarity and/or sequence identity in its amino acid sequence in comparison with that the original antibody or antigen binding fragment amino acid sequence. The degree of similarity between two sequences is based upon the percentage of identities (identical amino acids) and of conservative substitution.

Generally, the degree of similarity and identity between variable chains has been determined herein using the Blast2 sequence program (Tatiana A. Tatusova, Thomas L.

Madden (1999), "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences", FEMS Microbiol Lett. 174:247-250) using default settings, i.e., blastp program, BLOSUM62 matrix (open gap 11 and extension gap penalty 1; gapx dropoff 50, expect 10.0, word size 3) and activated filters.

Percent identity will therefore be indicative of amino acids which are identical in comparison with the original peptide and which may occupy the same or similar position.

Percent similarity will be indicative of amino acids which are identical and those which are replaced with conservative amino acid substitution in comparison with the original peptide at the same or similar position.

Variants of the present invention therefore comprise those which may have at least 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity with an original sequence or a portion of an original sequence.

Exemplary embodiments of variants are those having at least 81% sequence identity to a sequence described herein and 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Other exemplary embodiments of variants are those having at least 82% sequence identity to a sequence described herein and 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Further exemplary embodiments of variants are those having at least 85% sequence identity to a sequence described herein and 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Other exemplary embodiments of variants are those having at least 90% sequence identity to a sequence described herein and 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Additional exemplary embodiments of variants are those having at least 95% sequence identity to a sequence described herein and 95%, 96%, 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

Yet additional exemplary embodiments of variants are those having at least 97% sequence identity to a sequence described herein and 97%, 98%, 99% or 100% sequence similarity with an original sequence or a portion of an original sequence.

For a purpose of concision the applicant provides herein a Table 1B illustrating exemplary embodiments of individual variants encompassed by the present invention and comprising the specified % sequence identity and % sequence similarity. Each "X" is to be construed as defining a given variant.

Table 1B	Percent (%) sequence identity																				
Percent (%) sequence similarity	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
80	X																				
81	X	X																			
82	X	X	X																		
83	X	X	X	X																	
84	X	X	X	X	X																
85	X	X	X	X	X	X															
86	X	X	X	X	X	X	X														
87	X	X	X	X	X	X	X	X													
88	X	X	X	X	X	X	X	X	X												
89	X	X	X	X	X	X	X	X	X	X											
90	X	X	X	X	X	X	X	X	X	X	X										
91	X	X	X	X	X	X	X	X	X	X	X	X									
92	X	X	X	X	X	X	X	X	X	X	X	X	X								
93	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
94	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
95	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
96	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
97	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
98	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
99	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
100	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

The present invention encompasses CDRs, light chain variable domains, heavy chain variable domains, light chains, heavy chains, antibodies and/or antigen binding fragments which comprise at least 80% identity with the sequence described herein.

Exemplary embodiments of the antibody or antigen binding fragment of the present invention are those comprising a light chain variable domain comprising a sequence selected from the group consisting of a sequence at least 70%, 75%, 80% identical to

SEQ ID NO.:16, a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:20, a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:24, a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:105, a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:109 and a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:126.

These light chain variable domain may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:27, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:28 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:29.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO.:27.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO.:27.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence at least 90 % identical to SEQ ID NO.:28.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO.:28.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO.:29.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO.:29.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:33, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:34 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:35.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO.:33.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO.:33.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO.:34.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO.:34.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO.:35.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO.:35.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:39, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:40 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:41.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO.:39.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO.:39.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO.:40.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO.:40.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO.:41.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO.:41.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:158, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:159 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:160.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO.:158.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO.:158.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO.:159.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO.:159.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO.:160.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO.:160.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:164, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:165 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:166.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO.:164.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO.:164.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO.:165.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO.:165.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO.:166.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO.:166.

The light chain variable domain listed above may comprise a CDRL1 sequence at least 80 % identical to SEQ ID NO.:170, a CDRL2 sequence at least 80 % identical to SEQ ID NO.:171 and a CDRL3 sequence at least 80 % identical to SEQ ID NO.:172.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be at least 90 % identical to SEQ ID NO.:170.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL1 sequence which may be 100% identical to SEQ ID NO.: 170.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be at least 90 % identical to SEQ ID NO.: 171.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL2 sequence which may be 100% identical to SEQ ID NO.: 171.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be at least 90 % identical to SEQ ID NO.: 172.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRL3 sequence which may be 100% identical to SEQ ID NO.: 172.

An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:16 and having up to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:16. A SEQ ID NO.:16 variant is provided in SEQ ID NO.:178.

An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical

to the CDR amino acid sequence of SEQ ID NO.:20 and having up to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:20.

An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:24 and having up to 21 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:24. A SEQ ID NO.:24 variant is provided in SEQ ID NO.:182.

An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:105 and having up to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:105.

An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:109 and having up to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:109.

An exemplary embodiment of a variant antibody light chain variable region encompasses a light chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:126 and having up to 21 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:126.

In some instances, the variant antibody light chain variable region may comprise amino acid deletions or additions (in combination or not with amino acid substitutions). Often 1, 2, 3, 4 or 5 amino acid deletions or additions may be tolerated.

In an exemplary embodiment, the antibody or antigen binding fragment may comprise a heavy chain variable domain comprising a sequence selected from the group consisting of a sequence at least 80% identical to SEQ ID NO.:18, a sequence at least 70%. 75%,

80% identical to SEQ ID NO.:22, a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:26, a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:132, a sequence at least 70%. 75%, 80% identical to SEQ ID NO.: 145 and a sequence at least 70%. 75%, 80% identical to SEQ ID NO.:153.

These heavy chain variable domains may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:30, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:31 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:32.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.:30.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.:30.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.:31.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.:31.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.:32.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.:32.

The heavy chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:36, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:37 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:38.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.:36.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.:36.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.:37.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.:37.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.:38.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.:38.

The heavy chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:42, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:43 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:44.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.:42.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.:42.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.:43.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.:43.

In yet a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.:44.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.:44.

The heavy chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:161, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:162 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:163.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.:161.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.:161.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.:162.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.:162.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.:163.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.:163.

The heavy chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:167, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:168 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:169.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.:166.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.:166.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.:168.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.:168.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.:169.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.:169.

The heavy chain variable domain listed above may comprise a CDRH1 sequence at least 80 % identical to SEQ ID NO.:173, a CDRH2 sequence at least 80 % identical to SEQ ID NO.:174 and a CDRH3 sequence at least 80 % identical to SEQ ID NO.:175.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be at least 90 % identical to SEQ ID NO.:173.

In an exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH1 sequence which may be 100% identical to SEQ ID NO.: 173.

In an additional exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be at least 90 % identical to SEQ ID NO.: 174.

In a further exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH2 sequence which may be 100% identical to SEQ ID NO.: 174.

In another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be at least 90 % identical to SEQ ID NO.: 175.

In yet another exemplary embodiment of the present invention, any of the antibodies provided herein may comprise a CDRH3 sequence which may be 100% identical to SEQ ID NO.: 175.

An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:18 and having up to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:18. A SEQ ID NO.:18 variant is provided in SEQ ID NO.:179.

An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are

100% identical to the CDR amino acid sequence of SEQ ID NO.:22 and having up to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:22.

An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:26 and having up to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:26. A SEQ ID NO.:26 variant is provided in SEQ ID NO.:183.

An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:132 and having up to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:132.

An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:153 and having up to 23 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:153.

An exemplary embodiment of a variant antibody heavy chain variable region encompasses a heavy chain variable region having CDR amino acid sequences that are 100% identical to the CDR amino acid sequence of SEQ ID NO.:145 and having up to 22 amino acid modifications (e.g., conservative or non-conservative amino acid substitutions) in its framework region in comparison with the framework region of SEQ ID NO.:145.

In some instances, the variant antibody heavy chain variable region may comprise amino acid deletions or additions (in combination or not with amino acid substitutions). Often 1, 2, 3, 4 or 5 amino acid deletions or additions may be tolerated.

Production of the antibodies in cells

The anti-KAAG1 antibodies that are disclosed herein can be made by a variety of methods familiar to those skilled in the art, such as hybridoma methodology or by recombinant DNA methods.

In an exemplary embodiment of the invention, the anti-KAAG1 antibodies may be produced by the conventional hybridoma technology, where a mouse is immunized with an antigen, spleen cells isolated and fused with myeloma cells lacking HGPRT expression and hybrid cells selected by hypoxanthine, aminopterin and thymine (HAT) containing media.

In an additional exemplary embodiment of the invention, the anti-KAAG1 antibodies may be produced by recombinant DNA methods.

In order to express the anti-KAAG1 antibodies, nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein or any other may be inserted into an expression vector, i.e., a vector that contains the elements for transcriptional and translational control of the inserted coding sequence in a particular host. These elements may include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' un-translated regions. Methods that are well known to those skilled in the art may be used to construct such expression vectors. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination.

A variety of expression vector/host cell systems known to those of skill in the art may be utilized to express a polypeptide or RNA derived from nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with baculovirus vectors; plant cell systems transformed with viral or bacterial expression vectors; or animal cell systems. For long-term production of recombinant proteins in mammalian systems, stable expression in cell lines may be effected. For example, nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may be transformed into cell lines using expression vectors that may

contain viral origins of replication and/or endogenous expression elements and a selectable or visible marker gene on the same or on a separate vector. The invention is not to be limited by the vector or host cell employed. In certain embodiments of the present invention, the nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may each be ligated into a separate expression vector and each chain expressed separately. In another embodiment, both the light and heavy chains able to encode any one of a light and heavy immunoglobulin chains described herein may be ligated into a single expression vector and expressed simultaneously.

Alternatively, RNA and/or polypeptide may be expressed from a vector comprising nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein using an *in vitro* transcription system or a coupled *in vitro* transcription/translation system respectively.

In general, host cells that contain nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein and/or that express a polypeptide encoded by the nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein, or a portion thereof, may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA/DNA or DNA/RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques that include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or amino acid sequences. Immunological methods for detecting and measuring the expression of polypeptides using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). Those of skill in the art may readily adapt these methodologies to the present invention.

Host cells comprising nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein may thus be cultured under conditions for the transcription of the corresponding RNA (mRNA, siRNA, shRNA etc.) and/or the expression of the polypeptide from cell culture. The polypeptide produced by a cell may be secreted or may be retained intracellularly depending on the sequence and/or the vector used. In an exemplary embodiment, expression vectors containing nucleotide

sequences able to encode any one of a light and heavy immunoglobulin chains described herein may be designed to contain signal sequences that direct secretion of the polypeptide through a prokaryotic or eukaryotic cell membrane.

Due to the inherent degeneracy of the genetic code, other DNA sequences that encode the same, substantially the same or a functionally equivalent amino acid sequence may be produced and used, for example, to express a polypeptide encoded by nucleotide sequences able to encode any one of a light and heavy immunoglobulin chains described herein. The nucleotide sequences of the present invention may be engineered using methods generally known in the art in order to alter the nucleotide sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed polypeptide in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. In an exemplary embodiment, anti-KAAG1 antibodies that contain particular glycosylation structures or patterns may be desired. Post-translational processing, which cleaves a "prepro" form of the polypeptide, may also be used to specify protein targeting, folding, and/or activity. Different host cells that have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and W138) are available commercially and from the American Type Culture Collection (ATCC) and may be chosen to ensure the correct modification and processing of the expressed polypeptide.

Those of skill in the art will readily appreciate that natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence resulting in translation of a fusion polypeptide containing heterologous polypeptide moieties in any of the aforementioned host systems. Such heterologous polypeptide moieties may facilitate purification of fusion polypeptides using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding

protein, thioredoxin, calmodulin binding peptide, 6-His (His), FLAG, c-myc, hemaglutinin (HA), and antibody epitopes such as monoclonal antibody epitopes.

In yet a further aspect, the present invention relates to a polynucleotide which may comprise a nucleotide sequence encoding a fusion protein. The fusion protein may comprise a fusion partner (e.g., HA, Fc, etc.) fused to the polypeptide (e.g., complete light chain, complete heavy chain, variable regions, CDRs etc.) described herein.

Those of skill in the art will also readily recognize that the nucleic acid and polypeptide sequences may be synthesized, in whole or in part, using chemical or enzymatic methods well known in the art. For example, peptide synthesis may be performed using various solid-phase techniques and machines such as the ABI 431A Peptide synthesizer (PE Biosystems) may be used to automate synthesis. If desired, the amino acid sequence may be altered during synthesis and/or combined with sequences from other proteins to produce a variant protein.

Antibody conjugates

The antibody or antigen binding fragment of the present invention may be conjugated with a detectable moiety (i.e., for detection or diagnostic purposes) or with a therapeutic moiety (for therapeutic purposes)

A "detectable moiety" is a moiety detectable by spectroscopic, photochemical, biochemical, immunochemical, chemical and/or other physical means. A detectable moiety may be coupled either directly and/or indirectly (for example via a linkage, such as, without limitation, a DOTA or NHS linkage) to antibodies and antigen binding fragments thereof of the present invention using methods well known in the art. A wide variety of detectable moieties may be used, with the choice depending on the sensitivity required, ease of conjugation, stability requirements and available instrumentation. A suitable detectable moiety include, but is not limited to, a fluorescent label, a radioactive label (for example, without limitation, ^{125}I, In^{111}, Tc^{99}, I^{131} and including positron emitting isotopes for PET scanner etc), a nuclear magnetic resonance active label, a luminiscent label, a chemiluminescent label, a chromophore label, an enzyme label (for example and without limitation horseradish peroxidase, alkaline phosphatase, etc.), quantum dots and/or a nanoparticle. Detectable moiety may cause and/or produce a detectable signal thereby allowing for a signal from the detectable moiety to be detected.

In another exemplary embodiment of the invention, the antibody or antigen binding fragment thereof may be coupled (modified) with a therapeutic moiety (e.g., drug, cytotoxic moiety).

In an exemplary embodiment, the anti-KAAG1 antibodies and antigen binding fragments may comprise a chemotherapeutic or cytotoxic agent. For example, the antibody and antigen binding fragments may be conjugated to the chemotherapeutic or cytotoxic agent. Such chemotherapeutic or cytotoxic agents include, but are not limited to, Yttrium-90, Scandium-47, Rhenium-186, Iodine-131, Iodine-125, and many others recognized by those skilled in the art (e.g., lutetium (e.g., Lu^{177}), bismuth (e.g., Bi^{213}), copper (e.g., Cu^{67})). In other instances, the chemotherapeutic or cytotoxic agent may be comprised of, among others known to those skilled in the art, 5-fluorouracil, adriamycin, irinotecan, taxanes, pseudomonas endotoxin, ricin and other toxins.

Alternatively, in order to carry out the methods of the present invention and as known in the art, the antibody or antigen binding fragment of the present invention (conjugated or not) may be used in combination with a second molecule (e.g., a secondary antibody, etc.) which is able to specifically bind to the antibody or antigen binding fragment of the present invention and which may carry a desirable detectable, diagnostic or therapeutic moiety.

Pharmaceutical compositions of the antibodies and their use

Pharmaceutical compositions of the anti-KAAG1 antibodies (conjugated or not) are also encompassed by the present invention. The pharmaceutical composition may comprise an anti-KAAG1 antibody or an antigen binding fragment and may also contain a pharmaceutically acceptable carrier.

Other aspects of the invention relate to a composition which may comprise the antibody or antigen binding fragment described herein and a carrier.

The present invention also relates to a pharmaceutical composition which may comprise the antibody or antigen binding fragment described herein and a pharmaceutically acceptable carrier.

Yet other aspects of the invention relate to the use of the isolated antibody or antigen binding fragment described herein in the treatment or diagnosis of ovarian cancer.

In addition to the active ingredients, a pharmaceutical composition may contain pharmaceutically acceptable carriers comprising water, PBS, salt solutions, gelatins, oils, alcohols, and other excipients and auxiliaries that facilitate processing of the active compounds into preparations that may be used pharmaceutically. In other instances, such preparations may be sterilized.

As used herein, "pharmaceutical composition" means therapeutically effective amounts of the agent together with pharmaceutically acceptable diluents, preservatives, solubilizers, emulsifiers, adjuvant and/or carriers. A "therapeutically effective amount" as used herein refers to that amount which provides a therapeutic effect for a given condition and administration regimen. Such compositions are liquids or lyophilized or otherwise dried formulations and include diluents of various buffer content (e.g., Tris-HCl., acetate, phosphate), pH and ionic strength, additives such as albumin or gelatin to prevent absorption to surfaces, detergents (e.g., Tween 20, Tween 80, Pluronic F68, bile acid salts). Solubilizing agents (e.g., glycerol, polyethylene glycerol), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., thimerosal, benzyl alcohol, parabens), bulking substances or tonicity modifiers (e.g., lactose, mannitol), covalent attachment of polymers such as polyethylene glycol to the protein, complexation with metal ions, or incorporation of the material into or onto particulate preparations of polymeric compounds such as polylactic acid, polyglycolic acid, hydrogels, etc, or onto liposomes, microemulsions, micelles, unilamellar or multilamellar vesicles, erythrocyte ghosts, or spheroplasts. Such compositions will influence the physical state, solubility, stability, rate of in vivo release, and rate of in vivo clearance. Controlled or sustained release compositions include formulation in lipophilic depots (e.g., fatty acids, waxes, oils). Also comprehended by the invention are particulate compositions coated with polymers (e.g., poloxamers or poloxamines). Other embodiments of the compositions of the invention incorporate particulate forms protective coatings, protease inhibitors or permeation enhancers for various routes of administration, including parenteral, pulmonary, nasal, oral, vaginal, rectal routes. In one embodiment the pharmaceutical composition is administered parenterally, paracancerally, transmucosally, transdermally, intramuscularly, intravenously, intradermally, subcutaneously, intraperitonealy, intraventricularly, intracranially and intratumorally.

Further, as used herein "pharmaceutically acceptable carrier" or "pharmaceutical carrier" are known in the art and include, but are not limited to, 0.01-0.1 M or 0.05 M phosphate

buffer or 0.8 % saline. Additionally, such pharmaceutically acceptable carriers may be aqueous or non-aqueous solutions, suspensions, and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's orfixed oils. Intravenous vehicles include fluid and nutrient replenishers, electrolyte replenishers such as those based on Ringer's dextrose, and the like. Preservatives and other additives may also be present, such as, for example, antimicrobials, antioxidants, collating agents, inert gases and the like.

For any compound, the therapeutically effective dose may be estimated initially either in cell culture assays or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the concentration range and route of administration. Such information may then be used to determine useful doses and routes for administration in humans. These techniques are well known to one skilled in the art and a therapeutically effective dose refers to that amount of active ingredient that ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating and contrasting the ED_{50} (the dose therapeutically effective in 50% of the population) and LD_{50} (the dose lethal to 50% of the population) statistics. Any of the therapeutic compositions described above may be applied to any subject in need of such therapy, including, but not limited to, mammals such as dogs, cats, cows, horses, rabbits, monkeys, and humans.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

The term "treatment" for purposes of this disclosure refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

The anti-KAAG1 antibodies and antigen binding fragments therein may have therapeutic uses in the treatment of various cancer types, such as ovarian cancer, renal cancer, colon cancer, lung cancer, melanoma, etc. In an exemplary embodiment, the antibodies and fragments have therapeutic uses in ovarian cancer. In certain instances, the anti-KAAG1 antibodies and fragments may interact with cancer cells that express KAAG1 and induce an immunological reaction by mediating ADCC. In other instances, the anti-KAAG1 antibodies and fragments may block the interaction of KAAG1 with its protein partners.

The anti-KAAG1 antibodies and antigen binding fragments therein may have therapeutic uses in the treatment of various types of ovarian cancer. Several different cell types may give rise to different ovarian cancer histotypes. The most common form of ovarian cancer is comprised of tumors that originate in the epithelial cell layer of the ovary or the fallopian tube. Such epithelial ovarian cancers include serous tumors, endometroid tumors, mucinous tumors, clear cell tumors, and borderline tumors. In other embodiments, the anti-KAAG1 antibodies and antigen binding fragments therein have uses in the treatment of other types of ovarian cancer such as germ line and sex cord ovarian cancer.

In certain instances, the anti-KAAG1 antibodies and antigen binding fragments therein may be administered concurrently in combination with other treatments given for the same condition. As such, the antibodies may be administered with anti-mitotics (eg., taxanes), platinum-based agents (eg., cisplatin), DNA damaging agents (eg. Doxorubicin) and other anti-cancer therapies that are known to those skilled in the art. In other instances, the anti-KAAG1 antibodies and antigen binding fragments therein may be administered with other therapeutic antibodies. These include, but are not limited to, antibodies that target EGFR, CD-20, and Her2.

The present invention relates in a further aspect thereof to a method for inhibiting the growth of a KAAG1-expressing cell, the method which may comprise contacting the cell with an effective amount of the antibody or antigen binding fragment described herein.

The present invention also encompasses method of treating cancer or inhibiting the growth of a KAAG1 expressing cells in a mammal, the method may comprise

administering the antibody or antigen binding fragment described herein to a mammal in need.

In further aspects, the present invention provides method of treatment, diagnostic methods and method of detection using the antibody or antigen binding fragment of the present invention and the use of these antibodies or antigen binding fragment in the manufacture of a pharmaceutical composition or drug for such purposes.

Method of treatment encompassed by the present invention includes administering an antibody or antigen binding fragment described herein to a mammal in need, and especially to a patient having or susceptible of having a cancer.

The invention also provides in further aspects, methods for reducing tumor spread, tumor invasion, tumor formation or for inducing tumor lysis, which may comprise administering an isolated antibody or antigen binding fragment to a mammal in need.

The invention therefore relates to the use of the isolated antibody described herein in the (manufacture of a pharmaceutical composition for) treatment of cancer, reduction of tumor spread, tumor invasion, tumor formation or for inducing tumor lysis of KAAG1-expressing tumor cells.

The antibody or antigen binding fragment may more particularly be applicable for malignant tumor including, for example, a malignant tumor having the ability to metastasize and/or tumor cells characterized by anchorage-independent growth.The antibody or antigen binding fragment of the present invention may also be used in the diagnosis of cancer. The diagnosis of cancer may be performed *in vivo* by administering the antibody or antigen binding fragment of the present invention to a mammal having or suspected of having a cancer. The diagnosis may also be performed *ex vivo* by contacting a sample obtained from the mammal with the antibody or antigen binding fragment and determining the presence or absence of cells (tumor cells) expressing KAAG1.

The present invention also encompasses method of detecting cancer or detecting a KAAG1 expressing cells in a mammal, the method may comprise administering the antibody or antigen binding fragment described herein to a mammal in need.

The present invention relates in another aspect thereof to a method for detecting a KAAG1-expressing cell, the method may comprise contacting the cell with an antibody or antigen binding fragment described herein and detecting a complex formed by the antibody and the KAAG1-expressing cell. Exemplary embodiments of antibodies or antigen binding fragments used in detection methods are those which are capable of binding to the extracellular region of KAAG1.

Other exemplary embodiments of antibodies or antigen binding fragments used in detection methods are those which bind to KAAG1 expressed at the surface of a tumor cells.

Patients which would benefit from treatment, detection or diagnostic methods described herein are those which have or are suspected of having ovarian cancer (e.g., serous, endometroid, clear cell or mucinous), skin cancer (e.g., melanomas, squamous cell carcinomas), renal cancer (e.g., papillary cell carcinomas, clear cell carcinomas), colorectal cancer (e.g., colorectal carcinomas), sarcoma, leukemia, brain tumor, thyroid tumor, breast cancer (e.g., mammary carcinomas), prostate cancer (e.g., prostatic carcinomas), oesophageal tumor, bladder tumor, lung tumor (e.g., lung carcinomas) or head and neck tumor and especially when the cancer is characterized as being malignant and/or when the KAAG1-expressing cells are characterized by anchorage-independent growth.

Especially encompassed by the present invention are patients having or susceptible of having ovarian cancer (e.g., serous, endometroid, clear cell or mucinous), skin cancer (e.g., melanomas, squamous cell carcinomas) or renal cancer (e.g., papillary cell carcinomas) and especially when the cancer is characterized as being malignant and/or when the KAAG1-expressing cells are characterized by anchorage-independent growth.

Another aspect of the invention relates a method for detecting KAAG1 (SEQ ID NO.:2), a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2 or a secreted form of circulating form of KAAG1 or KAAG1 variant, the method may comprise contacting a cell expressing KAAG1 or the KAAG1 variant or a sample (biopsy, serum, plasma, urine etc.) comprising or suspected of comprising KAAG1 or the KAAG1 variant with the antibody or antigen binding fragments described herein and measuring binding. The sample may originate from a mammal (e.g., a human) which may have cancer (e.g.,

ovarian cancer) or may be suspected of having cancer (e.g., ovarian cancer). The sample may be a tissue sample obtained from the mammal or a cell culture supernatant.

In accordance with the invention the sample may be a serum sample, a plasma sample, a blood sample or ascitic fluid obtained from the mammal. The antibody or antigen binding fragment described herein may advantageously detect a secreted or circulating form (circulating in blood) of KAAG1.

The method may comprise quantifying the complex formed by the antibody or antigen binding fragment bound to KAAG1 or to the KAAG1 variant.

The binding of an antibody to an antigen will cause an increase in the expected molecular weight of the antigen. A physical change therefore occurs upon specific binding of the antibody or antigen binding fragment and the antigen.

Such changes may be detected using, for example, electrophoresis followed by Western blot and coloration of the gel or blot, mass spectrometry, HPLC coupled with a computer or else. Apparatus capable of computing a shift in molecular weight are known in the art and include for example, Phosphorimager™.

When the antibody comprises for example a detectable label, the antigen-antibody complex may be detected by the fluorescence emitted by the label, radiation emission of the label, enzymatic activity of a label provided with its substrate or else.

Detection and/or measurement of binding between an antibody or antigen binding fragment and an antigen may be performed by various methods known in the art. Binding between an antibody or antigen binding fragment and an antigen may be monitored with an apparatus capable of detecting the signal emitted by the detectable label (radiation emission, fluorescence, color change etc.). Such apparatus provides data which indicates that binding as occurred and may also provide indication as to the amount of antibody bound to the antigen. The apparatus (usually coupled with a computer) may also be capable of calculating the difference between a background signal (e.g., signal obtained in the absence of antigen-antibody binding) or background noise and the signal obtained upon specific antibody-antigen binding. Such apparatuses may thus provide the user with indications and conclusions as to whether the antigen has been detected or not.

Additional aspects of the invention relates to kits which may include one or more container containing one or more antibodies or antigen binding fragments described herein.

Nucleic acids, vectors and cells

Antibodies are usually made in cells allowing expression of the light chain and heavy chain expressed from a vector(s) comprising a nucleic acid sequence encoding the light chain and heavy chain.

The present therefore encompasses nucleic acids capable of encoding any of the CDRs, light chain variable domains, heavy chain variable domains, light chains, heavy chains described herein.

The present invention therefore relates in a further aspect to a nucleic acid encoding a light chain variable domain and/or a heavy chain variable domain of an antibody which is capable of specific binding to KAAG1.

In accordance with an embodiment of the invention, the nucleic acid may especially encode a light chain variable domain and/or heavy chain variable domain of an antibody which may be capable of inducing killing (elimination, destruction, lysis) of KAAG1-expressing tumor cells.

In accordance with another embodiment of the invention, the nucleic acid may especially encode a light chain variable domain and/or heavy chain variable domain of an antibody which may be capable of reducing spreading of KAAG1- expressing tumor cells.

In accordance with yet another embodiment of the invention, the nucleic acid may particularly encode a light chain variable domain and/or heavy chain variable domain of an antibody which may be capable of decreasing or impairing formation of KAAG1-expressing tumors.

Exemplary embodiments of nucleic acids of the present invention include nucleic acids encoding a light chain variable domain comprising:

a. a CDRL1 sequence selected from the group consisting of SEQ ID NO.:74 and SEQ ID NO.:75;
b. a CDRL2 sequence selected from the group consisting of SEQ ID NO.:76, SEQ ID NO.: 77 and SEQ ID NO.:78, or;

c. a CDRL3 sequence selected from the group consisting of SEQ ID NO.:79, SEQ ID NO.:80 and SEQ ID NO.:81.

In accordance with the present invention, the nucleic acid may encode a light chain variable domain which may comprise at least two CDRs of a CDRL1, a CDRL2 or a CDRL3.

Also in accordance with the present invention, the nucleic acid may encode a light chain variable domain which may comprise one CDRL1, one CDRL2 and one CDRL3.

The present invention also relates to a nucleic acid encoding a heavy chain variable domain comprising:

a. a CDRH1 sequence comprising SEQ ID NO.:82;
b. a CDRH2 sequence selected from the group consisting of SEQ ID NO.:83, SEQ ID NO.:84, SEQ ID NO.:85, SEQ ID NO.:86 and SEQ ID NO.:87, or;
c. a CDRH3 sequence selected from the group consisting of SEQ ID NO.:88, SEQ ID NO.:89 and SEQ ID NO.:90.

In accordance with the present invention, the nucleic acid may encode a heavy chain variable domain which may comprise at least two CDRs of a CDRH1, a CDRH2 or a CDRH3.

In accordance with the present invention, the nucleic acid may encode a heavy chain variable domain which may comprise one CDRH1, one CDRH2 and one CDRH3.

Also encompassed by the present invention are nucleic acids encoding antibody variants having at least one conservative amino acid substitution.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution in at least two of the CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least one conservative amino acid substitution in the 3 CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitutions in at least one of the CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitutions in at least two of the CDRs.

In accordance with the present invention, the nucleic acid may encode a CDR comprising at least two conservative amino acid substitutions in the 3 CDRs.

Other aspects of the invention relate to a nucleic acid encoding a light chain variable domain having at least 70%. 75%, 80% sequence identity to a sequence selected from the group consisting of SEQ ID NO.:16, SEQ ID NO.:20, SEQ ID NO.:24, SEQ ID NO.:105, SEQ ID NO.:106, SEQ ID NO.:107, SEQ ID NO.:108, SEQ ID NO.:109, SEQ ID NO.:110, SEQ ID NO.:111, SEQ ID NO.:112, SEQ ID NO.:113, SEQ ID NO.:114, SEQ ID NO.:115, SEQ ID NO.:116, SEQ ID NO.:117, SEQ ID NO.:118, SEQ ID NO.:119, SEQ ID NO.:120, SEQ ID NO.:121, SEQ ID NO.:122, SEQ ID NO.:123, SEQ ID NO.:124, SEQ ID NO.:125, SEQ ID NO.:126, SEQ ID NO.:127. SEQ ID NO.:128, SEQ ID NO.:129, SEQ ID NO.:130 and SEQ ID NO.:131.

Yet other aspects of the invention relate to a nucleic acid encoding a heavy chain variable domain having at least 70%. 75%, 80% sequence identity to a sequence selected from the group consisting of SEQ ID NO.:18, SEQ ID NO.:22, SEQ ID NO.:26, SEQ ID NO.:132, SEQ ID NO.:133, SEQ ID NO.:134, SEQ ID NO.:135, SEQ ID NO.:136, SEQ ID NO.:137, SEQ ID NO.:138, SEQ ID NO.:139, SEQ ID NO.:140, SEQ ID NO.:141, SEQ ID NO.:142, SEQ ID NO.:143, SEQ ID NO.:144, SEQ ID NO.:145, SEQ ID NO.:146, SEQ ID NO.:147, SEQ ID NO.:148, SEQ ID NO.:149, SEQ ID NO.:150, SEQ ID NO.:151, SEQ ID NO.:152, SEQ ID NO.:153, SEQ ID NO.:154, SEQ ID NO.:155, SEQ ID NO.:156, SEQ ID NO.:157.Other aspects of the invention relates to the use of a nucleic acid selected from the group consisting of SEQ ID NO.:1, a fragment of 10 to 884 nucleotides of SEQ ID NO.:1 and a complement of any of the preceding for impairing migration or survival of tumor cells expressing KAAG1. Exemplary embodiments of such nucleic acid comprise siRNAs, antisense, ribozymes and the like.

In yet another aspect, the present invention relates to a vector comprising the nucleic acids described herein.

In accordance with the present invention, the vector may be an expression vector.

Vector that contains the elements for transcriptional and translational control of the inserted coding sequence in a particular host are known in the art. These elements may include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' un-translated regions. Methods that are well known to those skilled in the art may be used to construct such expression vectors. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination.

In another aspect the present invention relates to an isolated cell which may comprise the nucleic acid described herein.

The isolated cell may comprise a nucleic acid encoding a light chain variable domain and a nucleic acid encoding a heavy chain variable domain either on separate vectors or on the same vector. The isolated cell may also comprise a nucleic acid encoding a light chain and a nucleic acid encoding a heavy chain either on separate vectors or on the same vector.

In accordance with the present invention, the cell may be capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

In another aspect, the present invention provides a cell which may comprise and/or may express the antibody described herein.

In accordance with the invention, the cell may comprise a nucleic acid encoding a light chain variable domain and a nucleic acid encoding a heavy chain variable domain.

The cell may be capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

The examples below are presented to further outline details of the present invention.

EXAMPLES

Example 1

This example describes the pattern of expression of the *KAAG1* gene in ovarian tumors and ovarian cancer cell line.

PCR analysis was performed to verify the percentage of ovarian tumors that express the mRNA encoding KAAG1 (indicated as AB-0447 in the Figure). The results showed that the *KAAG1* gene is expressed in greater than 85% of ovarian tumors from all stages of the disease and 100% of late stage tumors. The expression of KAAG1 is lower or undetectable in LMP samples (see Fig. 1A). For each sample, 1 μg of amplified RNA was reverse transcribed with random hexamers using Thermoscript RT (Invitrogen). The cDNA was diluted and 1/200th of the reaction was used as template for each PCR reaction with gene-specific primers as indicated. The primers used to amplify the KAAG1 mRNA contained the sequences shown in SEQ ID NOS:45 and 46. PCR reactions were carried out in 96-well plates and half of the 25 μl reaction was electrophoresed on a 1% agarose gel. The gels were visualized and photographed with a gel documentation system (BioRad). The upper panel of Fig. 1A shows the results from 6 LMP samples (LMP) and 22 ovarian tumor and 6 ovarian cell line (last 6 lanes on the right, OVCa) samples. The lower panel of Fig. 1 shows the RNA samples from 30 normal tissues that were tested as indicated.

KAAG1 expression was weakly detected in a few normal tissues whereas the mRNA was evident in the fallopian tube and the pancreas (see Fig. 1A). The amount of total RNA used in these reactions was controlled with parallel PCR amplifications of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), a housekeeping gene, and the results showed that equivalent starting material was present in each sample (see Fig. 1A). The primers used to amplify the GAPDH gene contained the sequences shown in SEQ ID NOs: 47 and 48. Thus, the expression of the KAAG1 gene fulfills an important selection criteria: it is over-expressed in a large proportion of ovarian tumors and its expression is low or absent in most normal tissues. These data suggest that ovarian tumors may be specifically targeted with high affinity monoclonal antibodies against KAAG1.

Early stage cancer or tumors tend to be made up of cells that are in a high state of differentiation but as the tumor progresses to a more aggressive and invasive state, the cancer cells become increasingly undifferentiated. There are needs to identify factors that contribute to this transition and exploit these proteins as targets for the development of therapeutics. Several ovarian cancer cell lines are available that were derived from primary tumors and serve as excellent models for the functional studies. The expression of KAAG1 was examined in these cell lines. Four lines termed TOV-21G, TOV-112D,

TOV-1946, and TOV-2223G were established from primary tumors whereas OV-90 and OV-1946 are cell lines derived from cells contained in ascites fluid of patients with advanced ovarian cancer. Total RNA from cells established from primary tumors (see in Fig. 1B, lanes 1, TOV-21G; 2, TOV-112D; 5, TOV-1946; 6, TOV-2223G) and cells established from ascitic cells (lanes 3, OV-90; 4, OV-1946) was converted to cDNA with reverse transcriptase and used as template in PCR reactions with KAAG1-specific primers(SEQ ID NOS:45 and 46). As a negative control, the reaction was carried out with total RNA from normal ovary. Equal amounts of starting material were utilized as evidenced by parallel PCR reactions with GAPDH (SEQ ID NOS:47 and 48). A sample of the PCR reaction was electrophoresed on an agarose gel and visualized with ethidium bromide. As shown in Fig. 1B, KAAG1 was detectable but weakly expressed in the cell lines from the primary tumors and PCR reactions performed at a higher number of cycles revealed the KAAG1 transcript in all four of these cell lines. Conversely, both cell lines established from the ascitic fluid cells exhibited high level of the KAAG1 transcript. The increased expression in cells from the ascitic fluid suggests that the environment of the cells influences the regulation of the KAAG1 gene.

Ascitic cells are associated with advanced disease and the pattern of expression disclosed in Fig. 1B implies that increased KAAG1 levels are associated with anchorage-independent growth. This question was addressed by culturing the cells in hanging droplets, a condition that prevents the cells from adhering to the petri dish, as is the case when they are grown as monolayers. These so called three-dimensional cultures allow the cells to associate and the formation of spheroids is observed (see Fig. 1C). Spheroids were cultures as follows: TOV-112D, OV-90, or TOV-21G cells (4 000 in 15 μl) were incubated for 4 days in medium in the absence (*left* panels, Fig. 1C) or presence of 5% FBS (*right* panels, Fig. 1C, +5% serum). The magnification of the image was set to 100x. These spheroids have been extensively characterized and exhibit many of the properties found in primary tumors including morphological and functional properties as well as the molecular signature as measured by microarray-based expression profiling.

Total RNA was isolated from spheroid preparations and RT-PCR was performed as described for Fig. 1A. TOV-21G, TOV-112D, OV-90 cells were seeded as described in the legend for Fig. 1C under conditions to produce spheroids. After 4 days, total RNA was isolated and used to perform RT-PCR reactions with KAAG1-specific primers (SEQ ID NOS:45 and 46). PCR reactions were electrophoresed on agarose gels. Conducting

parallel reactions to amplify GAPDH (SEQ ID NOS:47 and 48) demonstrated that equal amounts of starting material were present in each sample. The following acronyms are used in Fig. 1D: *Ce.*, cells grown as monolayers; *Sph.*, cells grown as spheroids. Strikingly, KAAG1 expression was up-regulated when TOV-21G and TOV-112D were grown as spheroids (see Fig. 1D). In the case of the OV-90 cells, the level of expression of the KAAG1 gene was unchanged and remained very high. Presumably, the level of expression attained in the cell lines derived from the ascitic fluid, as exemplified by the OV-90 cells and the OV-1946 cells (see Fig. 1A) has reached a maximum.

These results correlated with the previous data showing high expression in cell lines derived from ascitic fluid and confirm that expression of KAAG1 is influenced by the microenvironment of the cancer cells. Additionally, the up-regulation of KAAG1 transcription that was observed in spheroids implies that high levels of KAAG1 are present in malignant ovarian cancer.

Example 2

This example describes *in vitro* results that suggest a critical role for KAAG1 in the survival of ovarian cancer cells.

With the demonstration that KAAG1 expression is regulated in ovarian cancer cells, the function of this gene in these cells was examined. To address this question, *in vitro* assays were conducted to determine if this protein plays a role in cancer cell proliferation, migration, and/or survival. RNAi was used to knock down the expression of the endogenous KAAG1 gene in the TOV-21G ovarian cancer cell line. The design of two separate short-hairpin RNA (shRNA) sequences was performed using web-based software that is freely available to those skilled in the art (Qiagen for example). These chosen sequences, usually 19-mers, were included in two complementary oligonucleotides that form the template for the shRNAs, i.e. the 19-nt sense sequence, a 9-nt linker region (loop), the 19-nt antisense sequence followed by a 5-6 poly-T tract for termination of the RNA polymerase III. The sequences of the 19-mers that were used to knock down the expression of KAAG1 are shown in SEQ ID NOS:49 and 50. Appropriate restriction sites were inserted at the ends of these oligonucleotides to facilitate proper positioning of the inserts so that the transcriptional start point is at a precise location downstream of the hU6 promoter. The plasmid utilized in all RNA interference studies, pSilencer 2.0 (SEQ ID NO.:51), was purchase from a commercial supplier (Ambion,

Austin, TX). Two different shRNA expression vectors were constructed to increase the chance of observing RNAi effects and the specificity of phenotypic observations. TOV-21G cells were seeded in 6-well plates and transfected 24h later with 1 μg of pSil-shRNA vector. Sh.1 and sh.2 were used to designate 2 different shRNA sequences targeting the KAAG1 gene. Stable transfectants were selected for 5 – 7 days, expanded, and grown to confluence. All of the following *in vitro* cell-based assays were performed using these stably transfected cell lines that contain shRNAs specific for KAAG1.

The migration or mobility of the cells was measured in a standard cell motility assay. This scratch assay, as it is called, measures the speed at which cells fill a denuded area in a confluent monolayer. As illustrated in Fig. 2A, TOV-21G cells containing the scrambled shRNA filled up the wound almost completely after 24h compared to the control untreated cells (compare middle-left panel with left panel). By contrast, the ability of TOV-21G cells expressing KAAG1 shRNAs to fill the denuded area was greatly reduced. In fact, the number of cells that filled the denuded area in the presence of the KAAG1 shRNA cells more closely resembled the number of cells at time 0h (compare the left panel with the right panels).

To examine the longer-term effects of reduced expression of KAAG1 in ovarian cancer cells, the cells were extensively diluted and cultured for 10 days in a colony survival assay. TOV-21G cells were seeded in 12-well plates at a density of 50 000 cells/well and transfected 24h later with 1 μg of pSil-shRNA vector. Sh-1 and sh-2 are used to designate 2 different shRNA sequences targeting the same gene. The next day, fresh medium was applied containing 2 μg/ml puromycin and the selection of the cells was carried out for 3 days. The cells were washed and fresh medium without puromycin was added and growth continued for another 5 days. To visualize the remaining colonies, the cells were washed in PBS and fixed and stained simultaneously in 1% crystal violet/10% ethanol in PBS for 15 minutes at room temperature. Following extensive washing in PBS, the dried plates were scanned for photographic analysis. A significant decrease in the survival of the cancer cell line was observed and a representative experiment is displayed in Fig. 2B. Identical results were obtained when the shRNAs were transfected into another ovarian cancer cell line, TOV-112D.

Thus, taken together, the regulated expression of KAAG1 in detached cells coupled with the requirement of this gene in the migration and the survival of ovarian cancer cells

supports an important role for KAAG1 in ovarian cancer cells. Furthermore, these experiments suggest that an antagonist of KAAG1 protein, such as a monoclonal antibody, would result in reduced invasiveness and decreased tumor survival.

Example 3

This example provides details pertaining to the family of monoclonal antibodies that bind to KAAG1.

The antibodies that bind KAAG1 were generated using the Biosite phage display technology. A detailed description of the technology and the methods for generating these antibodies can be found in the U.S. Patent No. 6,057,098. Briefly, the technology utilizes stringent panning of phage libraries that display the antigen binding fragments (Fabs). After a several rounds of panning, a library, termed the Omniclonal, was obtained that was enriched for recombinant Fabs containing light and heavy chain variable regions that bound to KAAG1 with very high affinity and specificity. From this library, more precisely designated Omniclonal AL0003Z1, 96 individual recombinant monoclonal Fabs were prepared from *E. coli* and tested for KAAG1 binding.

To measure the relative binding of each individual monoclonal antibody, recombinant human KAAG1 was produced in 293E cells using the large-scale transient transfection technology (Durocher et al., 2002; Durocher, 2004). The entire coding region of the KAAG1 cDNA was amplified by PCR using a forward primer that incorporated a BamHI restriction site (SEQ ID NO.:52) and a reverse primer that incorporated a HindIII restriction site (SEQ ID NO.:53). The resulting PCR product measured 276 base pairs and following digestion with BamHI and HindIII, the fragment was ligated into the expression vector pYD5 (SEQ ID NO.:54) that was similarly digested with the same restriction enzymes. The pYD5 expression plasmid contains the coding sequence for the human Fc domain that allows fusion proteins to be generated as well as the sequence encoding the IgG1 signal peptide to allow the secretion of the fusion protein into the culture medium. For each milliliter of cells, one microgram of the expression vector, called pYD5-0447, was transfected in 293E cells grown in suspension to a density of 1.5 – 2.0 million cells/ml. The transfection reagent used was polyethylenimine (PEI), (linear, MW 25,000, Cat# 23966 Polysciences, Inc., Warrington, PA) which was included at a DNA:PEI ratio of 1:3. Growth of the cells was continued for 5 days after which the culture medium was harvested for purification of the recombinant Fc-KAAG1 fusion protein. The

protein was purified using Protein-A agarose as instructed by the manufacturer (Sigma-Aldrich Canada Ltd., Oakville, ON). A representative polyacrylamide gel showing a sample of the purified Fc-KAAG1 (indicated as Fc-0447) is shown in Fig. 3A.

The 96-well master plate of monoclonal preparations contained different concentrations of purified anti-KAAG1 Fabs in each well. A second stock master plate was prepared by diluting the Fabs to a final concentration of 10 μg/ml from which all subsequent dilutions were performed for ELISA measurements. To carry out the binding of Fc-KAAG1 to the monoclonal preparations, the Fc-KAAG1 was biotinylated with NHS-biotin (Pierce, Rockford, IL) and 10 ng/well was coated in a streptavidin 96-well plate. One nanogram of each Fab monoclonal preparation was added to each well and incubated at room temperature for 30 minutes. Bound antibody was detected with HRP-conjugated mouse anti-kappa light chain antibody in the presence of TMB liquid substrate (Sigma-Aldrich Canada Ltd., Oakville, ON) and readings were conducted at 450 nm in microtiter plate reader. As shown in Fig. 3B, a total of 48 (highlighted in grey) monoclonal antibodies displayed significant binding in this assay (>0.1 arbitrary OD_{450} units). The antibodies were purposely diluted to 1 ng/well to accentuate the binding of those antibodies with the most affinity for KAAG1. As a control, the antibodies did not bind to biotinylated Fc domain. These data also revealed that the binding of the antibodies varied from well to well indicating that they exhibited different affinities for KAAG1.

Example 4

This example describes the epitope mapping studies to determine which region of KAAG1 the antibodies bind to.

To further delineate the regions of KAAG1 that are bound by the monoclonal antibodies, truncated mutants of KAAG1 were expressed and used in the ELISA. As for the full length KAAG1, the truncated versions were amplified by PCR and ligated into BamHI/HindIII digested pYD5. The primers that were used combined the forward oligonucleotide with the sequence shown in SEQ ID NO.:52 with primers of SEQ ID NOS:55 and 56, to produce Fc-fused fragments that ended at amino acid number 60 and 35 of KAAG1, respectively. The expression of these mutants was conducted as was described above for the full length Fc-KAAG1 and purified with Protein-A agarose. A representative gel of the protein preparations that were used in the ELISA is shown in

Fig. 4A and a schematic of the mutant proteins used for epitope mapping is depicted in Fig. 4B.

The results showed that the library was comprised of antibodies that could bind to each of the delineated KAAG1 regions. In particular, of the 48 mAbs that bound to KAAG1 in the first ELISA, nine (wells A2, A12, C2, C4, D1, E10, F1, H3, and H8) were found to interact with the first 35 amino acids of KAAG1 whereas five (D12, E8, F5, G10, and H5) were found to interact with the last 25 amino acids of KAAG1. Thus, the remaining 34 antibodies interacted with a region of KAAG1 spanned by amino acids 36 – 59. These results were in agreement with the sequence analysis of 24 representative light and heavy chain variable regions. Indeed, alignment of these sequences revealed that the antibodies clustered into three groups based on the percentage identity in their respective CDRs. Antibodies contained in each cluster all interacted with the same region of KAAG1.

Therefore, based on the relative binding affinity of the mAb, differential epitope interaction characteristics, and the differences in variable domain sequences, three antibodies from the plate described in Example 3 were selected for further analysis as exemplary anti-KAAG1 monoclonal antibodies.

Example 5

This example discloses the methods used to convert the Fabs into full IgG1 chimeric monoclonal antibodies. A scheme of the methodology is presented in Fig. 5.

Aside from the possibility of conducting interaction studies between the Fab monoclonals and the KAAG1 protein, the use of Fabs is limited with respect to conducting meaningful *in vitro* and *in vivo* studies to validate the biological function of the antigen. Thus, it was necessary to transfer the light and heavy chain variable regions contained in the Fabs to full antibody scaffolds, to generate mouse-human chimeric IgG1s. The expression vectors for both the light and heavy immunoglobulin chains were constructed such that i) the original bacterial signal peptide sequences upstream of the Fab expression vectors were replaced by mammalian signal peptides and ii) the light and heavy chain constant regions in the mouse antibodies were replaced with human constant regions. The methods to accomplish this transfer utilized standard molecular biology techniques that

are familiar to those skilled in the art. A brief overview of the methodology is described here (see Fig. 5).

Light chain expression vector – an existing mammalian expression plasmid, called pTTVH8G (Durocher et al., 2002), designed to be used in the 293E transient transfection system was modified to accommodate the mouse light chain variable region. The resulting mouse-human chimeric light chain contained a mouse variable region followed by the human kappa constant domain. The cDNA sequence encoding the human kappa constant domain was amplified by PCR with primers OGS1773 and OGS1774 (SEQ ID NOS:57 and 58, respectively). The nucleotide sequence and the corresponding amino acid sequence for the human kappa constant region are shown in SEQ ID NOS:59 and 60, respectively. The resulting 321 base pair PCR product was ligated into pTTVH8G immediately downstream of the signal peptide sequence of human VEGF A (NM_003376). This cloning step also positioned unique restriction endonuclease sites that permitted the precise positioning of the cDNAs encoding the mouse light chain variable regions. The sequence of the final expression plasmid, called pTTVK1, is shown in SEQ ID NO.:61. Based on the sequences disclosed in Table 3, PCR primers specific for the light chain variable regions of antibodies 3D3, 3G10, and 3C4 (SEQ ID NOS:15, 19, and 23, respectively) were designed that incorporated, at their 5'-end, a sequence identical to the last 20 base pairs of the VEGF A signal peptide. The sequences of these primers are shown in SEQ ID NOS:62, 63, and 64. The same reverse primer was used to amplify all three light chain variable regions since the extreme 3'-ends were identical. This primer (SEQ ID NO.:65) incorporated, at its 3'-end, a sequence identical to the first 20 base pairs of the human kappa constant domain. Both the PCR fragments and the digested pTTVK1 were treated with the 3' – 5' exonuclease activity of T4 DNA polymerase resulting in complimentary ends that were joined by annealing. The annealing reactions were transformed into competent *E. coli* and the expression plasmids were verified by sequencing to ensure that the mouse light chain variable regions were properly inserted into the pTTVK1 expression vector. Those skilled in the art will readily recognize that the method used for construction of the light chain expression plasmids applies to all anti-KAAG1 antibodies contained in the original Fab library.

Heavy chain expression vector – the expression vector that produced the heavy chain immunoglobulins was designed in a similar manner to the pTTVK1 described above for

production of the light chain immunoglobulins. Plasmid pYD11 (Durocher et al., 2002), which contains the human IgGK signal peptide sequence as well as the CH2 and CH3 regions of the human Fc domain of IgG1, was modified by ligating the cDNA sequence encoding the human constant CH1 region. PCR primers OGS1769 and OGS1770 (SEQ ID NOS:66 and 67), designed to contain unique restriction endonuclease sites, were used to amplify the human IgG1 CH1 region containing the nucleotide sequence and corresponding amino acid sequence shown in SEQ ID NOS:68 and 69. Following ligation of the 309 base pair fragment of human CH1 immediately downstream of the IgGK signal peptide sequence, the modified plasmid (SEQ ID NO.:70) was designated pYD15. When a selected heavy chain variable region is ligated into this vector, the resulting plasmid encodes a full IgG1 heavy chain immunoglobulin with human constant regions. Based on the sequences disclosed in Table 3, PCR primers specific for the heavy chain variable regions of antibodies 3D3, 3G10, and 3C4 (SEQ ID NOS:17, 21, and 25, respectively) were designed that incorporated, at their 5'-end, a sequence identical to the last 20 base pairs of the IgGK signal peptide. The sequences of these primers are shown in SEQ ID NOS:71 (3D3 and 3G10 have the same 5'-end sequence) and 72. The same reverse primer was used to amplify all three heavy chain variable regions since the extreme 3'-ends were identical. This primer (SEQ ID NO.:73) incorporated, at its 3'-end, a sequence identical to the first 20 base pairs of the human CH1 constant domain. Both the PCR fragments and the digested pYD15 were treated with the 3' – 5' exonuclease activity of T4 DNA polymerase resulting in complimentary ends that were joined by annealing. The annealing reactions were transformed into competent *E. coli* and the expression plasmids were verified by sequencing to ensure that the mouse heavy chain variable regions were properly inserted into the pYD15 expression vector. Those skilled in the art will readily recognize that the method used for construction of the heavy chain expression plasmids applies to all anti-KAAG1 antibodies contained in the original Fab library.

Expression of human IgG1s in 293E cells – The expression vectors prepared above that encoded the light and heavy chain immunoglobulins were expressed in 293E cells using the transient transfection system (Durocher et al., 2002). The methods used for co-transfecting the light and heavy chain expression vectors were described in Example 3. The ratio of light to heavy chain was optimized in order to achieve the most yield of antibody in the tissue culture medium and it was found to be 9:1 (L:H). The ability of the

chimeric anti-KAAG1 monoclonal antibodies to bind to recombinant Fc-KAAG1 was measured in the ELISA and compared with the original mouse Fabs. The method was described in Example 3. As depicted in Fig. 6, the binding of the 3D3, and 3G10 chimeric IgG1 monoclonal antibodies was very similar to the Fabs. In the case of the 3C4, the binding activity of the chimeric was slightly less than the Fab. Despite this, this result shows that the transposition of the variable domains from the mouse Fabs into a human IgG1 backbone did not significantly affect the capacity of the light and heavy chain variable regions to confer KAAG1 binding.

Example 6

This example describes the use of anti-KAAG1 antibodies to block the activity of KAAG1 in ovarian cancer cell models.

Example 2 disclosed RNAi studies showing that KAAG1 played an important role in the behavior of ovarian cancer cells. The monoclonal antibodies described above were used to determine whether it was possible to reproduce these results by targeting KAAG1 at the cell surface. TOV-21G and OV-90 cells were cultured under conditions to produce spheroids and treated with 10 μg/ml of 3D3, 3G10, or 3C4 anti-KAAG1 chimeric monoclonal antibody. As illustrated in Fig. 7, both cell lines efficiently formed spheroids when left untreated (parental) or when treated with antibody dilution buffer (control). In contrast, the presence of anti-KAAG1 antibodies resulted in loosely packed structures and in certain cases, the cells were unable to assemble into spheroids. These results confirm the earlier observations and suggest that the anti-KAAG1 monoclonal antibodies can modulate the activity of KAAG1 during the formation of spheroids. Since spheroid formation by cancer cell lines is an *in vitro* model for tumor formation, the results also suggest that blocking KAAG1 could lead to decreased tumor formation *in vivo*.

Example 7

This example describes the use of anti-KAAG1 antibodies for detecting the expression of KAAG1 in ovarian tumors.

As a means of confirming the expression of KAAG1 protein in ovarian cancer tumors and in order determine if expression of the gene correlated with the presence of the protein, immunohistochemistry was conducted. Tissue microarrays were obtained that contained dozens of ovarian tumor samples generated from patient biopsies. Paraffin-embedded

epithelial ovarian tumor samples were placed on glass slides and fixed for 15 min at 50 °C. Deparaffinization was conducted by treating 2x with xylene followed by dehydration in successive 5 min washes in 100%, 80%, and 70% ethanol. The slides were washed 2x in PBS for 5 min and treated with antigen retrieval solution (citrate-EDTA) to unmask the antigen. Endogenous peroxide reactive species were removed by incubating slides with H_2O_2 in methanol and blocking was performed by incubating the slides with serum-free blocking solution (Dakocytomation) for 20 min at room temperature. The primary mAb (anti-KAAG1 3D3) was added for 1 h at room temperature. KAAG1-reactive antigen was detected by incubating with biotin-conjugated mouse anti-kappa followed by streptavidin-HRP tertiary antibody. Positive staining was revealed by treating the slides with DAB-hydrogen peroxide substrate for less than 5 min and subsequently counterstained with hematoxylin. The KAAG1 protein was found to be expressed at very high levels in the vast majority of ovarian tumor samples. A representative array containing 70 tumors is depicted in Fig. 8A. As demonstrated by the expression profiling studies that were performed using RT-PCR, KAAG1 transcripts were present in greater than 85% of ovarian tumor samples analyzed. Clearly, there is an excellent correlation between the transcription of the KAAG1 gene and the presence of the protein in ovarian cancer. Some of the samples were inspected at a higher magnification to determine which cells were expressing the KAAG1 protein. As depicted in Fig. 8B, KAAG1 is predominantly expressed in the surface epithelium of ovarian tumors. In addition, strong intensity was observed on the apical side of these epithelial cells (see arrows in Fig. 8B, magnification: 20x). Finally, immunohistochemistry was repeated on ovarian tumor samples that originated from different histotypes. As explained earlier, epithelial ovarian cancer can be classified into 4 major histotypes: serous, endometroid, clear cell, and mucinous. The expression of KAAG1 was detected in all types of epithelial ovarian cancer, in particular serous and endometroid histotypes (see Fig. 8C).

Taken together, these immunohistochemical studies illustrate the utility of detecting KAAG1 in ovarian cancer with the monoclonal antibodies.

Example 8

IgG_1 antibodies against KAAG1 can mediate ADCC

Antibody-Dependent Cell Cytotoxicity (ADCC) is a mechanism of cell-mediated immunity whereby effector cells, typically natural killer (NK) cells, of the immune system actively

lyse target cells that have been bound by specific antibodies. The interaction between the NK cells and the antibody occurs via the constant Fc domain of the antibody and high-affinity Fcγ receptors on the surface of the NK cells. IgG_1s have the highest affinity for the Fc receptors while IgG_2 mAbs exhibit very poor affinity. For this reason the chimeric antibodies targeting KAAG1 were designed as IgG_1s. This type of effector function that is mediated in this manner can often lead to the selective killing of cancer cells that express high level of antigen on their cell surfaces.

An *in vitro* assay to measure ADCC activity of the anti-KAAG1 IgG_1 chimeric antibodies was adapted from a previously published method, which measured the ADCC activity of the anti-CD20 rituxan in the presence of a lymphoma cell line called WIL2-S (Idusogie *et al.*, (2000) J. Immunol. **164**, 4178-4184). Human peripheral blood mononuclear cells (PBMNCs) were used as a source of NK cells which were activated in the presence of increasing concentration of the 3D3 chimeric IgG_1 antibody (see Figure 13). The target cells were incubated with the activated PBMNCs at a ratio of 1 to 25. As shown, cell death increased in a dose-dependent manner both in the presence of OVCAR-3 and the lymphoma cell line, the latter of which was shown to express KAAG1 by RT-PCR (not shown). As a positive control, the results from the published method were reproduced where high level of ADCC was obtained for rituxan in the presence of WIL2-S cells.

ADCC was also observed with other ovarian cancer cell lines that express relatively high levels of KAAG1. These results demonstrate that IgG_1 antibodies that are specific for KAAG1, as exemplified by 3D3, can enhance the lysis of cancer cells which express the antigen on their cell surface.

Example 9

Antibodies against KAAG1 can reduce the invasion of ovarian tumors

Patients that develop ovarian cancer have lesions that typically initiate by an uncontrolled growth of the cells in the epithelial layer of the ovary or, in some instances, the fallopian tube. If detected early, these primary tumors are surgically removed and first-line chemotherapy can result in very good response rates and improved overall survival. Unfortunately, 70% of the patients will suffer recurrent disease resulting in the spread of hundreds of micro-metastatic tumors throughout the abdominal cavity. Second-line therapies can be efficacious, but often patients either respond poorly or the

tumors develop chemoresistance. Treatment options are limited and there are urgent needs for new therapies to circumvent resistance to cytotoxic drugs.

In order to test the efficacy of anti- KAAG1 antibodies *in vivo*, an animal model of ovarian cancer was used that is the closest representation of the clinical manifestation of the disease in humans. The TOV-112D cell line is of endometrioid origin and expresses the KAAG1 antigen as measured by RT-PCR. Previous IHC studies showed that ovarian tumors of the endometrioid histotype contain strong expression of KAAG1 thus rendering the 112D cell line an appropriate selection for testing anti- KAAG1 antibodies.

The intra-peritoneal inoculation of the TOV-112D cell line in SCID mice resulted in the implantation of dozens of micro-metastatic tumors that closely resemble those that are observed in humans. Mice treated with PBS, the diluent for the antibodies, contained upon examination, an average of 25 – 30 tumors per animal (Figure 14A and 14B). In some cases, the number of tumors was so high in the abdominal cavity of these mice that the number of tumors could not be easily determine; these mice were excluded from the statistical analysis. When the mice were treated with the 3C4 and 3D3 antibodies, the number of micro-metastatic tumors was drastically reduced. In addition, there was at least one animal per group treated with anti- KAAG1 where no tumors were seen. A second experiment was conducted in mice containing a larger number of TOV-112D tumors (> 50/animal) and very similar results were obtained. Moreover, there was very little difference between the groups treated with the 3C4 compared to the 3D3 antibody. However, the tendency in these *in vivo* experiments as well as the results obtained in the cell-based assays show that the 3D3 antibody displayed slightly more efficacy. Whether, this is due to a more accessible epitope or a higher affinity of 3D3 compared to 3C4 for the antigen still remains to be established. The results from these two experiments demonstrated that targeting KAAG1 on the surface of ovarian cancer cells could lead to a significant reduction in the spread of the tumors *in vivo*.

Furthermore, these findings are in complete agreement with the observations that were made in the cell-based assays. For example, the increased expression of the KAAG1 mRNA in the spheroids compared to cell lines grown as monolayers; the reduction in cell migration in the presence of KAAG1 shRNAs, the reduction in the ability of cell lines to form spheroids when treated with KAAG1 antibodies; and finally, enhancement of ADCC

activity by anti- KAAG1 IgG_1s. Taken together, the results strongly suggest that targeting KAAG1 with an antibody has great therapeutic potential in recurrent ovarian cancer.

Example 10

KAAG1 is expressed in skin tumors and renal cell carcinomas and is a therapeutic target in these indications.

The mRNA profiling studies that were conducted showed that the transcript encoding the KAAG1 antigen was highly expressed in cell lines derived from melanoma samples and renal carcinomas. These results were disclosed in Sooknanan *et al.*, 2007. To confirm the transcriptional regulation of the *KAAG1* gene in these cancer types, immunohistochemistry was performed with an anti-KAAG1 antibody on human skin tumor tissue microarrays (Pantomics Inc., Richmond, CA) containing several sections isolated from squamous cell carcinomas and melanomas. The analysis of this array showed that there was very strong staining in biopsies isolated from squamous cell carcinomas and melanomas (Figure 15, top panel). Both of these types are among the most common forms of skin cancers and interestingly, the squamous cell carcinomas are the most metastatic, a fact that again links the expression of KAAG1 to an invasive phenotype. As previously observed, the presence of KAAG1 was very weak or absent on the three normal skin samples that were contained on the array. Similarly, KAAG1 was detected in many of the samples contained in an array of renal cancer. Most of the positive samples were predominantly of the papillary cell carcinoma type and a few clear cell carcinomas expressed KAAG1 protein. Papillary carcinomas represent approximately 20% of renal cancer cases.

In order to test if the function of KAAG1 is the same in these types of cancer compared to its role in ovarian cancer, cell lines derived from melanoma and renal cell carcinomas were obtained and tested in the spheroid culture assay (see Example 1 and 6). For the melanoma model, A375 and SK-MEL5 cells, two malignant melanoma cell lines, were cultured under conditions that allowed them to form spheroids in the presence of 5% FBS. The cultures were incubated with or without the anti-KAAG1 chimeric 3D3 antibody at a concentration of 5 μg/ml. As shown in Figure 16, inclusion of 3D3 antibody in the cultures prevented the proper assembly of spheroid structures in melanoma cell lines. This result suggested that KAAG1 plays a similar role in melanoma as it does in ovarian cancer. Cell lines derived from renal cell carcinoma were also tested. The A-498 cell line is a renal papillary cell carcinoma cell line whereas the 786-O is a renal clear cell

carcinoma. As depicted in Figure 16, only the A-498 spheroids were affected by the presence of the 3D3 anti-KAAG1 antibody while the 786-O cell line was unaffected in this assay. These results parallel the immunohistochemistry results described above and indicate that the inhibition of spheroids formation is dependent on the presence of KAAG1 on the surface of renal cancer cells derived predominantly from papillary kidney cancers. It is possible however, that the anti-KAAG1 antibody may work in other types of assays for renal clear cell carcinoma.

Taken together, these data are strongly supportive of a critical function in role of KAAG1 in melanoma and kidney cancer and indicate that blocking KAAG1 with antibodies in these indications has therapeutic potential.

Example 11

KAAG1 is expressed on the surface of ovarian cancer cells. The combined results from the bioinformatics analysis of the primary structure of the cDNA encoding KAAG1, biochemical studies, and immunohistochemical detection of the protein in epithelial cells suggested that the KAAG1 antigen was located on the cell surface. However, more direct evidence was required to demonstrate that KAAG1 is indeed a membrane-bound protein. In one approach, ovarian cancer cell lines known to express KAAG1 were plated in micro-titer plates, fixed under conditions that do not permeate the cells, and incubated with increasing concentration of anti- KAAG1 chimeric antibodies. Following extensive washing of the cells, bound antibody was detected with HRP-conjugated anti-human IgG as a secondary antibody in a modified cell-based ELISA (see Figure 17A). The first observation that can be made from these experiments is that the antibodies could be specifically captured by the cells suggesting that the KAAG1 was present at the cell surface. Secondly, the amount of binding was strongest on SKOV-3 cells and the TOV-21G cells exhibited the weakest binding. This was in complete agreement with RT-PCR data which demonstrated that the KAAG1 mRNA was expressed in similar proportions in these cell lines (not shown). Additionally, the 3D3 antibody produced the strongest signal implying that the epitope targeted by this antibody was the most accessible in this assay. The 3G10 could only detect KAAG1 in the cell line that expressed the highest level of AB-0447 (SKOV-3 cells, see right panel of Figure 17A). A second approach used was flow cytometry. In this case, a mouse 3D3 anti-KAAG1 antibody was incubated with SKOV-3 ovarian cancer cells at saturating conditions and following extensive washing, the bound 3D3 anti-KAAG1 antibody was detected with anti-mouse IgG conjugated to

FITC in a flow cytometer. As shown in Figure 17B, the signal at the surface of SKOV-3 cells was much higher compared to same cells labeled with the negative control, an anti-KLH (Keyhole limpet hemocyanin) antibody, specific for a non-mammalian unrelated protein, which was at a fluorescence level the same as the background readings. Taken together, these results demonstrate that KAAG1 is located on the surface of cells.

Example 12

Methods for the use of humanized anti-KAAG1 antibodies.

On the basis of both the *in vitro* and preliminary *in vivo* results, two mouse anti-KAAG1 antibody candidates, designated 3D3 and 3C4, were selected for humanization using *in silico* modeling using methods familiar to those in the art. In brief, the variable regions of the murine antibodies were modeled in 3D based on available crystal structures of mouse, humanized, and fully human variable regions that displayed high sequence homology and similar CDR loop lengths. The CDRs are the amino acid sequences that contribute to antigen binding; there are 3 CDRs on each antibody chain. Additionally, the framework regions, the amino acid sequences that intervene between the CDRs, were modified by standard homology comparison between mouse and human antibody sequences resulting in the 'best-fit' human sequence. These modifications ensured that the proper positioning of the CDR loops was maintained to ensure maximum antigen binding in the humanized structure as well as preserving the potential N- and O-linked glycosylation sites. The sequence of both the heavy and light chain variable regions in the humanized (h) 3D3 and 3G4 resulted in 96% and 94% humanization, respectively. The structure of the 3D3 and 3C4 models for each antibody is shown in Figure 18A and 18B, respectively. As illustrated in these structures, the 3D3 required the maintenance of 3 unusual amino acids (Figure 18A, Met93 and Gly94 on the heavy chain and Ser57 on the light chain) because of their proximity to the CDRs. Modeling predicted that replacement of these mouse amino acids with human equivalents might compromise binding of the antibody with the KAAG1 antigen. In the case of 3C4, 6 amino acids were considered unusual (Figure 18B, Glu1, Gln72 and Ser98 on the heavy chain and Thr46, Phe49 and Ser87 on the light chain). In both figures, the light chain CDRs are indicated by L1, L2, and L3 for CDR1, CDR2, and CDR3, respectively, whereas the heavy chain CDRs are indicated by H1, H2, and H3 for CDR1, CDR2, and CDR3, respectively.

The sequences that encode the complete anti-KAAG1 3D3 immunoglobulin light and heavy chains are shown in SEQ ID NO.:176 and 177, respectively. The variable region of the humanized 3D3 light chain is contained between amino acids 21-133 of SEQ ID NO.:176 and is shown in SEQ ID NO.:178. The variable region of the humanized 3D3 heavy chain is contained between amino acids 20-132 of SEQ ID NO.:177 and is shown in SEQ ID NO.:179. The sequences that encode the complete anti-KAAG1 3C4 immunoglobulin light and heavy chains are shown in SEQ ID NO.:180 and 181, respectively. The variable region of the humanized 3C4 light chain is contained between amino acids 21-127 of SEQ ID NO.:180 and is shown in SEQ ID NO.:182. The variable region of the humanized 3C4 heavy chain is contained between amino acids 19-136 of SEQ ID NO.:181 and is shown in SEQ ID NO.:183.

Following assembly of expression vectors and production of the h3D3 in transfected mammalian cells (see Example 5), several assays were performed to demonstrate the bio-equivalence of the humanization process. Since an antibody harboring effector functions was required, the h3D3 was assembled as a human IgG_1. ELISA-based assays were performed to directly compare the ability of the h3D3 to recombinant KAAG1. The methods used to perform these tests were as described in Example 3 using recombinant Fc-KAAG1. As shown in Figure 19A, the binding activity of the h3D3 was identical to that of the chimeric 3D3.

More precise measurements were conducted using Surface Plasmon Resonance (SPR) in a Biacore instrument. Kinetic analysis was used to compare the affinity of the chimeric 3D3 with the h3D3 as well as with hybrid antibodies encompassing different permutations of the light and heavy chains (see Figure 19B). Briefly, anti-human Fc was immobilized on the Biacore sensor chip and chimeric or h3D3 was captured on the chip. Different concentrations of monomeric recombinant KAAG1 were injected and the data were globally fitted to a simple 1:1 model to determine the kinetic parameters of the interaction. The kinetic parameters of the chimeric 3D3 were tabulated in Figure 19B (m3D3). The average K_D of the chimeric 3D3 was 2.35×10^{-10} M. In comparison, all permutations of the chimeric(C)/humanized(H) displayed very similar kinetic parameters. The average K_D of the chimeric light chain expressed with the chimeric heavy chain (indicated as 'CC' in Figure 19B) was 2.71×10^{-10} M, the average K_D of the humanized light chain expressed with the chimeric heavy chain (indicated as 'HC' in Figure 19B) was 3.09×10^{-10} M, the average K_D of the chimeric light chain expressed with the

humanized heavy chain (indicated as 'CH' in Figure 19B) was 5.05 x 10^{-10} M, and the average K_D of the humanized light chain expressed with the humanized heavy chain (indicated as 'HH' in Figure 19B) was 4.39 x 10^{-10} M. The analyses indicated that the humanization of 3D3 conserved the binding activity of the original mouse antibody.

The biological function of the h3D3 was evaluated in the spheroid culture assay (see Example 6). SKOV-3 ovarian cancer cells were cultured in the presence of 5% FBS in the presence of h3D3 or a non-KAAG1 binding isotype control antibody. The results (shown in Figure 19C), indicated that treatment with either the buffer or the non-related IgG did not inhibit the formation of the compact 3-D structures. In contrast, both the chimeric 3D3 and the humanized 3D3 prevented the spheroids from forming. The results are shown in duplicate (left and right panels). These results indicate that the biological activity of the chimeric 3D3 was conserved in the humanized 3D3 and suggests that the h3D3 will behave in an identical manner.

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SEQ ID NO.:1

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CTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCT
TCCCGGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGACCGTGCCCTCCAGC
AGCTTGGGCACCCAGACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAA
GAAAGTTGAGCCCAAATCTTGTGAATTCACTCACACATGCCCACCGTGCCCAGCACCTGAACTCC
TGGGGGGACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACC
CCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTA
CGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGT
ACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAG
CAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATG
AGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCCGGGAAATGATCCCCCGAC
CTCGACCTCTGGCTAATAAAGGAAATTTATTTTCATTGCAATAGTGTGTTGGAATTTTTTGTGTC
TCTCACTCGGAAGGACATATGGGAGGGCAAATCATTTGGTCGAGATCCCTCGGAGATCTCTAGCT
AGAGCCCCGCCGCCGGACGAACTAAACCTGACTACGGCATCTCTGCCCCTTCTTCGCGGGGCAGT
GCATGTAATCCCTTCAGTTGGTTGGTACAACTTGCCAACTGAACCCTAAACGGGTAGCATATGCT
TCCCGGGTAGTAGTATATACTATCCAGACTAACCCTAATTCAATAGCATATGTTACCCAACGGGA
AGCATATGCTATCGAATTAGGGTTAGTAAAAGGGTCCTAAGGAACAGCGATGTAGGTGGGCGGGC
CAAGATAGGGGCGCGATTGCTGCGATCTGGAGGACAAATTACACACACTTGCGCCTGAGCGCCAA
GCACAGGGTTGTTGGTCCTCATATTCACGAGGTCGCTGAGAGCACGGTGGGCTAATGTTGCCATG
GGTAGCATATACTACCCAAATATCTGGATAGCATATGCTATCCTAATCTATATCTGGGTAGCATA
GGCTATCCTAATCTATATCTGGGTAGCATATGCTATCCTAATCTATATCTGGGTAGTATATGCTA
TCCTAATTTATATCTGGGTAGCATAGGCTATCCTAATCTATATCTGGGTAGCATATGCTATCCTA
ATCTATATCTGGGTAGTATATGCTATCCTAATCTGTATCCGGGTAGCATATGCTATCCTAATAGA
GATTAGGGTAGTATATGCTATCCTAATTTATATCTGGGTAGCATATACTACCCAAATATCTGGAT
AGCATATGCTATCCTAATCTATATCTGGGTAGCATATGCTATCCTAATCTATATCTGGGTAGCAT

AGGCTATCCTAATCTATATCTGGGTAGCATATGCTATCCTAATCTATATCTGGGTAGTATATGCT
ATCCTAATTTATATCTGGGTAGCATAGGCTATCCTAATCTATATCTGGGTAGCATATGCTATCCT
AATCTATATCTGGGTAGTATATGCTATCCTAATCTGTATCCGGGTAGCATATGCTATCCTCACGA
TGATAAGCTGTCAAACATGAGAATTAATTCTTGAAGACGAAAGGGCCTCGTGATACGCCTATTTT
TATAGGTTAATGTCATGATAATAATGGTTTCTTAGACGTCAGGTGGCACTTTTCGGGGAAATGTG
CGCGGAACCCCTATTTGTTTATTTTTCTAAATACATTCAAATATGTATCCGCTCATGAGACAATA
ACCCTGATAAATGCTTCAATAATATTGAAAAAGGAAGAGTATGAGTATTCAACATTTCCGTGTCG
CCCTTATTCCCTTTTTTGCGGCATTTTGCCTTCCTGTTTTTGCTCACCCAGAAACGCTGGTGAAA
GTAAAAGATGCTGAAGATCAGTTGGGTGCACGAGTGGGTTACATCGAACTGGATCTCAACAGCGG
TAAGATCCTTGAGAGTTTTCGCCCCGAAGAACGTTTTCCAATGATGAGCACTTTTAAAGTTCTGC
TATGTGGCGCGGTATTATCCCGTGTTGACGCCGGGCAAGAGCAACTCGGTCGCCGCATACACTAT
TCTCAGAATGACTTGGTTGAGTACTCACCAGTCACAGAAAAGCATCTTACGGATGGCATGACAGT
AAGAGAATTATGCAGTGCTGCCATAACCATGAGTGATAACACTGCGGCCAACTTACTTCTGACAA
CGATCGGAGGACCGAAGGAGCTAACCGCTTTTTTGCACAACATGGGGGATCATGTAACTCGCCTT
GATCGTTGGGAACCGGAGCTGAATGAAGCCATACCAAACGACGAGCGTGACACCACGATGCCTGC
AGCAATGGCAACAACGTTGCGCAAACTATTAACTGGCGAACTACTTACTCTAGCTTCCCGGCAAC
AATTAATAGACTGGATGGAGGCGGATAAAGTTGCAGGACCACTTCTGCGCTCGGCCCTTCCGGCT
GGCTGGTTTATTGCTGATAAATCTGGAGCCGGTGAGCGTGGGTCTCGCGGTATCATTGCAGCACT
GGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTATCTACACGACGGGGAGTCAGGCAACTATGG
ATGAACGAAATAGACAGATCGCTGAGATAGGTGCCTCACTGATTAAGCATTGGTAACTGTCAGAC
CAAGTTTACTCATATATACTTTAGATTGATTTAAAACTTCATTTTTAATTTAAAAGGATCTAGGT
GAAGATCCTTTTTGATAATCTCATGACCAAAATCCCTTAACGTGAGTTTTCGTTCCACTGAGCGT
CAGACCCCGTAGAAAAGATCAAAGGATCTTCTTGAGATCCTTTTTTTCTGCGCGTAATCTGCTGC
TTGCAAACAAAAAAACCACCGCTACCAGCGGTGGTTTGTTTGCCGGATCAAGAGCTACCAACTCT
TTTTCCGAAGGTAACTGGCTTCAGCAGAGCGCAGATACCAAATACTGTCCTTCTAGTGTAGCCGT
AGTTAGGCCACCACTTCAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTA
CCAGTGGCTGCTGCCAGTGGCGATAAGTCGTGTCTTACCGGGTTGGACTCAAGACGATAGTTACC
GGATAAGGCGCAGCGGTCGGGCTGAACGGGGGGTTCGTGCACACAGCCCAGCTTGGAGCGAACGA
CCTACACCGAACTGAGATACCTACAGCGTGAGCATTGAGAAAGCGCCACGCTTCCCGAAGGGAGA
AAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGAGCTTCCAGG
GGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTT
TGTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTC
CTGGCCTTTTGCTGGCCTTTTGCTCACATGTTCTTTCCTGCGTTATCCCCTGATTCTGTGGATAA
CCGTATTACCGCCTTTGAGTGAGCTGATACCGCTCGCCGCAGCCGAACGACCGAGCGCAGCGAGT
CAGTGAGCGAGGAAGCGTACATTTATATTGGCTCATGTCCAATATGACCGCCATGTTGACATTGA
TTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATAGCCCATATATGGAGTT
CCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGA
CGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTG
GAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTCCGCCCCC
TATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTACGGGACT
TTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTGATGCGGTTTTGGCAG
TACACCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTCCAAGTCTCCACCCCATTGACGT
CAATGGGAGTTTGTTTTGGCACCAAAATCAACGGGACTTTCCAAAATGTCGTAATAACCCCGCCC
CGTTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTCTATATAAGCAGAGCTCGTTTAGTG
AACCGTCAGATCCTCACTCTCTTCCGCATCGCTGTCTGCGAGGGCCAGCTGTTGGGCTCGCGGTT
GAGGACAAACTCTTCGCGGTCTTTCCAGTACTCTTGGATCGGAAACCCGTCGGCCTCCGAACGGT
ACTCCGCCACCGAGGGACCTGAGCGAGTCCGCATCGACCGGATCGGAAAACCTCTCGAGAAAGGC
GTCTAACCAGTCACAGTCGCAAGGTAGGCTGAGCACCGTGGCGGGCGGCAGCGGGTGGCGGTCGG
GGTTGTTTCTGGCGGAGGTGCTGCTGATGATGTAATTAAAGTAGGCGGT

SEQ ID NO.:71

GGGTTCCAGGTTCCACTGGCGAGGTTCAGCTGCAGCAGTCTGT

SEQ ID NO.:72
GGGTTCCAGGTTCCACTGGCGAGGTGCAGCTTCAGGAGTCAGG

SEQ ID NO.:73
GGGGCCAGGGGAAAGACAGATGGGCCCTTCGTTGAGGC

SEQ ID NO.: 91: Exemplary embodiment of CDRL1
K-S-S-Q-S-L-L-N/H-S/T-S/N/D-N/G-Q/N/K-K/L-N-Y-L-A

SEQ ID NO.:92: Exemplary embodiment of CDRL1
K-A-S-Q-D-I-H-N/T-Y/F-L-N

SEQ ID NO93: Exemplary embodiment of CDRL2
F-A-S-T-R-E-S

SEQ ID NO.: 94: Exemplary embodiment of CDRL2
L-V-S-K-L-D-S

SEQ ID NO.:95: Exemplary embodiment of CDRL2
R-A-N-R-L-V-D

SEQ ID NO.:96: Exemplary embodiment of CDRL3
Q-Q-H-Y-S-T-P-L-T

SEQ ID NO.:97: Exemplary embodiment of CDRL3
W/L-Q-Y/G-D/T-A/E/H-F-P-R-T

SEQ ID NO.:98: Exemplary embodiment of CDRH1 1
G-Y-T/I-F-T-D/E-Y-E/N-M/I/V-H

SEQ ID NO.:99: Exemplary embodiment of CDRH1
G-F-T/S-I-T-S-G-Y-G-W-H

SEQ ID NO.:100: Exemplary embodiment of CDRH2
V/N/G-I/L-D-P-E/A/G-T/Y-G-X-T-A

SEQ ID NO.:101: Exemplary embodiment of CDRH2
Y-I-N/S-F/Y-N/D-G

SEQ ID NO.:102: Exemplary embodiment of CDRH3
M-G-Y-S/A-D-Y

SEQ ID NO.:103: Exemplary embodiment of CDRH3
A-S-S-Y-D-G-F-L-A-Y

SEQ ID NO.:104: Exemplary embodiment of CDRH3 3
A-R/W-W/F-G-L-R-Q/N

SEQ ID NO.:158

KSSQSLLHSDGKTYLN

SEQ ID NO.:159
LVSKLDS

SEQ ID NO.:160
WQGTHFPRT

SEQ ID NO.:161
GYTFTD YNMH

SEQ ID NO.:162
YINPYNDVTE

SEQ ID NO.:163
AWFGL RQ

SEQ ID NO.:164
RSSKSLLHSNGN TYLY

SEQ ID NO.:165
RMSNLAS

SEQ ID NO.:166
MQHLEYPYT

SEQ ID NO.:167
GDTFTD YYMN

SEQ ID NO.:168
DINPNYGGIT

SEQ ID NO.:169
QAYYRNS DY

SEQ ID NO.:170
KASQDVGTAVA

SEQ ID NO.:171
WTSTRHT

SEQ ID NO.:172
QQHYSIPLT

SEQ ID NO.:173
GYIFTDYEIH

SEQ ID NO.:174
VIDPETGNTA

SEQ ID NO.:175

MGYSDY

SEQ ID NO.:176
MVLQTQVFISLLLWISGAYGDIVMTQSPDSLAVSLGERATINCKSSQSLLNSNFQKNFLA
WYQQKPGQPPKLLIYFASTRESSVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHY
STPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD
NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC

SEQ ID NO.:177
MDWTWRILFLVAAATGTHAEVQLVQSGAEVKKPGASVKVSCKASGYIFTDYEIHWVRQ
APGQGLEWMGVIDPETGNTAFNQKFKGRVTITADTSTSTAYMELSSLTSEDTAVYYCM
GYSDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSW
NSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEP
KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE
KTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNY
KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID N:178
DIVMTQSPDSLAVSLGERATINCKSSQSLLNSNFQKNFLAWYQQKPGQPPKLLIYFAST
RESSVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQHYSTPLTFGQGTKLEIK

SEQ ID NO.:179
EVQLVQSGAEVKKPGASVKVSCKASGYIFTDYEIHWVRQAPGQGLEWMGVIDPETGN
TAFNQKFKGRVTITADTSTSTAYMELSSLTSEDTAVYYCMGYSDYWGQGTLVTVSS

SEQ ID NO.:180
MVLQTQVFISLLLWISGAYGDIVMTQSPSSLSASVGDRVTITCKASQDIHNFLNWFQQK
PGKAPKTLIFRANRLVDGVPSRFSGSGSGTDYTLTISSLQPEDFATYSCLQYDEIPLTFG
QGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGN
SQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO.:181
MDWTWRILFLVAAATGTHAEVQLQESGPGLVKPSQTLSLTCTVSGFSITSGYGWHWIR
QHPGKGLEWIGYINYDGHNDYNPSLKSRVTISQDTSKNQFSLKLSSVTAADTAVYYCAS
SYDGLFAYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV
SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKK
VEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEV
KFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPA
PIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPEN
NYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
K

SEQ ID No.:182
DIVMTQSPSSLSASVGDRVTITCKASQDIHNFLNWFQQKPGKAPKTLIFRANRLVDGVP
SRFSGSGSGTDYTLTISSLQPEDFATYSCLQYDEIPLTFGQGTKLEIK

SEQ ID NO.:183
EVQLQESGPGLVKPSQTLSLTCTVSGFSITSGYGWHWIRQHPGKGLEWIGYINYDGHN
DYNPSLKSRVTISQDTSKNQFSLKLSSVTAADTAVYYCASSYDGLFAYWGQGTLVTVS

Table A: Light chains variable region of selected antibodies

	SEQID NO:	
3z1A02L	105	DAVMTQIPLTLSVTIGQPASLSC **KSSQSLLHSDGK TYLN** WLLQRPGQSPKRLIS **LVSKLDS** GVPDRFTGSGSGTDFTLKISRVEAEDLGLYYC **WQGTHFPRT** FAGGTNLEIK
3z1F06L	106	SIVMTQTPLTLSVTIGQPASITC **KSSQSLLYSDGK TYLN** WLLQRPGQSPKRLIS **LVSKLDS** GVPDGFTGSGSGTDFTLKISRVEAEDLGVYYC **WQGTHFPRT** FGGGTKLEIK
3z1E08L	107	DAVMTQIPLTLSVTIGQPASISC **KSSQSLLHSDGK TYLN** WLLQRPGQSPKRLIY **LVSKLDS** GVPDRFTGSGSGTDFTLKISRVEAEDLGVYYC **WQGTHFPRT** FGGGTKLEIK
3z1G10L	108	DVLMTQTPRSLSVSLGDQASISC **RSSQSLLHSNGN TYLE** WYLQKPGQPPKVLIY **KVSNRFS** GVPDRFSGSGSGTDFTLKISGVEAEDLGVYYC **FQGSHVPLT** FGAGTKLELK
3z1E10L	109	DIVMTQAAPSVPVTPGESVSISC **RSSKSLLHSNGN TYLY** WFLQRPGQSPQLLIY **RMSNLAS** GVPDRFSGSGSGTAFTLRISRVEAEDVGVYYC **MQHLEYPYT** FGGGTKLEIK
3z1A09L	110	DIVMTQSPSSLAMSLGQKVTMSC **KSSQSLLNSNNQLNYLA** WYQQKPGQSPKLLVY **FASTRKS** GVPDRFIGSGSGTDFTLTITSVQAEDLADYFC **QQHFNTPLT** FGAGTKLELK
3z1B01L	111	DIVMTQSPSSLAISVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVF **FASTRES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSIPLT** FGAGTKLELK
3z1G05L	112	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVF **FASTRES** GVPDRFIGSGSGTDFTLTITSVQAEDLADYFC **QQHYSIPLT** FGSGTKLELK
3z1B02L	113	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVY **FASTRES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSIPLT** FGAGTKLELK
3z1B08L	114	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVY **FASTRES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1G08L	115	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVY **FASTRES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1F07L	116	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLIY **FASTRES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1E09L	117	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVY **FASTRES** GVPDRFIGSGSGTEFTLTITSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1C03L	118	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVY **FGSTRES** GVPDRFIGSGSGTDFTLTISGVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1E12L	119	DIVMTQSPSSLAMSVGQKVTMNC **KSSQSLLNRSNQKNYLA** WYQQKPGQSPKLLVY **FASTRES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSIPLT** FGAGTKLELK
4z1A02L	120	DIVMTQSPSSLAMSVGQKVTMNC **KSSQSLLNNSNQKNYLA** WYQQKPGQSPKLLLY **FASTRES** GVPDRFIGSGSGTYFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLDLK
3z1F10L	121	DIVMTQSPSSLTMSVGQKVTMSC **KSSQSLLNTSNQLNYLA** WYQQKPGQSPKLLVY **FASTTES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1F04L	122	DIVMTQSPSSLTVTAGEKVTMSC **KSSQSLLNTSNQKNYLA** WYQQKPGQSPKLLVY **FASTRAS** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1B11L	123	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVY **FASTRES** GVPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1D03L	124	DIVMTQSPSSLAVSIGQKVTMNC **KSSQSLLNSNFQKNFLA** WYQQKPGQSPKLLIY **FASTRES** SIPDRFIGSGSGTDFTLTISSVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1C03L	125	DIVMTQSPSSLAMSVGQKVTMSC **KSSQSLLNSSNQKNYLA** WYQQKPGQSPKLLVY **FGSTRES** GVPDRFIGSGSGTDFTLTISGVQAEDLADYFC **QQHYSTPLT** FGAGTKLELK
3z1G12L	126	DIVMTQSPKFMSTSVGDRVSITC **KASQDVG TAVA** WYQQKPGQSPELLIY **WTSTRHT** GVPDRFSGSGSGTDFTLTISSVQAEDLADYFC **QQHYSIPLT** FGAGTKLELR
3z1C04L	127	DIVMSQSPSSMYASLGERVTITC **KASQDIH NFLN** WFQQKPGKSPKTLIF **RANRLVD** GVPSRFSGSGSGQDYSLTISSLEFEDLGIYSC **LQYDEIPLT** FGAGTKLELR
3z1D01L	128	DIKMTQSPSSMYASLGERVTITC **KASQDIH TYLN** WFQQKPGKSPETLIY **RANRLVD** GVPSRFSGSGSGQDYSLTISSLEYEDMGIYYC **LQYDEFPLT** FGAGTKLELK
3z1C02L	129	DIQMTQSPSSMYASLGERVTLTC **KASQDIH NYLN** WFQQKPGKSPKTLIH **RANRLVA** GVPSRFSGSGSGQDYSLTISSLEYEDLGIYYC **LQYDAFPLT** FGAGTKLELK
3z1E06L	130	DIQMTQSPSSMYASLGERVTLTC **KASQDIH NYLN** WFQQKPGKSPKTLIH **RANRLVA** GVPSRFSGSGSGQDYSLTISSLEYEDLGIYYC **LQYDAFPLT** FGAGTKLELK
3z1H03L	131	DIVMSQSPSSMYASLGERVTITC **KASQDIH RFLN** WFQQKPGKSPKTLIF **HANRLVD** GVPSRFSGSGSGLDYSLTISSLEYEDMGIYFC **LQYDAFPLT** FGAGTKLELK

Table B: Heavy chains variable region of selected antibodies

	SEQID NO:	
3z1A02H	132	HEIQLQQSGPELVKPGASVKMSCKTS **GYTFTD YNMH** WVKQKPGQGLEWIG **YINPYNDVTE** YNEKFKGRATLTSDKSSSTAYMDLSSLTSDDSAVYFC **AWFGL RQ** WGQGTLVTVST
3z1F06H	133	HEVQLQQSGPELVKPGASVKMSCKAS **GYIFTE YNIH** WVKQKPGQGPEWIG **NINPYNDVTE** YNEKFKGKATLTSDKASSTAYMDLSSLTSEDSAVYYC **ARWGL RN** WGQGTLVTVSA
3z1E08H	134	HEVQLQQSVPELVKPGASVKMSCKTS **GYTFTE YNMH** WVKQKPGQGPEWIG **NINPYNNVTE** YNEKFKGKATLTSDKSSSTAYLDLSSLTSEDSAVYYC **ARWGL RN** WGQGTLVTVSA
3z1A09H	135	HQVQVQQPGAELVRPGASVTLSCKAS **GYIFTD YEVH** WVRQRPVHGLEWIG **VIDPETGDTA** YNQKFKGKATLTADKSSSTAYMELSSLTAEDSAVYYC **IGYA DY** WGQGTTLTVSS
3z1B01H	136	HQVQLQQPGAELVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGGTA** YNQKFKGKATLTTDKSSSTAYMELRSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3z1B02H	137	HEVQLQQSGAELVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGATA** YNQKFKGKATLTADKSSSTAYMELSSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3z1F04H	138	HEVQLQQSGAELVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGSTA** YNQKFKGKATLTADKASSTAYMELSSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3Z1E09H	139	HEVQLQQSGAELVRPGASATLSCKAS **GYTFTD YEMH** WVKQTPVHGLEWIG **VIDPETGSTA** YNQKFKGKATLTADKSSSTAYMELSSLTSEDSAVYYC **MGYA DY** WGQGTTLTVSS
3z1B08H	140	HEVQLQQSGAELVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGDTA** YNQNFTGKATLTADKSSSTAYMELSSLTSEDSAVYYC **MGYA DY** WGQGTTLTVSS
3z1G08H	141	HQVQLKQSGAELVRPGASVTLSCKAS **GYTFTD YEVH** WVKQTPVHGLEWIG **VIDPATGDTA** YNQKFKGKATLTADKSSSTAYMEVSSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3z1F07H	142	HQAYLQQSGAELVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGDTA** YNQKFKDKATLTADKASSTAYMELSSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3z1E12H	143	HQVQLQQSEAELVKPGASVKLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGDTA** YNQKFKGKATLTADKSSSTAYMELSRLTSEDSAVYYC **MGHS DY** WGQGTTLTVSS
3Z1D03H	144	HEVQLQQSVAELVRPGASVTLSCKAS **GYIFTD YEIH** WVKQTPVHGLEWIG **VIDPETGNTA** FNQKFKGKATLTADISSSTAYMELSSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3z1G12H	145	HEVQLQQSVAELVRPGASVTVSCKAS **GYIFTD YEIH** WVKQTPAHGLEWIG **VIDPETGNTA** FNQKFKGKATLTADISSSTAYMELSSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3z1F10H	146	HEVQLQQSVAELVRPGAPVTLSCKAS **GYTFTD YEVH** WVKQTPVHGLEWIG **VIDPETGATA** YNQKFKGKATLTADKSSSAAYMELSRLTSEDSAVYYC **MSYS DY** WGQGTTLTVSS
3z1C03H	147	HEVQLQQSVAEVVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGVTA** YNQRFRDKATLTTDKSSSTAYMELSSLTSEDSAVYFC **MGYS DY** WGQGTTLTVSS
3z1C03H	148	HEVQLQQSVAEVVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VIDPETGVTA** YNQRFRDKATLTTDKSSSTAYMELSSLTSEDSAVYFC **MGYS DY** WGQGTTLTVSS
3z1G05H	149	HQVQLQQPGAELVRPGASVTLSCKAS **GYTFTD YEIH** WVKQTPVHGLEWIG **VLDPGTGRTA** YNQKFKDKATLSADKSSSTAYMELSSLTSEDSAVYYC **MSYS DY** WGPGTTLTVSS
3z1B11H	150	HEVQLQQSVAELVRPGASVTLSCKAS **GYTFTD YEMH** WVKQTPVRGLEWIG **VIDPATGDTA** YNQKFKGKATLTADKSSSAAFMELSSLTSEDSAVYYC **MGYS DY** WGQGTTLTVSS
3z1E06H	151	HQVQLQQSGAELVRPGASVTLSCKAS **GYTFSD YEMH** WVKQTPVHGLEWIG **GIDPETGDTV** YNQKFKGKATLTADKSSSTAYMELSSLTSEDSAVYYC **ISYAM DY** WGQGTSVTVSS
4z1A02H	152	HQVKLQQSGTELVRPGASVTLSCKAS **GYKFTD YEMH** WVKQTPVHGLEWIG **GIDPETGGTA** YNQKFKGKAILTADKSSTTAYMELRSLTSEDSAVYYC **ISYAM DY** WGQGTSVTVSS
3z1E10H	153	HEVQLQQSGPELVKPGASVKISCKAS **GDTFTD YYMN** WVKQSHGKSLEWIG **DINPNYGGIT** YNQKFKGKATLTVDTSSSTAYMELRGLTSEDSAVYYC **QAYYRNS DY** WGQGTTLTVSS
3Z1G10H	154	HEIQLQQSGPELVKPGASVKISCKAS **GYTFTD NYMN** WVKQSHGKSLEWIG **DINPYYGTTT** YNQKFKGKATLTVDKSSRTAYMELRGLTSEDSAVYYC **ARDDWF DY** WGQGTLVTVSA
3z1D01H	155	HEVQLQESGPDLVKPSQSLSLTCTVT **GFSITSGYGWH** WIRQFPGDKLEWMG **YIS FNGDYN** YNPSLKSRISITRDTSKNQFFLQLSSVTTEDTATYYC **ASSYDGLFAY** WGQGTLVTVSA
3z1C02H	156	HDVQLQESGPDLVKPSQSLSLTCTVT **GFSITSGYGWH** WIRQFPGNKLEWMG **YIS FNGDSN** YNPSLKSRISITRDTSKNQFFLQLNSVTSEDTATYYC **ASSYDGLFAY** WGQGPLVTVSA
3z1C04H	157	HEVQLQESGPDLVKPSQSLSLTCTVT **GFSITSGYGWH** WIRQFPGNKLEWMG **YIN YDGHND** YNPSLKSRISITQDTSKNQFFLQLNSVTTEDTATYYC **ASSYDGLFAY** WGQGTLVTVSA

1. An isolated antibody or an antigen binding fragment thereof, wherein said antibody or antigen binding fragment thereof is capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or is capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2.

2. An isolated antibody or an antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1; SEQ ID NO.:2), selected from the group consisting of an antibody or antigen binding fragment thereof comprising:

a. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16; and

i. a CDRL1 of formula $X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\,is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of formula $FX_{1c}STX_{2c}X_{3c}S$ (SEQ ID NO.:76) wherein X_{1c} is A or G; X_{2c} is R or T, and; X_{3c} is E, K or A; and

iii. a CDRL3 of formula $X_{1f}QX_{2f}X_{3f}X_{4f}X_{5f}PLT$ (SEQ ID NO.:79) wherein X_{1f} is Q or L; X_{2f} is Y or H; X_{3f} is D, F or Y; X_{4f} is E, A, N or S, and; X_{5f} is I, F or T; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18; and

i. a CDRH1 of formula $GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82) wherein X_{1i} is T, I or K; X_{2i} is T or S; X_{3i} is D or E; X_{4i} is E, N or D, and; X_{5i} is M, I or V;

ii. a CDRH2 of formula $X_{1j}X_{2j}DPX_{3j}TGX_{4j}TX_{5j}$ (SEQ ID NO.:83) wherein X_{1j} is V or G; X_{2j} is I or L; X_{3j} is A, G or E; X_{4j} is R, G, D, A, S, N or V, and; X_{5j} is A or V; and

iii. a CDRH3 of formula $MX_{1o}X_{2o}X_{3o}DY$ (SEQ ID NO.:88) wherein X_{1o} is G or S; X_{2o} is Y or H, and; X_{3o} is A or S or a CDRH3 of formula $IX_{1p}YAX_{2p}DY$ (SEQ ID NO.:89) wherein;X_{1p} may be G or S and; X_{2p} may be absent or M;

b. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:20; and

i. a CDRL1 of formula a CDRL1 of formula $X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\,is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of formula $X_{1d}VSX_{2d}X_{3d}X_{4d}S$ (SEQ ID NO.:77) wherein X_{1d} is L or K; X_{2d} is K or N; X_{3d} is L or R and; X_{4d} is D or F; and

iii. a CDRL3 of formula $X_{1h}QGX_{2h}HX_{3h}PX_{4h}T$ (SEQ ID NO.:81) wherein X_{1h} is W or F; X_{2h} is S or T; X_{3h} is F or V, and;X_{4h} is R or L; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:22; and

iv. a CDRH1 of SEQ ID NO.:36;

v. a CDRH2 of formula $DINPX_{1n}YGX_{2n}X_{3n}T$ (SEQ ID NO.:87) Wherein X_{1n} is N or Y, X_{2n} is G or T and; X_{3n} is I or T; and

vi. a CDRH3 of SEQ ID NO.:38;

c. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24; and

i. a CDRL1 of formula $KASQDX_{1b}X_{2b}X_{3b}X_{4b}X_{5b}X_{6b}$ (SEQ ID NO.:75), wherein X_{1b} is V or I; X_{2b} is G or H; X_{3b} is T, N or R; X_{4b} is F, Y or A; X_{5b} is V or L, and; X_{6b} is N or A;

ii. a CDRL2 of formula X_{1e}ANRLVX_{2e} (SEQ ID NO.:78), wherein X_{1e} is R or H and; X_{2e} is D or A; and

iii. a CDRL3 of formula X_{1f}Q$X_{2f}X_{3f}X_{4f}X_{5f}$PLT (SEQ ID NO.:79) wherein X_{1f} is Q or L; X_{2f} is Y or H; X_{3f} is D, F or Y; X_{4f} is E, A, N or S, and; X_{5f} is I, F or T; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:26; and

iv. a CDRH1 of SEQ ID NO.:42;

v. a CDRH2 of formula Y$IX_{1l}X_{2l}X_{3l}$G$X_{4l}X_{5l}X_{6l}$ (SEQ ID NO.:85) wherein X_{1l} is S or N; X_{2l} is F or Y; X_{3l} is D, E or N; X_{4l} is D or H; X_{5l} is Y, S or N; and X_{6l} is D, E or N; and

vi. a CDRH3 of SEQ ID NO.:44;

d. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:105; and

i. a CDRL1 of formula X_{1a}SSX_{2a}SLL$X_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\,is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of formula X_{1d}VS$X_{2d}X_{3d}X_{4d}$S (SEQ ID NO.:77) wherein X_{1d} is L or K; X_{2d} is K or N; X_{3d} is L or R and; X_{4d} is D or F; and

iii. a CDRL3 of formula X_{1h}QGX_{2h}HX_{3h}PX_{4h}T (SEQ ID NO.:81) Wherein X_{1h} is W or F; X_{2h} is S or T; X_{3h} is F or V, and; X_{4h} is R or L ; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132; and

iv. a CDRH1 of formula $GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82) wherein X_{1i} is T, I or K; X_{2i} is T or S; X_{3i} is D or E; X_{4i} is E, N or D, and; X_{5i} is M, I or V;

v. a CDRH2 of formula $X_{1m}INPYNX_{2m}VTE$ (SEQ ID NO.:86) wherein X_{1m} is N or Y, and; X_{2m} is E, D or N; and

vi. a CDRH3 of formula $AX_{1q}X_{2q}GLRX_{3q}$ (SEQ ID NO.:90) wherein X_{1q} is R or W; X_{2q} is W or F and; X_{3q} is Q or N;

e. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:109; and

i. a CDRL1 of formula $X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K or R; $X_{2a\ is}$ Q or K; X_{3a} is Y, N or H; X_{4a} is S, T, N or R; X_{5a} is absent, S or N; X_{6a} is D, F or N; X_{7a} is G or Q; X_{8a} is K, L or N; X_{9a} is T or N; X_{10a} is Y or F, and X_{11a} is A, N, E or Y;

ii. a CDRL2 of SEQ ID NO.:165; and

iii. a CDRL3 of SEQ ID NO.:166; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:153; and

iv. a CDRH1 of SEQ ID NO.:167;

v. a CDRH2 of formula $DINPX_{1n}YGX_{2n}X_{3n}T$ (SEQ ID NO.:87) wherein X_{1n} is N or Y, X_{2n} is G or T and; X_{3n} is I or T ; and

vi. a CDRH3 of SEQ ID NO.:169; and

f. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:126; and

i. a CDRL1 of formula $KASQDX_{1b}X_{2b}X_{3b}X_{4b}X_{5b}X_{6b}$ (SEQ ID NO.:75) wherein X_{1b} is V or I; X_{2b} is G or H; X_{3b} is T, N or R; X_{4b} is F, Y or A; X_{5b} is V or L, and; X_{6b} is N or A;

ii. a CDRL2 of SEQ ID NO.:171; and

iii. a CDRL3 of formula $X_{1f}QX_{2f}X_{3f}X_{4f}X_{5f}PLT$ (SEQ ID NO.:79) wherein X_{1f} is Q or L; X_{2f} is Y or H; X_{3f} is D, F or Y; X_{4f} is E, A, N or S, and; X_{5f} is I, F or T; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:145; and

iv. a CDRH1 of formula $GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82) wherein X_{1i} is T, I or K; X_{2i} is T or S; X_{3i} is D or E; X_{4i} is E, N or D, and; X_{5i} is M, I or V;

v. a CDRH2 of formula $X_{1j}X_{2j}DPX_{3j}TGX_{4j}TX_{5j}$ (SEQ ID NO.:83) wherein X_{1j} is V or G; X_{2j} is I or L; X_{3j} is A, G or E; X_{4j} is R, G, D, A, S, N or V, and; X_{5j} is A or V; and

vi. a CDRH3 of formula $MX_{1o}X_{2o}X_{3o}DY$ (SEQ ID NO.:88) wherein X_{1o} is G or S; X_{2o} is Y or H, and; X_{3o} is A or S.

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

a. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16 and having a CDRL1 of amino acid sequence KSSQSLLNSNFQKNFLA (SEQ ID NO. :27) KSSQSLLNRSNQKNYLA, KSSQSLLNNSNQKNYLA, KSSQSLLNTSNQLNYLA, KSSQSLLNTSNQKNYLA, KSSQSLLNSNNQLNYLA or KSSQSLLNSSNQKNYLA;

b. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16 and having a CDRL2 of amino acid sequence FASTRES (SEQ ID NO. :28), FASTTES, FGSTRES, FASTRKS or FASTRAS;

c. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16 and having a CDRL3 of amino acid sequence QQHYSTPLT (SEQ ID NO.:29), QQHYSIPLT or QQHFNTPLT;.

d. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and having a CDRH1 of amino acid

sequence GYIFTDYEIH (SEQ ID NO. :30), GYIFTDYEVH, GYTFTDYEVH, GYTFTDYEMH, GYTFSDYEMH, GYKFTDYEMH or GYTFTDYEIH;

e. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and having a CDRH2 of amino acid sequence VIDPETGNTA (SEQ ID NO. :31), VIDPATGDTA, VIDPETGDTA, VIDPETGVTA, VIDPETGSTA, VIDPETGGTA, VLDPGTGRTA, VIDPETGATA, GIDPETGDTV or GIDPETGGTA;

f. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and having a CDRH3 of amino acid sequence MGYSDY (SEQ ID NO. :32), MGHSDY or MGYADY;

g. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24 and having a CDRL1 of amino acid sequence KASQDIHNFLN (SEQ ID NO.:39), KASQDIHRFLN, KASQDIHNYLN or KASQDIHTYLN;

h. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24 and having a CDRL2 of amino acid sequence RANRLVD (SEQ ID NO.:40), HANRLVD or RANRLVA;

i. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24 and having a CDRL3 of amino acid sequence LQYDEIPLT (SEQ ID NO.:41) LQYDAFPLT or LQYDEFPLT;

j. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:26 and having a CDRH1 of amino acid sequence GFSITSGYGWH (SEQ ID NO. :42);

k. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:26 and having a CDRH2 of amino acid sequence YINYDGHND (SE ID NO. :43), YISFNGDYN or YISFNGDSN;

l. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:26 and having a CDRH3 of amino acid sequence ASSYDGLFAY (SEQ ID NO. :44);

m. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:105 and having a CDRL1 of amino acid sequence KSSQSLLHSDGKTYLN (SEQ ID NO. :158) or KSSQSLLYSDGKTYLN;

n. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:105 and having a CDRL2 of amino acid sequence LVSKLDS (SEQ ID NO. :159);

o. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:105 and having a CDRL3 of amino acid sequence WQGTHFPRT (SEQ ID NO. :160);

p. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132 and having a CDRH1 of amino acid sequence GYTFTDYNMH (SEQ ID NO. :161), GYIFTEYNIH or GYTFTEYNMH;

q. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132 and having a CDRH2 of amino acid sequence YINPYNDVTE (SEQ ID NO. :162), NINPYNDVTE or NINPYNNVTE ;

r. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132 and having a CDRH3 of amino acid sequence AWFGLRQ (SEQ ID NO. :163) or ARWGLRN;

s. a light chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:16 and comprising a CDRL1 of SEQ ID NO.:27, a CDRL2 of SEQ ID NO.:28 and a CDRL3 of SEQ ID NO.:29 and a heavy chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID

NO.:18 and comprising a CDRH1 of SEQ ID NO.:30, a CDRH2 of SEQ ID NO.:31 and a CDRH3 of SEQ ID NO.:32;

t. a light chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:20 and comprising a CDRL1 of SEQ ID NO.:33, a CDRL2 of SEQ ID NO.:34 and a CDRL3 of SEQ ID NO.:35 and a heavy chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:22 and comprising a CDRH1 of SEQ ID NO.:36, a CDRH2 of SEQ ID NO.:37 and a CDRH3 of SEQ ID NO.:38;

u. a light chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:24 and comprising a CDRL1 of SEQ ID NO.:39, a CDRL2 of SEQ ID NO.:40 and a CDRL3 of SEQ ID NO.:41 and a heavy chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:26 and comprising a CDRH1 of SEQ ID NO.:42, a CDRH2 of SEQ ID NO.:43 and a CDRH3 of SEQ ID NO.:44;

v. a light chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:105 and comprising a CDRL1 of SEQ ID NO.:158, a CDRL2 of SEQ ID NO.:159 and a CDRL3 of SEQ ID NO.:160 and a heavy chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:132 and comprising a CDRH1 of SEQ ID NO.:161, a CDRH2 of SEQ ID NO.:162 and a CDRH3 of SEQ ID NO.:163;

w. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:109 and comprising a CDRL1 of SEQ ID NO.:164, a CDRL2 of SEQ ID NO.:165 and a CDRL3 of SEQ ID NO.:166 and a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:153 and comprising a CDRH1 of SEQ ID NO.:167, a CDRH2 of SEQ ID NO.:168 and a CDRH3 of SEQ ID NO.:169;

x. a light chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:126 and comprising a CDRL1 of SEQ ID NO.:170, a CDRL2 of SEQ ID NO.:171 and a CDRL3 of SEQ ID NO.:172 and a heavy chain variable domain comprising a sequence at least 80% identical or at least 90% identical to SEQ ID NO.:145 and comprising a CDRH1 of SEQ ID NO.:173, a CDRH2 of SEQ ID NO.:174; and a CDRH3 of SEQ ID NO.:175, or;

y. a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16 and comprising:

i. a CDRL1 of formula $X_{1a}SSX_{2a}SLLX_{3a}X_{4a}X_{5a}X_{6a}X_{7a}X_{8a}X_{9a}X_{10a}LX_{11a}$ (SEQ ID NO.:74) wherein X_{1a} is K; $X_{2a\ is}$ Q; X_{3a} is N; X_{4a} is S, T, N or R; X_{5a} is S or N; X_{6a} is F or N; X_{7a} is Q; X_{8a} is K or L; X_{9a} is N; X_{10a} is Y or F, and X_{11a} is A;

ii. a CDRL2 of formula $FX_{1c}STX_{2c}X_{3c}S$ (SEQ ID NO.:76) wherein X_{1c} is A or G; X_{2c} is R or T, and; X_{3c} is E, K or A; and

iii. a CDRL3 of formula $X_{1f}QX_{2f}X_{3f}X_{4f}X_{5f}PLT$ (SEQ ID NO.:79) wherein X_{1f} is Q; X_{2f} is H; X_{3f} is F or Y; X_{4f} is N or S, and; X_{5f} is I or T; and

a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and comprising:

i. a CDRH1 of formula $GYX_{1i}FX_{2i}X_{3i}YX_{4i}X_{5i}H$ (SEQ ID NO.:82) wherein X_{1i} is T or I; X_{2i} is T; X_{3i} is D; X_{4i} is E and; X_{5i} is M, I or V;

ii. a CDRH2 of formula $X_{1j}X_{2j}DPX_{3j}TGX_{4j}TX_{5j}$ (SEQ ID NO.:83) wherein X_{1j} is V; X_{2j} is I; X_{3j} is A, G or E; X_{4j} is R, G, D, A, S, N or V, and; X_{5j} is A; and

iii. a CDRH3 of formula $MX_{1o}X_{2o}X_{3o}DY$ (SEQ ID NO.:88) wherein X_{1o} is G; X_{2o} is Y or H, and; X_{3o} is A or S.

4. The isolated antibody or antigen binding fragment thereof of claim 3, comprising:

a. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16 and having a CDRL1 of amino acid sequence KSSQSLLNSNFQKNFLA (SEQ ID NO. :27) or KSSQSLLNSSNQKNYLA;

b. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16 and having a CDRL2 of amino acid sequence FASTRES (SEQ ID NO. :28);

c. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16 and having a CDRL3 of amino acid sequence QQHYSTPLT (SEQ ID NO.:29) or QQHYSIPLT;

d. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and having a CDRH1 of amino acid sequence GYIFTDYEIH (SEQ ID NO. :30) or GYTFTDYEIH;

e. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and having a CDRH2 of amino acid sequence VIDPETGNTA (SEQ ID NO. :31);

f. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and having a CDRH3 of amino acid sequence MGYSDY (SEQ ID NO. :32) or MGYADY;

g. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24 and having a CDRL1 of amino acid sequence KASQDIHNFLN (SEQ ID NO.:39);

h. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24 and having a CDRL2 of amino acid sequence RANRLVD (SEQ ID NO.:40);

i. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:24 and having a CDRL3 of amino acid sequence LQYDEIPLT (SEQ ID NO.:41) or LQYDAFPLT;

j. the v chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:26 and having a CDRH2 of amino acid sequence YINYDGHND (SE ID NO. :43);

k. the light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:105 and having a CDRL1 of amino acid sequence KSSQSLLHSDGKTYLN (SEQ ID NO. :158);

l. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132 and having a CDRH1 of amino acid sequence GYTFTDYNMH (SEQ ID NO. :161);

m. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132 and having a CDRH2 of amino acid sequence YINPYNDVTE (SEQ ID NO. :162) ; or

n. the heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:132 and having a CDRH3 of amino acid sequence AWFGLRQ (SEQ ID NO. :163).

5. An isolated antibody or an antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1) and comprising:

a. three CDRs of a light chain variable domain defined in SEQ ID NO.:16 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:18;

b. three CDRs of a light chain variable domain defined in SEQ ID NO.:20 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:22;

c. three CDRs of a light chain variable domain defined in SEQ ID NO.:24 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:26;

d. three CDRs of a light chain variable domain defined in SEQ ID NO.:105 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:132;

e. three CDRs of a light chain variable domain defined in SEQ ID NO.:106 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:133;

f. three CDRs of a light chain variable domain defined in SEQ ID NO.:107 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:134;

g. three CDRs of a light chain variable domain defined in SEQ ID NO.:108 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:154;

h. three CDRs of a light chain variable domain defined in SEQ ID NO.:109 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:153;

i. three CDRs of a light chain variable domain defined in SEQ ID NO.:110 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:135;

j. three CDRs of a light chain variable domain defined in SEQ ID NO.:111 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:136;

k. three CDRs of a light chain variable domain defined in SEQ ID NO.:112 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:149;

l. three CDRs of a light chain variable domain defined in SEQ ID NO.:113 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:137;

m. three CDRs of a light chain variable domain defined in SEQ ID NO.:114 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:140;

n. three CDRs of a light chain variable domain defined in SEQ ID NO.:115 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:141;

o. three CDRs of a light chain variable domain defined in SEQ ID NO.:116 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:142;

p. three CDRs of a light chain variable domain defined in SEQ ID NO.:117 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:139;

q. three CDRs of a light chain variable domain defined in SEQ ID NO.:118 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:147;

r. three CDRs of a light chain variable domain defined in SEQ ID NO.:119 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:143;

s. three CDRs of a light chain variable domain defined in SEQ ID NO.:120 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:152;

t. three CDRs of a light chain variable domain defined in SEQ ID NO.:121 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:146;

u. three CDRs of a light chain variable domain defined in SEQ ID NO.:122 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:138;

v. three CDRs of a light chain variable domain defined in SEQ ID NO.:123 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:150;

w. three CDRs of a light chain variable domain defined in SEQ ID NO.:124 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:144;

x. three CDRs of a light chain variable domain defined in SEQ ID NO.:126 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:145;

y. three CDRs of a light chain variable domain defined in SEQ ID NO.:127 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:157;

z. three CDRs of a light chain variable domain defined in SEQ ID NO.:128 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:155;

aa. three CDRs of a light chain variable domain defined in SEQ ID NO.:129 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:156;

bb. three CDRs of a light chain variable domain defined in SEQ ID NO.:130 and three CDRs of a heavy chain variable domain defined in SEQ ID NO.:151;

cc. a light chain variable domain defined in SEQ ID NO.:16 and a heavy chain variable domain defined in SEQ ID NO.:18;

dd. a light chain variable domain defined in SEQ ID NO.:20 and a heavy chain variable domain defined in SEQ ID NO.:22;

ee. a light chain variable domain defined in SEQ ID NO.:24 and a heavy chain variable domain defined in SEQ ID NO.:26;

ff. a light chain variable domain defined in SEQ ID NO.:105 and a heavy chain variable domain defined in SEQ ID NO.:132;

gg. a light chain variable domain defined in SEQ ID NO.:106 and a heavy chain variable domain defined in SEQ ID NO.:133;

hh. a light chain variable domain defined in SEQ ID NO.:107 and a heavy chain variable domain defined in SEQ ID NO.:134;

ii. a light chain variable domain defined in SEQ ID NO.:108 and a heavy chain variable domain defined in SEQ ID NO.:154;

jj. a light chain variable domain defined in SEQ ID NO.:109 and a heavy chain variable domain defined in SEQ ID NO.:153;

kk. a light chain variable domain defined in SEQ ID NO.:110 and a heavy chain variable domain defined in SEQ ID NO.:135;

ll. a light chain variable domain defined in SEQ ID NO.:111 and a heavy chain variable domain defined in SEQ ID NO.:136;

mm. a light chain variable domain defined in SEQ ID NO.:112 and a heavy chain variable domain defined in SEQ ID NO.:149;

nn. a light chain variable domain defined in SEQ ID NO.:113 and a heavy chain variable domain defined in SEQ ID NO.:137;

oo. a light chain variable domain defined in SEQ ID NO.:114 and a heavy chain variable domain defined in SEQ ID NO.:140;

pp. a light chain variable domain defined in SEQ ID NO.:115 and a heavy chain variable domain defined in SEQ ID NO.:141;

qq. a light chain variable domain defined in SEQ ID NO.:116 and a heavy chain variable domain defined in SEQ ID NO.:142;

rr. a light chain variable domain defined in SEQ ID NO.:117 and a heavy chain variable domain defined in SEQ ID NO.:139;

ss. a light chain variable domain defined in SEQ ID NO.:118 and a heavy chain variable domain defined in SEQ ID NO.:147;

tt. a light chain variable domain defined in SEQ ID NO.:119 and a heavy chain variable domain defined in SEQ ID NO.:143;

uu. a light chain variable domain defined in SEQ ID NO.:120 and a heavy chain variable domain defined in SEQ ID NO.:152;

vv. a light chain variable domain defined in SEQ ID NO.:121 and a heavy chain variable domain defined in SEQ ID NO.:146;

ww. a light chain variable domain defined in SEQ ID NO.:122 and a heavy chain variable domain defined in SEQ ID NO.:138;

xx. a light chain variable domain defined in SEQ ID NO.:123 and a heavy chain variable domain defined in SEQ ID NO.:150;

yy. a light chain variable domain defined in SEQ ID NO.:124 and a heavy chain variable domain defined in SEQ ID NO.:144;

zz. a light chain variable domain defined in SEQ ID NO.:126 and a heavy chain variable domain defined in SEQ ID NO.:145;

aaa. a light chain variable domain defined in SEQ ID NO.:127 and a heavy chain variable domain defined in SEQ ID NO.:157;

bbb. a light chain variable domain defined in SEQ ID NO.:128 and a heavy chain variable domain defined in SEQ ID NO.:155;

ccc. a light chain variable domain defined in SEQ ID NO.:129 and a heavy chain variable domain defined in SEQ ID NO.:156;

ddd. a light chain variable domain defined in SEQ ID NO.:130 and a heavy chain variable domain defined in SEQ ID NO.:151;

eee. a light chain variable domain as set forth in SEQ ID NO.:178 and a heavy chain variable domain as set forth in SEQ ID NO.:179; or

fff. a light chain variable domain as set forth in SEQ ID NO.:182 and a heavy chain variable domain as set forth in SEQ ID NO.:183.

6. An isolated antibody or an antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1:SEQ ID NO.:2) comprising:

a. a heavy chain variable domain comprising three complementarity determining regions of SEQ ID NO.:18 and a light chain variable domain comprising three complementarity determining regions of SEQ ID NO.:16;

b. a heavy chain variable domain comprising a CDRH3 having a sequence of SEQ ID NO.: 32, a CDRH1 having a sequence of SEQ ID NO.: 30 and a CDRH2 having a sequence of SEQ ID NO.:31 and a light chain variable domain comprising a CDRL3 having a sequence of SEQ ID NO.:29, a CDRL1 having a sequence of SEQ ID NO.:27 and a CDRL2 having a sequence of SEQ ID NO.:28;

c. a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:18 and a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:16;

d. a heavy chain variable domain as defined in SEQ ID NO.:18 and a light chain variable domain as defined in SEQ ID NO.:16;

e. a heavy chain comprising a sequence at least 80% identical to SEQ ID NO.:6 and a light chain comprising a sequence at least 80% identical to SEQ ID NO.:4;

f. a heavy chain variable domain comprising a sequence as set forth in SEQ ID NO.:179 and a light chain variable domain comprising a sequence as set forth in SEQ ID NO.:178;

g. a heavy chain comprising a sequence as set forth in SEQ ID NO.:177 and a light chain comprising a sequence as set forth in SEQ ID NO.:176;

h. a heavy chain variable domain comprising three complementary determining regions of SEQ ID NO.:22 and a light chain variable domain comprising three complementary determining regions of SEQ ID NO.:20;

i. a heavy chain variable domain comprising a CDRH3 having a sequence of SEQ ID NO.: 38, a CDRH1 having a sequence of SEQ ID NO.: 36 and a CDRH2 having a sequence of SEQ ID NO.:37 and a light chain variable domain comprising a CDRL3 having a sequence of SEQ ID NO.:35, a CDRL1 having a sequence of SEQ ID NO.:33 and a CDRL2 having a sequence of SEQ ID NO.:34;

j. a heavy chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:22 and a light chain variable domain comprising a sequence at least 80% identical to SEQ ID NO.:20;

k. a heavy chain as defined in SEQ ID NO.:22 and a light chain as defined in SEQ ID NO.:20, or

l. a heavy chain comprising a sequence at least 80% identical to SEQ ID NO.:10 and a light chain comprising a sequence at least 80% identical to SEQ ID NO.:8.

7. An isolated antibody or antigen binding fragment thereof capable of specific binding to kidney associated antigen 1 (KAAG1) and comprising:

a. a light chain variable domain having the sequence: DIVMTQSPXSLAVS+G++XT+NCKSSQSLLNSNFQKNFLAWYQQ KPGQXPKLLIYFASTRESS+PDRFXGSGSGTDFTLTISS+QAED+A XY+CQQHYSTPLTFGXGTKLE+K, wherein + is a conservative substitution of a corresponding amino acid of SEQ ID NO. :16 and wherein X is an amino acid found at a corresponding position in SEQ ID NO.:16 or SEQ ID NO.:178; and

b. a heavy chain variable domain having the sequence: EVQLXQSXAE+X+PGASVX+SCKASGYIFTDYEIHWV+QXPXXG LEW+GVIDPETGNTAFNQKFKG+XT+TADXS+STAYMELSSLTSE D+AVYYCMGYSDYWGQGTX+TVSS, wherein + is a conservative substitution of a corresponding amino acid of SEQ ID NO.:18 and wherein X is an amino acid found at a corresponding position in SEQ ID NO.:18 or SEQ ID NO.:179.

8. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 7, conjugated with a therapeutic moiety or with a detectable moiety.

9. The isolated antibody or antigen binding fragment thereof of claim 8, wherein the therapeutic moiety comprises a cytotoxic agent.

10. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 9, wherein said antibody comprises amino acids of a constant region, amino acids of a constant region of a human antibody or comprises a human IgG1 constant region.

11. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 10, comprising framework amino acids of a human antibody.

12. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 11, wherein the antigen binding fragment thereof is a scFv, a Fab, a Fab' or a $(Fab')_2$.

13. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 12, wherein the antibody is selected from the group consisting of a monoclonal antibody, a polyclonal antibody, a chimeric antibody and a humanized antibody or an antigen binding fragment thereof.

14. The isolated antibody or antigen binding fragment thereof of claim 13, wherein the antibody is a monoclonal antibody, a chimeric antibody, a humanized antibody or an antigen binding fragment thereof.

15. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 14, for the treatment, detection or diagnosis of a cancer selected from the group consisting of ovarian cancer, skin cancer, renal cancer, colorectal cancer, sarcoma, leukemia, brain tumor, thyroid tumor, breast cancer, prostate cancer, oesophageal tumor, bladder tumor, lung tumor and head and neck tumor.

16. The isolated antibody or antigen binding fragment thereof of claim 15, wherein the cancer is a metastatic cancer or wherein the cancer is recurrent ovarian cancer.

17. The isolated antibody or antigen binding fragment thereof of claim 16, wherein the metastatic cancer is metastatic breast cancer.

18. The isolated antibody or antigen binding fragment thereof of any one of claims 1 to 14, for reducing tumor spread, tumor invasion or metastasis of tumor cells, or for use in the treatment of cancer comprising tumor cells expressing KAAG1 or a variant thereof, or for use in the detection of cancer comprising tumor cells expressing KAAG1 or a variant thereof.

19. An isolated antibody or an antigen binding fragment thereof capable of competing with the antibody or antigen binding fragment thereof of any one of claims 1 to 14.

20. An isolated nucleic acid encoding a light chain variable domain and/or a heavy chain variable domain of the antibody or antigen binding fragment thereof of any one of claims 1 to 14.

21. The isolated nucleic acid of claim 20, wherein the isolated nucleic acid encoding the light chain variable domain is as set forth in SEQ ID NO.:3 or SEQ ID NO.:15 and the nucleic acid encoding the heavy chain variable domain is as set forth in SEQ ID NO.:5 or SEQ ID NO.:17.

22. A vector comprising the nucleic acid of claim 20 or claim 21.

23. The vector of claim 22, wherein said vector is an expression vector.

24. An isolated cell comprising the nucleic acid of claim 20 or claim 21 or comprising or expressing the antibody or antigen binding fragment thereof of any one of claims 1 to 14.

25. The isolated cell of claim 24, wherein said cell comprises a nucleic acid encoding a light chain variable domain and a nucleic acid encoding a heavy chain variable domain and/or wherein said cell is capable of expressing, assembling and/or secreting an antibody or antigen binding fragment thereof.

26. A pharmaceutical composition comprising the antibody or antigen binding fragment thereof of any one of claims 1 to 14, and a pharmaceutically acceptable carrier.

27. A composition comprising the antibody or antigen binding fragment thereof of any one of claims 1 to 14, and a carrier.

28. A method of reducing tumor spread, metastasis of tumor cells, tumor invasion, tumor formation or for inducing tumor lysis or of treating cancer, the method comprising administering an isolated antibody or antigen binding fragment thereof capable of binding to KAAG1 (SEQ ID NO.:2) or to the variant to a subject in need, wherein the cancer, tumor or tumor cells comprises cells expressing KAAG1 or a variant thereof and wherein said antibody or antigen binding fragment thereof is as defined in claim 1, claim 6 or claim 7.

29. A method of detecting a tumor comprising cells expressing KAAG1 or a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2, the method

comprising administering the antibody or antigen binding fragment thereof of any one of claims 1 to 14, to a subject in need.

30. The method of claim 29, wherein the antibody or antigen binding fragment thereof binds to KAAG1 or to the KAAG1 variant expressed at the surface of the cells and/or wherein the cancer is selected from the group consisting of ovarian cancer, skin cancer, renal cancer, colorectal cancer, sarcoma, leukemia, brain tumor, thyroid tumor, breast cancer, prostate cancer, oesophageal tumor, bladder tumor, lung tumor and head and neck tumor.

31. A method for detecting KAAG1 (SEQ ID NO.:2) or a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2, the method comprising contacting a cell expressing KAAG1 or the KAAG1 variant or a sample comprising or suspected of comprising KAAG1 or the KAAG1 variant with the antibody of any one of claims 1 to 14 and measuring binding.

32. The method of claim 31, wherein the sample is from a mammal.

33. The method of claim 32, wherein the mammal has or is suspected of having cancer or metastatic cancer.

34. The method of any one of claims 31 to 33, wherein the sample is a serum sample, a plasma sample, a blood sample or a tissue sample obtained from the mammal or a cell culture or a supernatant.

35. The method of any one of claims 31 to 34, comprising quantifying the amount of antibody bound to KAAG1 or the KAAG1 variant.

36. A kit comprising the antibody of any one of claims 1 to 14.

37. Use of an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or comprising at least 10 contiguous amino acids of amino acid residues 36 to 60 of

SEQ ID NO.:2 to generate antibodies or antigen binding fragments thereof capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2, which antibodies or antigen binding fragments thereof are for treating cancer, detecting cancer, reducing tumor spread, reducing metastasis, tumor invasion, tumor formation or for inducing tumor lysis.

38. A composition for generating antibodies or antigen binding fragments thereof capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2, the composition comprising a polypeptide comprising an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or comprising at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2, wherein said polypeptide lacks amino acids 1-25 of SEQ ID NO.:2, and a carrier.

39. The composition of claim 38, characterized in that it is a pharmaceutical composition comprising a pharmaceutically acceptable carrier.

40. A method for generating antibodies or antigen binding fragments thereof capable of specific binding to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or capable of specific binding to at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2 for treating cancer, detecting cancer, reducing tumor spread, metastasis, tumor invasion, tumor formation or inducing tumor lysis, the method comprising administering a polypeptide comprising an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or comprising at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2.

41. Use of an antibody or antigen binding fragment thereof capable of binding to KAAG1 (SEQ ID NO.:2) or to a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2, wherein the antibody or antigen binding fragment thereof binds to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or

at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2 in the manufacture of a medicament for:

a. treatment of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof, wherein said antibody or antigen binding fragment thereof induces lysis of tumor cells, reduces spreading of tumor cells, decreases formation of tumor or decreases metastasis of tumor cells, wherein the tumor or tumor cells expresses KAAG1 or the KAAG1 variant thereof;

b. treatment of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof, wherein the antibody or antigen binding fragment thereof is as defined in claim 1, claim 6 or claim 7;

c. treatment of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof wherein the antibody or antigen binding fragment thereof is as defined in claim 1, claim 6 or claim 7 and comprises framework amino acids of a human antibody;

d. reducing tumor spread, wherein the tumor comprises cells expressing KAAG1 or the KAAG1 variant thereof;

e. reducing metastasis of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

f. reducing invasion of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

g. reducing formation of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

h. inducing tumor lysis of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

i. reducing spread of tumor cells expressing KAAG1 or the KAAG1 variant thereof;

j. diagnosis of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof; or

k. detection of tumor cells expressing KAAG1 or the KAAG1 variant thereof.

42. The use as defined in claim 41, part a, wherein the antibody or antigen binding fragment thereof binds to a surface of the cells.

43. The use as defined in claim 41, part a or any one of parts d to i, wherein the antibody or antigen binding fragment thereof is as defined in claim 1, claim 6 or claim 7.

44. Use of an antibody or an antigen binding fragment thereof capable of binding to KAAG1 (SEQ ID NO.: 2) or to a KAAG1 variant having at least 80% sequence identity with SEQ ID NO.:2 in the diagnosis of cancer comprising cells expressing KAAG1 or the KAAG1 variant thereof or in the detection of tumor cells expressing KAAG1 or the KAAG1 variant thereof, wherein the antibody or antigen binding fragment thereof binds to an epitope located within amino acids 36 to 60 of SEQ ID NO.:2 or at least 10 contiguous amino acids of amino acid residues 36 to 60 of SEQ ID NO.:2.

45. The use as defined in any one of claims 41 to 44 or the method of claim 28, wherein the cancer is selected from the group consisting of ovarian cancer, skin cancer, renal cancer, colorectal cancer, sarcoma, leukemia, brain tumor, thyroid tumor, breast cancer, prostate cancer, oesophageal tumor, bladder tumor, lung tumor and head and neck tumor.

46. The use or method as defined in claim 45, wherein the cancer is ovarian cancer.

47. The use or method as defined in claim 46, wherein the cancer is recurrent ovarian cancer.

48. The use or method as defined in any one of claims 41 to 47, wherein the cancer is metastatic.

49. A kit comprising a first vector encoding the light chain variable domain of the antibody or antigen binding fragment thereof of any one of claims 1 to 7 and a

second vector encoding the heavy chain variable domain of the antibody or antigen binding fragment thereof of any one of claims 1 to 7.

50. A method of making an antibody or an antigen binding fragment thereof comprising culturing an isolated cell so that the antibody or antigen binding fragment thereof of any one of claims 1 to 7 is produced.

51. The method of claim 49, further comprising conjugating a therapeutic moiety or a detectable moiety to the antibody or antigen binding fragment thereof.

Figure 1A

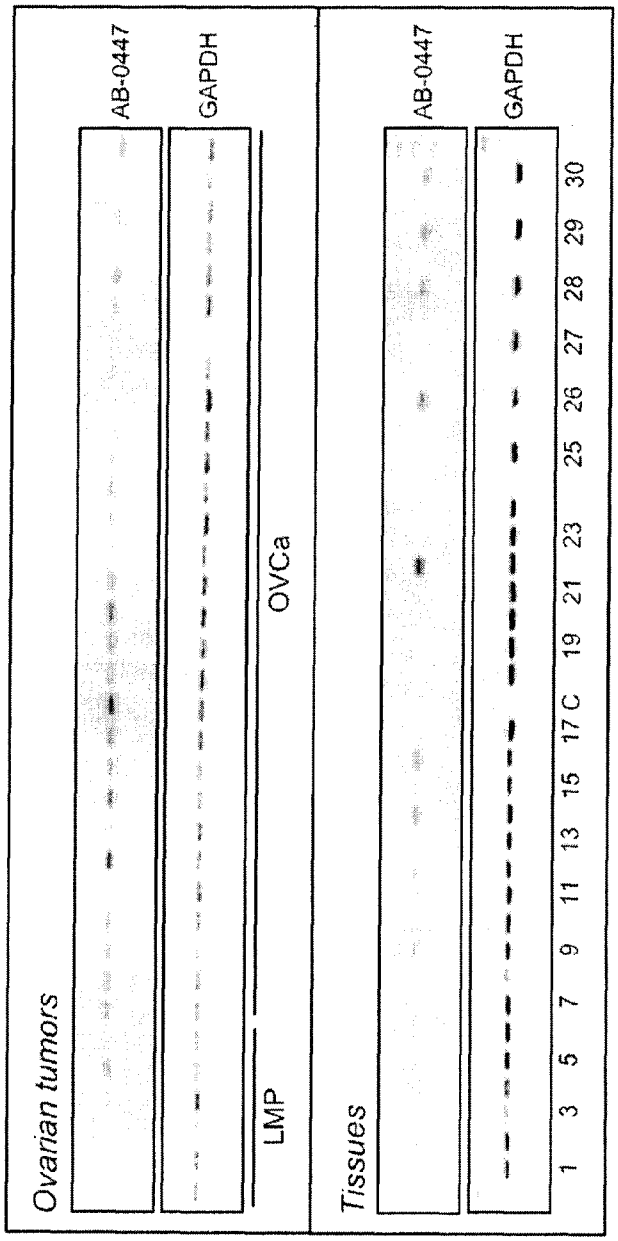
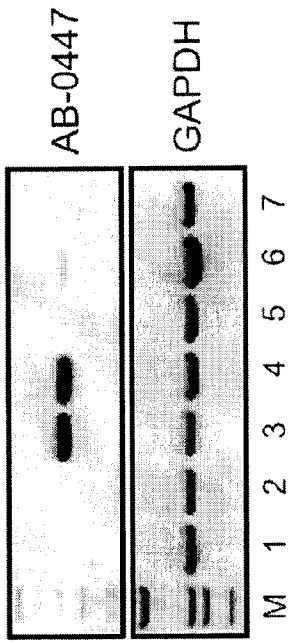

Ovarian tumors
AB-0447
GAPDH
LMP
OVCa
Tissues
AB-0447
GAPDH
1 3 5 7 9 11 13 15 17 C 19 21 23 25 26 27 28 29 30

Figure 1B



Figures 1C and 1D

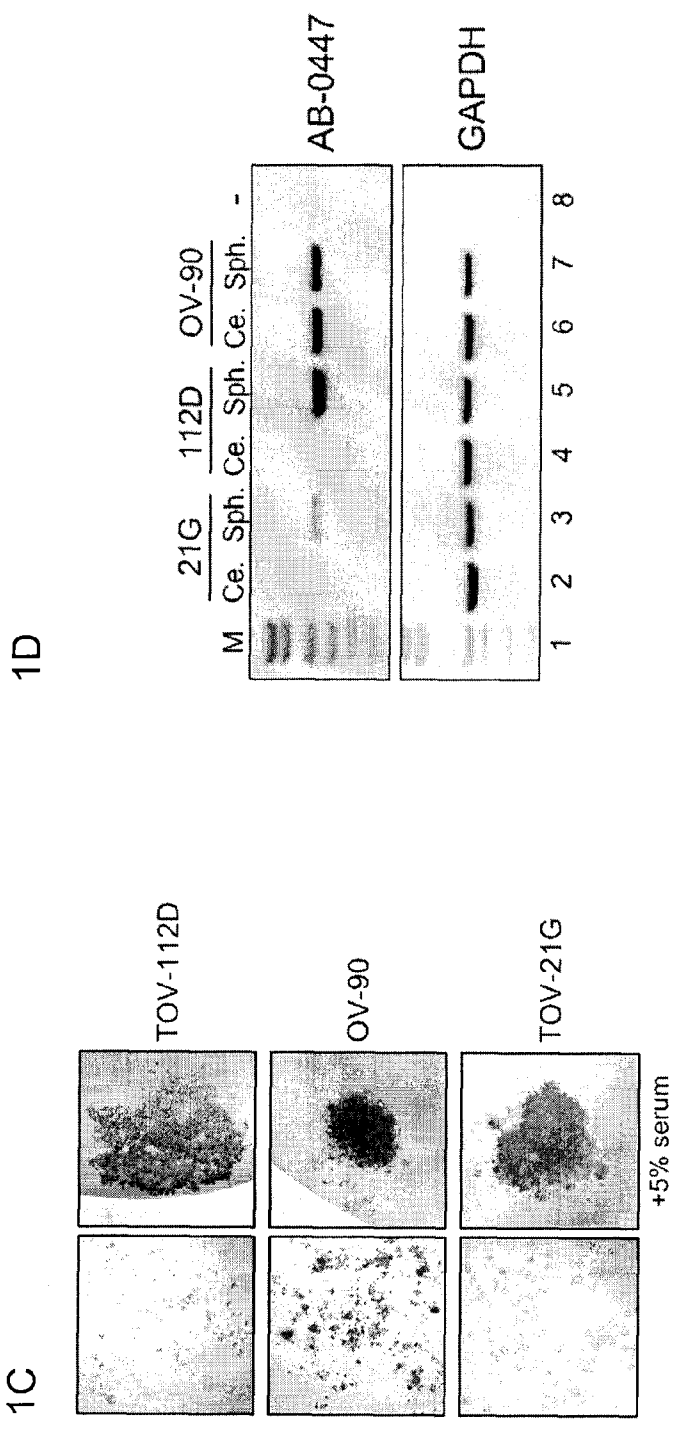


Figure 2A

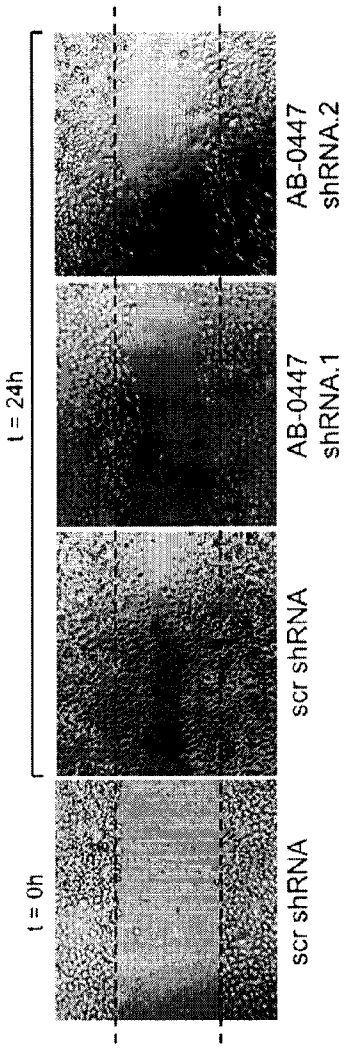


Figure 2B

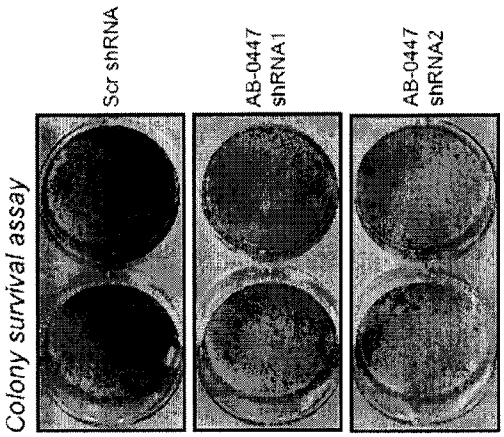

Scr shRNA
AB-0447 shRNA1
AB-0447 shRNA2
Colony survival assay

Figure 3A

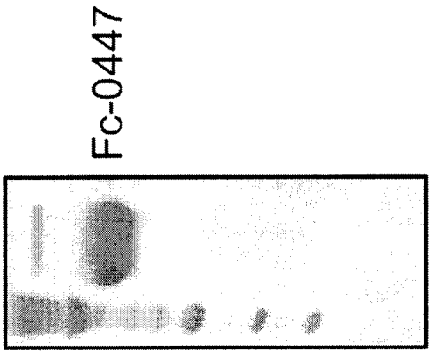
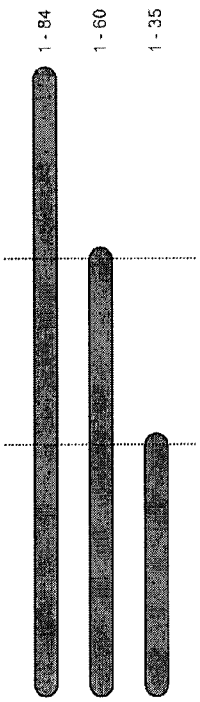


Figure 3B

	1	2	3	4	5	6	7	8	9	10	11	12
A	1.36	3.31	0.04	-0.05	0.01	0.03	0.04	0.57	1.53	0.00	1.79	-0.04
B	1.74	1.62	-0.08	-0.07	0.01	-0.02	-0.05	1.23	-0.10	0.03	1.17	-0.01
C	-0.01	0.32	1.04	**0.25**	-0.08	-0.11	-0.05	0.11	-0.06	0.61	0.05	-0.01
D	0.15	0.30	**1.21**	0.03	0.96	0.96	-0.09	-0.11	-0.05	-0.03	0.07	0.20
E	-0.01	0.02	0.58	0.57	1.26	1.21	0.40	0.22	1.78	0.02	-0.04	1.90
F	0.36	-0.03	-0.06	1.37	0.22	0.19	0.41	-0.05	-0.03	2.34	1.28	0.03
G	0.03	1.57	1.07	0.43	1.65	-0.01	0.43	1.72	1.55	**2.78**	-0.03	1.38
H	0.00	-0.01	0.23	0.00	0.27	0.02	0.00	0.00	0.85	0.15	0.10	0.03

Figures 4A and 4B

4B



4A

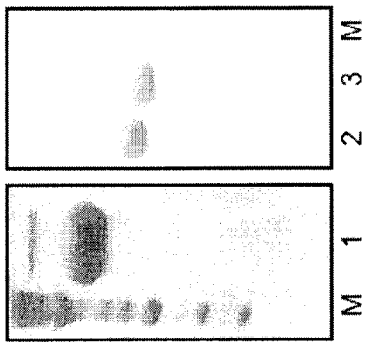
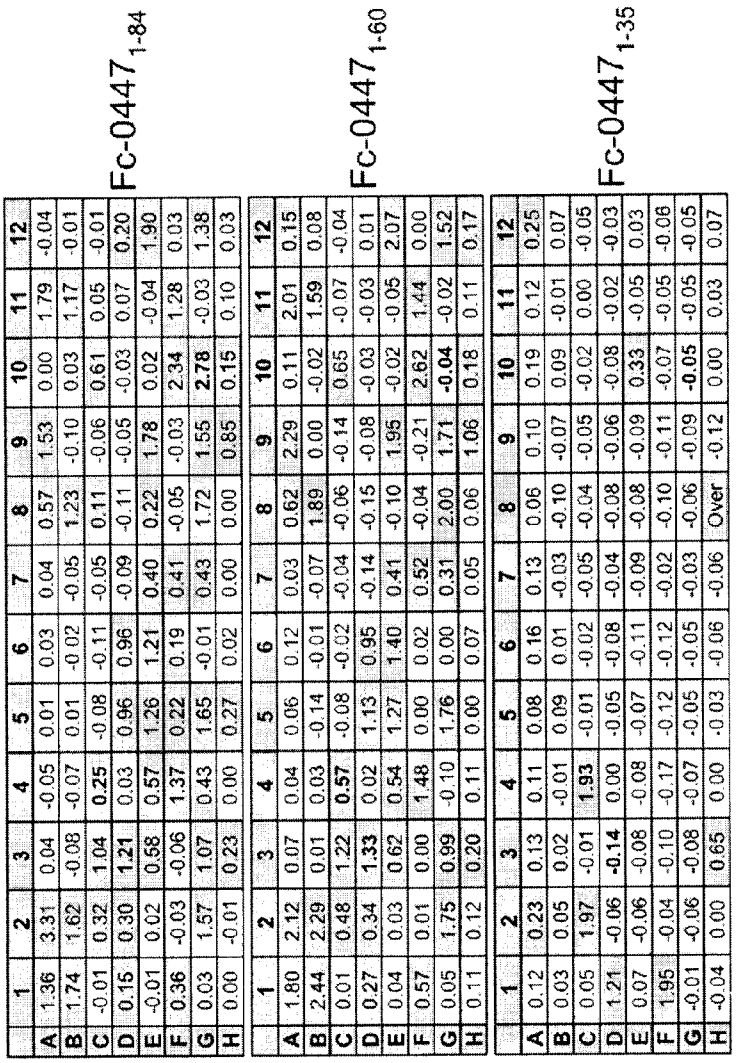


Figure 4C



Fc-0447 1-84

	1	2	3	4	5	6	7	8	9	10	11	12
A	1.36	3.31	0.04	-0.05	0.01	0.03	0.04	0.57	1.53	0.00	1.79	-0.04
B	1.74	1.62	-0.08	-0.07	0.01	-0.02	-0.05	1.23	-0.10	0.03	1.17	-0.01
C	-0.01	0.32	1.04	**0.25**	-0.08	-0.11	-0.05	0.11	-0.06	0.61	0.05	-0.01
D	0.15	0.30	**1.21**	0.03	0.96	0.96	-0.09	-0.11	-0.05	-0.03	0.07	0.20
E	-0.01	0.02	0.58	0.57	1.26	1.21	0.40	0.22	1.78	0.02	-0.04	1.90
F	0.36	-0.03	-0.06	1.37	0.22	0.19	0.41	-0.05	-0.03	2.34	1.28	0.03
G	0.03	1.57	1.07	0.43	1.65	-0.01	0.43	1.72	1.55	**2.78**	-0.03	1.38
H	0.00	-0.01	0.23	0.00	0.27	0.02	0.00	0.00	0.85	0.15	0.10	0.03

Fc-0447 1-60

	1	2	3	4	5	6	7	8	9	10	11	12
A	1.80	2.12	0.07	0.04	0.06	0.12	0.03	0.62	2.29	0.11	2.01	0.15
B	2.44	2.29	0.01	0.03	-0.14	-0.01	-0.07	1.89	0.00	-0.02	1.59	0.08
C	0.01	0.48	1.22	**0.57**	-0.08	-0.02	-0.04	-0.06	-0.14	0.65	-0.07	-0.04
D	0.27	0.34	**1.33**	0.02	1.13	0.95	-0.14	-0.15	-0.08	-0.03	-0.03	0.01
E	0.04	0.03	0.62	0.54	1.27	1.40	0.41	-0.10	1.95	-0.02	-0.05	2.07
F	0.57	0.01	0.00	1.48	0.00	0.02	0.52	-0.04	-0.21	2.62	1.44	0.00
G	0.05	1.75	0.99	-0.10	1.76	0.00	0.31	2.00	1.71	**-0.04**	-0.02	1.52
H	0.11	0.12	0.20	0.11	0.00	0.07	0.05	0.06	1.06	0.18	0.11	0.17

Fc-0447 1-35

	1	2	3	4	5	6	7	8	9	10	11	12
A	0.12	0.23	0.13	0.11	0.08	0.16	0.13	0.06	0.10	0.19	0.12	0.25
B	0.03	0.05	0.02	-0.01	0.09	0.01	-0.03	-0.10	-0.07	0.09	-0.01	0.07
C	0.05	1.97	-0.01	**1.93**	-0.01	-0.02	-0.05	-0.04	-0.05	-0.02	0.00	-0.05
D	1.21	-0.06	**-0.14**	0.00	-0.05	-0.08	-0.04	-0.08	-0.06	-0.08	-0.02	-0.03
E	0.07	-0.06	-0.08	-0.08	-0.07	-0.11	-0.09	-0.08	-0.09	0.33	-0.05	0.03
F	1.95	-0.04	-0.10	-0.17	-0.12	-0.12	-0.02	-0.10	-0.11	-0.07	-0.05	-0.06
G	-0.01	-0.06	-0.08	-0.07	-0.05	-0.05	-0.03	-0.06	-0.09	**-0.05**	-0.05	-0.05
H	-0.04	0.00	0.65	0.00	-0.03	-0.06	-0.06	Over	-0.12	0.00	0.03	0.07

Figure 5

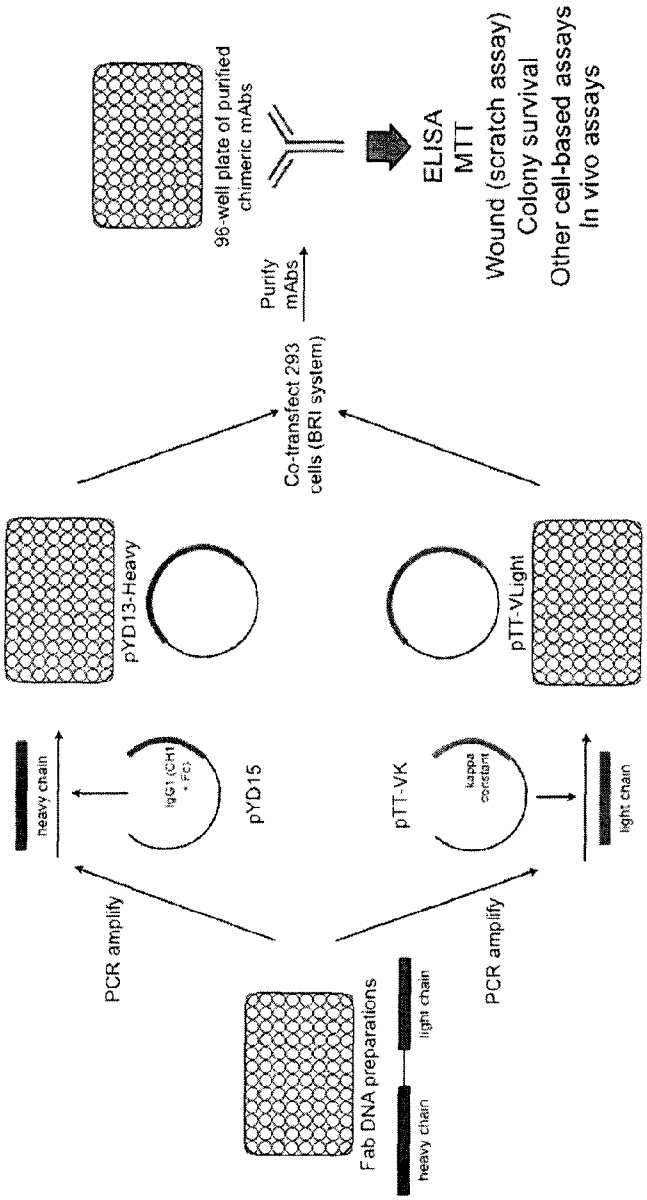

Fab DNA preparations
heavy chain
light chain
PCR amplify
PCR amplify
heavy chain
pYD15
IgG1 (CH1 + Fc)
pTT-VK
kappa constant
light chain
pYD13-Heavy
pTT-VLight
Co-transfect 293 cells (BRI system)
Purify mAbs
96-well plate of purified chimeric mAbs
ELISA
MTT
Wound (scratch assay)
Colony survival
Other cell-based assays
In vivo assays

Figure 6

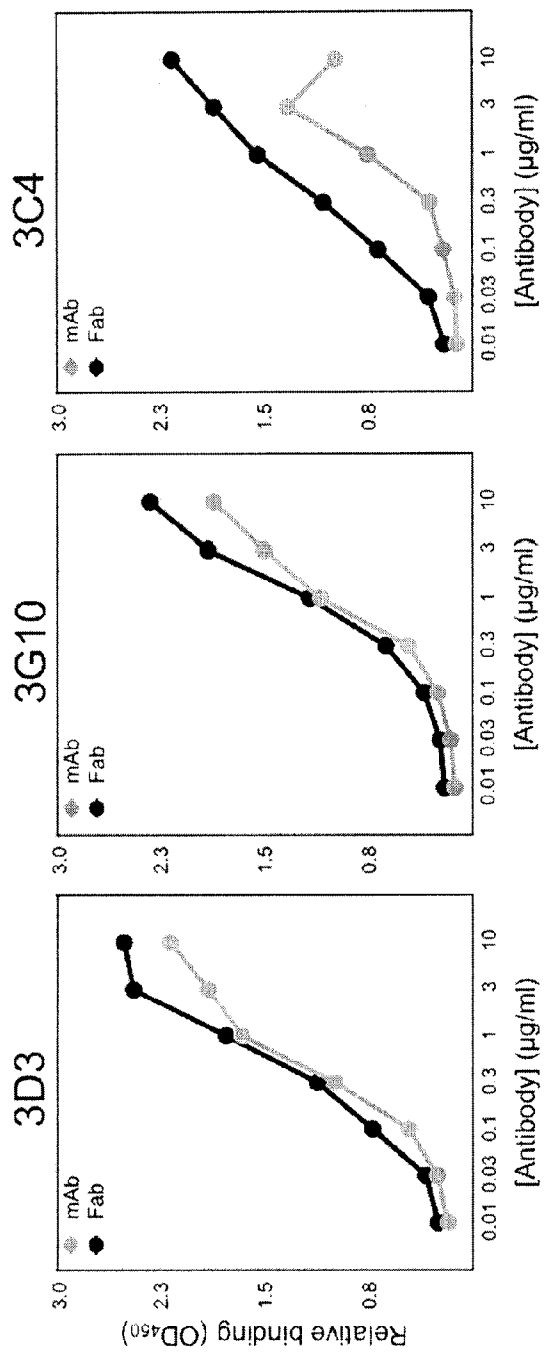

3D3
3G10
3C4
mAb
Fab
Relative binding (OD450)
[Antibody] (µg/ml)
3.0
2.3
1.5
0.8
0.01 0.03 0.1 0.3 1 3 10

Figure 7

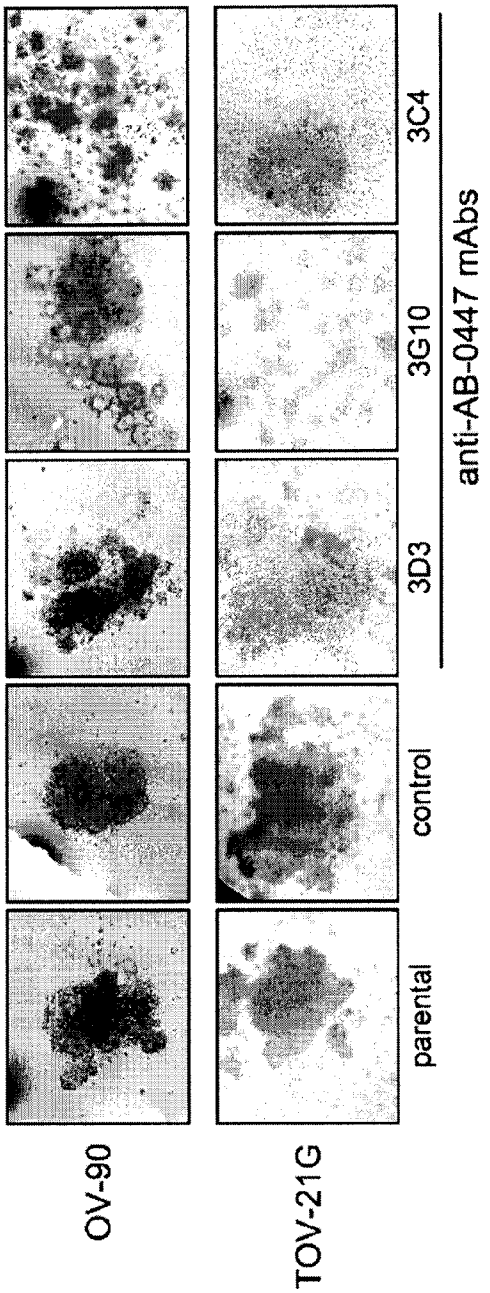


Figure 8A

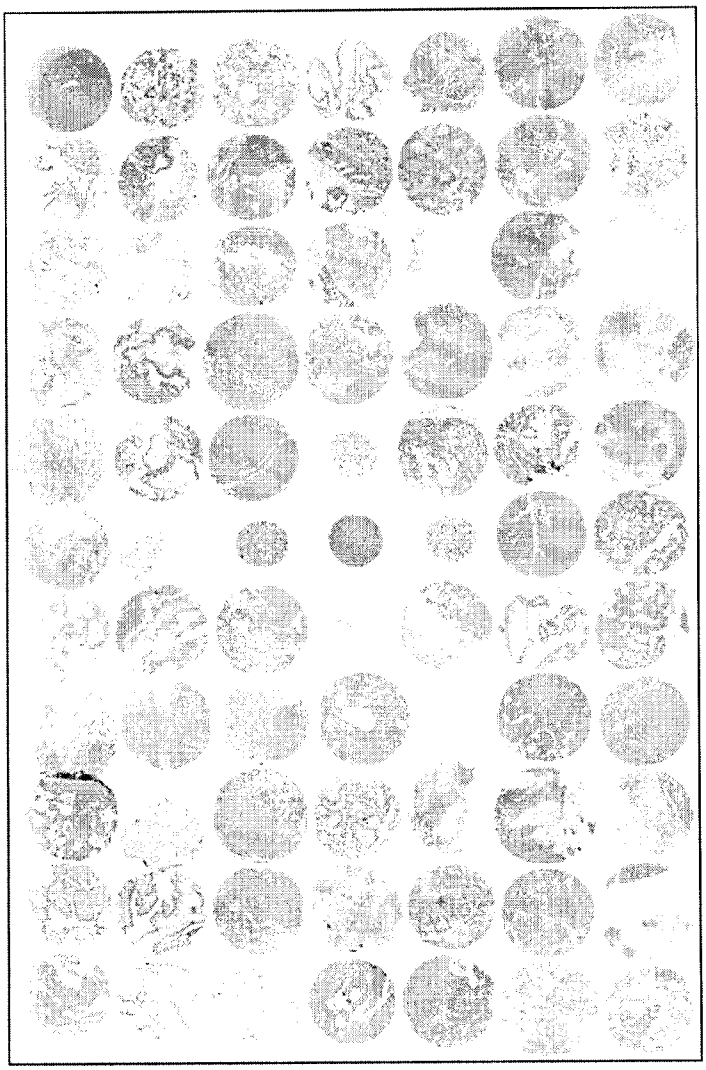


Figure 8B

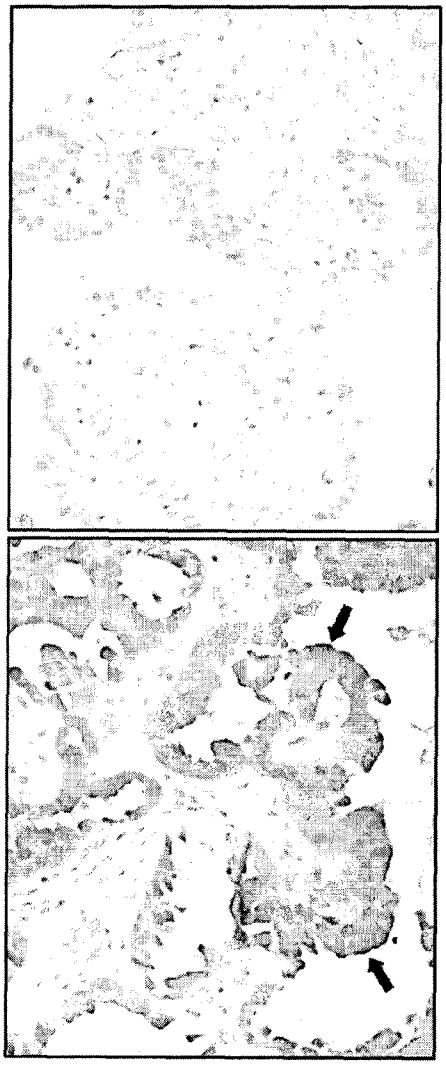
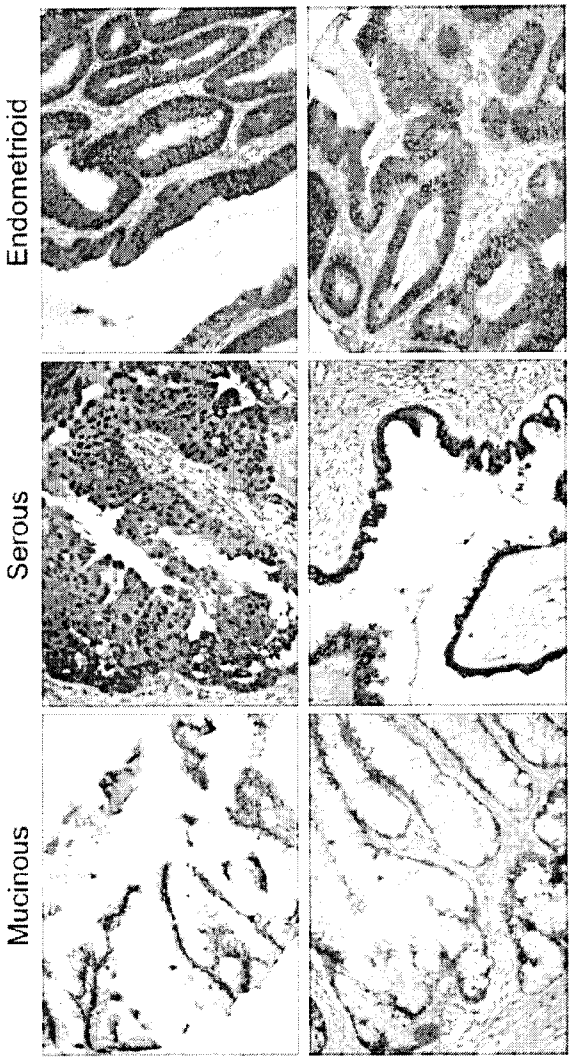


Figure 8C



CDRL1-alignment 1	CDRL1-alignment 2
RSSQSLLNSSNQKNYLA 17 (SEQID NO.:184) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:185) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:186) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:187) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:188) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:189) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:190) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:191) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:192) KSSQSLLNSSNQKNYLA 17 (SEQID NO.:193) KSSQSLLNKSNQKNYLA 17 (SEQID NO.:194) KSSQSLLNNSNQKNYLA 17 (SEQID NO.:195) KSSQSLLNTSNQLNYLA 17 (SEQID NO.:196) KSSQSLLNTSNQKNYLA 17 (SEQID NO.:197) KSSQSLLNSNNQLNYLA 17 (SEQID NO.:198) KSSQSLLNSNFQKNFLA 17 (SEQID NO.:199) KSSQSLLHS-DGKTYLN 16 (SEQID NO.:200) KSSQSLLHS-DGKTYLN 16 (SEQID NO.:201) KSSQSLLYS-DGKTYLN 16 (SEQID NO.:202) KSSQSLLHS-NGNTYLE 16 (SEQID NO.:203) RSSKSLLHS-NGNTYLY 16 (SEQID NO.:204) :**:*** .:*	KASQDIHNFLN 11 (SEQID NO.:205) KASQDIRAFLN 11 (SEQID NO.:206) KASQDIHNYLN 11 (SEQID NO.:207) KASQDIHNYLN 11 (SEQID NO.:208) KASQDIRTYLN 11 (SEQID NO.:209) KASQDVGTAVA 11 (SEQID NO.:210) *****: :

Figure 9A

CDRL2-alignment1	CDRL2-alignment 2	CDRL2-alignment 3
EASTRES 7 (SEQID NO.:211) EASTKES 7 (SEQID NO.:212) VASTTES 7 (SEQID NO.:213) EASTPES 7 (SEQID NO.:214) EASTKES 7 (SEQID NO.:215) VGSTRES 7 (SEQID NO.:216) EGSTPES 7 (SEQID NO.:217) EASTRES 7 (SEQID NO.:218) VASTRES 7 (SEQID NO.:219) VASTPES 7 (SEQID NO.:220) EASTRES 7 (SEQID NO.:221) VASTKES 7 (SEQID NO.:222) VASTPES 7 (SEQID NO.:223) EASTRES 7 (SEQID NO.:224) EASTKKS 7 (SEQID NO.:225) VASTPAS 7 (SEQID NO.:226) *.** *	LVSKLDS 7 (SEQID NO.:227) LVSKLDS 7 (SEQID NO.:228) IVSKLDS 7 (SEQID NO.:229) KVSNRFS 7 (SEQID NO.:230) **: *	PANRLVD 7 (SEQID NO.:231) RANRLVD 7 (SEQID NO.:232) HANRLVD 7 (SEQID NO.:233) PANRLVA 7 (SEQID NO.:234) RANRLVA 7 (SEQID NO.:235) :*****

Figure 9B

CDRL3-alignment1	CDRL3-alignment2	CDRL3-alignment3
QQHYSTPLT 9 (SEQID NO.:236) QQRYSTPLT 9 (SEQID NO.:237) QQRHYSTPLT 9 (SEQID NO.:238) QQHYSTPLT 9 (SEQID NO.:239) QQRTSTPLT 9 (SEQID NO.:240) QQRHYSTPLT 9 (SEQID NO.:241) QQHYSTPLT 9 (SEQID NO.:242) QQRTSTPLT 9 (SEQID NO.:243) QQRYSTPLT 9 (SEQID NO.:244) QQHYSTPLT 9 (SEQID NO.:245) QQHYSTPLT 9 (SEQID NO.:246) QQRYSIPLT 9 (SEQID NO.:247) QQHYSIPLT 9 (SEQID NO.:248) QQHYSIPLT 9 (SEQID NO.:249) QQRYSIPLT 9 (SEQID NO.:250) QQRYSIPLT 9 (SEQID NO.:251) QQHFNTPLT 9 (SEQID NO.:252) LQYDAFPLT 9 (SEQID NO.:253) LQYDAFPLT 9 (SEQID NO.:254) LQYDAFPLT 9 (SEQID NO.:255) LQYDEFPLT 9 (SEQID NO.:256) LQYDEIPLT 9 (SEQID NO.:257) *: ***	QQRYSIPLT 9 (SEQID NO.:247) QQHYSIPLT 9 (SEQID NO.:248) QQHYSIPLT 9 (SEQID NO.:249) QQRYSIPLT 9 (SEQID NO.:250) QQHYSIPLT 9 (SEQID NO.:251) QQHYSTPLT 9 (SEQID NO.:236) QQRYSTPLT 9 (SEQID NO.:237) QQHYSTPLT 9 (SEQID NO.:238) QQHYSTPLT 9 (SEQID NO.:239) QQRYSTPLT 9 (SEQID NO.:240) QQHYSTPLT 9 (SEQID NO.:241) QQHYSTPLT 9 (SEQID NO.:242) QQRYSTPLT 9 (SEQID NO.:243) QQRYSTPLT 9 (SEQID NO.:244) QQHYSTPLT 9 (SEQID NO.:245) QQHYSTPLT 9 (SEQID NO.:246) QQHFNTPLT 9 (SEQID NO.:252) ***: ***	WQGTHFPNT 9 (SEQID NO.:258) WQGTHFPNT 9 (SEQID NO.:259) WQGTHFPPT 9 (SEQID NO.:260) FQGSHVPLT 9 (SEQID NO.:261) :**:*.* *

Figure 9C

CDRH1-alignment1	CDRH1-alignment2
GYTFTDYEIH 10 (SEQID NO.:262) GYTFTDYEIR 10 (SEQID NO.:263) GXTFTDXEIR 10 (SEQID NO.:264) GYTFTDYEIH 10 (SEQID NO.:265) GYTFTDYEIN 10 (SEQID NO.:266) GXTFTDXEIR 10 (SEQID NO.:267) GYTFTDYEIH 10 (SEQID NO.:268) GYTFTDYEIN 10 (SEQID NO.:269) GXTFTDXEIR 10 (SEQID NO.:270) GYIFTDYEIH 10 (SEQID NO.:271) GYIFTDYEIN 10 (SEQID NO.:272) GXIFTDXEVR 10 (SEQID NO.:273) GXTFTDXEVR 10 (SEQID NO.:274) GYTFTDYEVN 10 (SEQID NO.:275) GYTFTDYEMR 10 (SEQID NO.:276) GYTFSDYEMH 10 (SEQID NO.:277) GYTFTDYEMN 10 (SEQID NO.:278) GYNFTDYEMR 10 (SEQID NO.:279) GXTFTDXNMR 10 (SEQID NO.:280) GYIFTEYNIH 10 (SEQID NO.:281) GYTFTEYNMN 10 (SEQID NO.:282) ** *::*::*	GFSITSGYGWN 11 (SEQID NO.:283) GFSITSGYGWR 11 (SEQID NO.:284) **********

Figure 10A

CDRH2-alignment1	CDRH2-alignment2
VIDPATGDTA 10 (SEQID NO.:285) VIDPATGDIA 10 (SEQID NO.:286) VIDPETGDTA 10 (SEQID NO.:287) VIDPETGDIA 10 (SEQID NO.:288) VIDPETGDIA 10 (SEQID NO.:289) VIDPETGDTA 10 (SEQID NO.:290) VIDPETGVTA 10 (SEQID NO.:291) VIDPETGVIA 10 (SEQID NO.:292) VIDPETGNTA 10 (SEQID NO.:293) VIDPETGNTA 10 (SEQID NO.:294) VIDPETGSIA 10 (SEQID NO.:295) VIDPETGSTA 10 (SEQID NO.:296) VIDPETGATA 10 (SEQID NO.:297) VIDPETGAIA 10 (SEQID NO.:298) GIDPETGDIV 10 (SEQID NO.:299) GIDPETGGTA 10 (SEQID NO.:300) VIDPETGGTA 10 (SEQID NO.:301) VLDPGTGKIA 10 (SEQID NO.:302) :** ** *.	VIDPATGDTA 10 (SEQID NO.:285) VIDPATGDTA 10 (SEQID NO.:286) VIDPETGDIA 10 (SEQID NO.:287) VIDPETGDIA 10 (SEQID NO.:288) VIDPETGDTA 10 (SEQID NO.:289) VIDPETGDTA 10 (SEQID NO.:290) VIDPETGVIA 10 (SEQID NO.:291) VIDPETGVTA 10 (SEQID NO.:292) VIDPETGNTA 10 (SEQID NO.:293) VIDPETGNIA 10 (SEQID NO.:294) VIDPETGSTA 10 (SEQID NO.:295) VIDPETGSTA 10 (SEQID NO.:296) VIDPETGAIA 10 (SEQID NO.:297) VIDPETGAIA 10 (SEQID NO.:298) VIDPETGGTA 10 (SEQID NO.:301) VLDPGTGKIA 10 (SEQID NO.:302) * :** ** **

CDRH2-alignment 3	CDRH2-alignment 4	CDRH2-alignment 5
YISFNGDYN 9 (SEQID NO.:303) YISFNGDSN 9 (SEQID NO.:304) YINYDGHND 9 (SEQID NO.:305) **.::*. :	NINPYNDVTE 10 (SEQID NO.:306) NINPYNNVTE 10 (SEQID NO.:307) YINPYNDVTE 10 (SEQID NO.:308) *****:***	DINPNYGGIT 10 (SEQID NO.:309) DINPYYGTIT 10 (SEQID NO.:310) **** ** *

Figure 10B

CDRH3-alignment1	CDRH3-alignment2
MSYSDY 6 (SEQID NO.:311) MSYSDY 6 (SEQID NO.:312) MGYSDY 6 (SEQID NO.:313) MGYSDY 6 (SEQID NO.:314) MGYSDY 6 (SEQID NO.:315) MGYSDY 6 (SEQID NO.:316) MGYSDY 6 (SEQID NO.:317) MGWSDY 6 (SEQID NO.:318) MGYSDY 6 (SEQID NO.:319) MGYSDY 6 (SEQID NO.:320) MGYSDY 6 (SEQID NO.:321) MGYSDY 6 (SEQID NO.:322) MGYSDY 6 (SEQID NO.:323) MGYADY 6 (SEQID NO.:324) MGYADY 6 (SEQID NO.:325) *.::**	ISYAMDY 7 (SEQID NO.:326) LSYAMDY 7 (SEQID NO.:327) IGYA-DY 6 (SEQID NO.:328) *.** **
CDRH3-alignment3	**CDRH3-alignment4**
ARWGLAN 7 (SEQID NO.:329) APWGLRN 7 (SEQID NO.:330) AWFGLPQ 7 (SEQID NO.:331) * :***:	ASSYDGLFAY 10 (SEQID NO.:332) ASSYDGLFAY 10 (SEQID NO.:333) ASSYDGLFAY 10 (SEQID NO.:334) **********

Figure 10C

Light chain variable region	% identity with SEQ.16 (% similarity with SEQ 16)	% identity with SEQ.20 (% similarity with SEQ 20)	% identity with SEQ.24 (% similarity with SEQ 24)	% identity with SEQ.105 (% similarity with SEQ 105)
SEQ ID NO:105	58% (71%)	69% (81%)	45% (66%)	100% (100%0
SEQ ID NO:106	59% (72%)	71% (83%)	48% (68%)	92% (96%)
SEQ ID NO:107	61% (74%)	74% (83%)	48% (68%)	95% (97%)
SEQ ID NO:108	63% (77%)	100% (100%)	50% (73%)	N.D.
SEQ ID NO:109	57% (74%)	68% (82%)	49% (72%)	N.D.
SEQ ID NO:110	88% (97%)	63% (77%)	56% (74%)	N.D.
SEQ ID NO:111	90% (97%)	63% (79%)	58% (76%)	N.D.
SEQ ID NO:112	88% (97%)	61% (79%)	56% (76%)	N.D.
SEQ ID NO:113	91% (97%)	64% (79%)	57% (76%)	N.D.
SEQ ID NO:114	92% (98%)	64% (78%)	56% (75%)	N.D.
SEQ ID NO:115	92% (98%)	64% (78%)	56% (75%)	N.D.
SEQ ID NO:116	92% (98%)	65% (78%)	57% (75%)	N.D.
SEQ ID NO:117	90% (98%)	62% (78%)	54% (75%)	N.D.
SEQ ID NO:118	90% (96%)	65% (79%)	54% (73%)	N.D.
SEQ ID NO:119	91% (96%)	64% (79%)	57% (75%)	N.D.
SEQ ID NO:120	90% (97%)	61% (77%)	54% (73%)	N.D.
SEQ ID NO:121	88% (95%)	61% (76%)	56% (74%)	N.D.
SEQ ID NO:122	88% (95%)	65% (78%)	56% (74%)	N.D.
SEQ ID NO:123	92% (98%)	64% (78%)	56% (75%)	N.D.
SEQ ID NO:124	100% (100%)	63% (77%)	56% (73%)	N.D.
SEQ ID NO:125	90% (96%)	65% (79%)	54% (73%)	N.D.
SEQ ID NO:126	69% (83%)	59% (76%)	62% (77%)	N.D.
SEQ ID NO:127	56% (73%)	50% (73%)	100% (100%)	N.D.
SEQ ID NO:128	54% (72%)	54% (73%)	89% (96%)	N.D.
SEQ ID NO:129	56% (75%)	53% (73%)	89% (94%)	N.D.
SEQ ID NO:130	56% (75%)	53% (73%)	89% (94%)	N.D.
SEQ ID NO:131	56% (74%)	57% (81%)	91% (94%)	N.D.

Figure 11

Heavy chain variable region	% identity with SEQ.18 (% similarity with SEQ 18)	% identity with SEQ.22 (% similarity with SEQ 22)	% identity with SEQ.26 (% similarity with SEQ 26)	% identity with SEQ.132 (% similarity with SEQ 132)
SEQ ID NO:132	66% (79%)	74% (81%)	47% (70%)	100% (100%)
SEQ ID NO:133	70% (80%)	73% (81%)	47% (66%)	87% (94%)
SEQ ID NO:134	68% (79%)	73% (81%)	48% (66%)	88% (95%)
SEQ ID NO:135	88% (96%)	66% (77%)	41% (64%)	N.D.
SEQ ID NO:136	92% (93%)	70% (80%)	41% (65%)	N.D.
SEQ ID NO:137	95% (96%)	71% (80%)	43% (66%)	N.D.
SEQ ID NO:138	94% (97%)	70% (80%)	42% (66%)	N.D.
SEQ ID NO:139	92% (96%)	71% (80%)	43% (66%)	N.D.
SEQ ID NO:140	92% (95%)	69% (78%)	42% (66%)	N.D.
SEQ ID NO:141	91% (96%)	68% (80%)	40% (66%)	N.D.
SEQ ID NO:142	91% (94%)	69% (78%)	39% (65%)	N.D.
SEQ ID NO:143	91% (95%)	71% (79%)	41% (64%)	N.D.
SEQ ID NO:144	100% (100%)	67% (77%)	41% (66%)	N.D.
SEQ ID NO:145	98% (99%)	68% (77%)	41% (66%)	N.D.
SEQ ID NO:146	92% (93%)	68% (77%)	41% (65%)	N.D.
SEQ ID NO:147	91% (95%)	66% (78%)	39% (66%)	N.D.
SEQ ID NO:148	91% (95%)	66% (78%)	39% (66%)	N.D.
SEQ ID NO:149	88% (92%)	66% (77%)	39% (65%)	N.D.
SEQ ID NO:150	92% (95%)	69% (79%)	43% (64%)	N.D.
SEQ ID NO:151	85% (93%)	71% (79%)	43% (66%)	N.D.
SEQ ID NO:152	83% (91%)	70% (78%)	42% (63%)	N.D.
SEQ ID NO:153	72% (78%)	85% (87%)	44% (65%)	N.D.
SEQ ID NO:154	67% (77%)	100% (100%)	47% (66%)	N.D.
SEQ ID NO:155	42% (63%)	45% (66%)	92% (98%)	N.D.
SEQ ID NO:156	40% (64%)	44% (66%)	91% (98%)	N.D.
SEQ ID NO:157	41% (66%)	47% (66%)	100% (100%)	N.D.

Figure 12

FIGURE 13

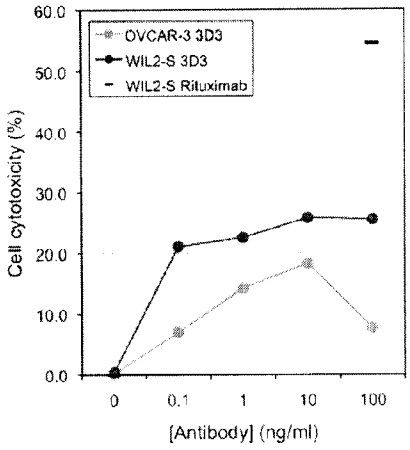


FIGURE 14

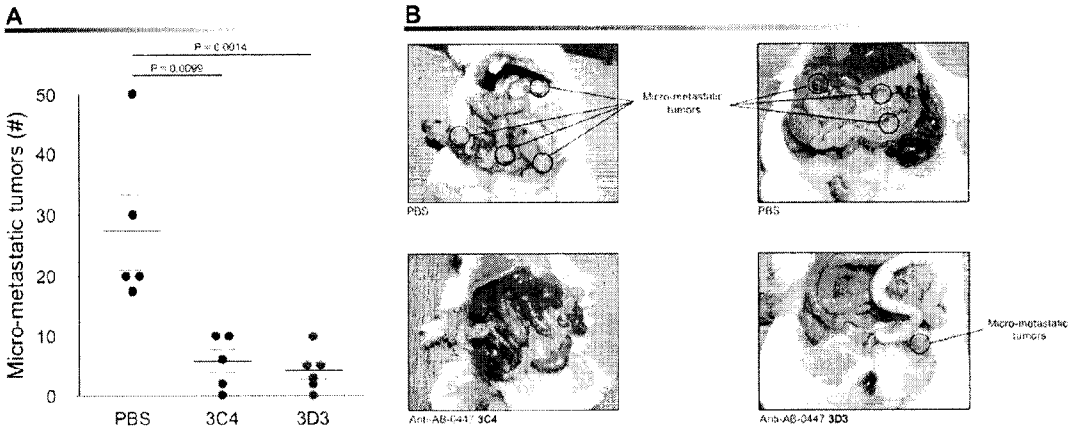


FIGURE 15

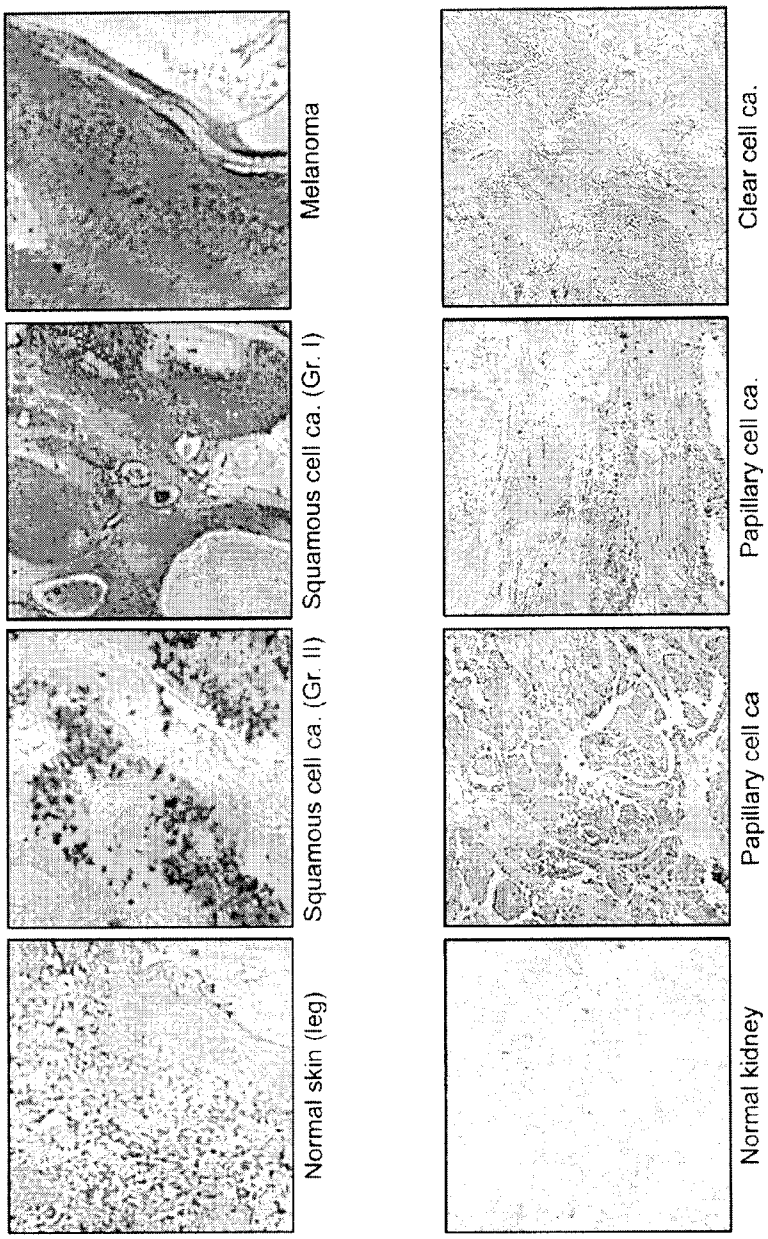

Normal skin (leg)
Squamous cell ca. (Gr. II)
Squamous cell ca. (Gr. I)
Melanoma
Normal kidney
Papillary cell ca
Papillary cell ca.
Clear cell ca.

FIGURE 16

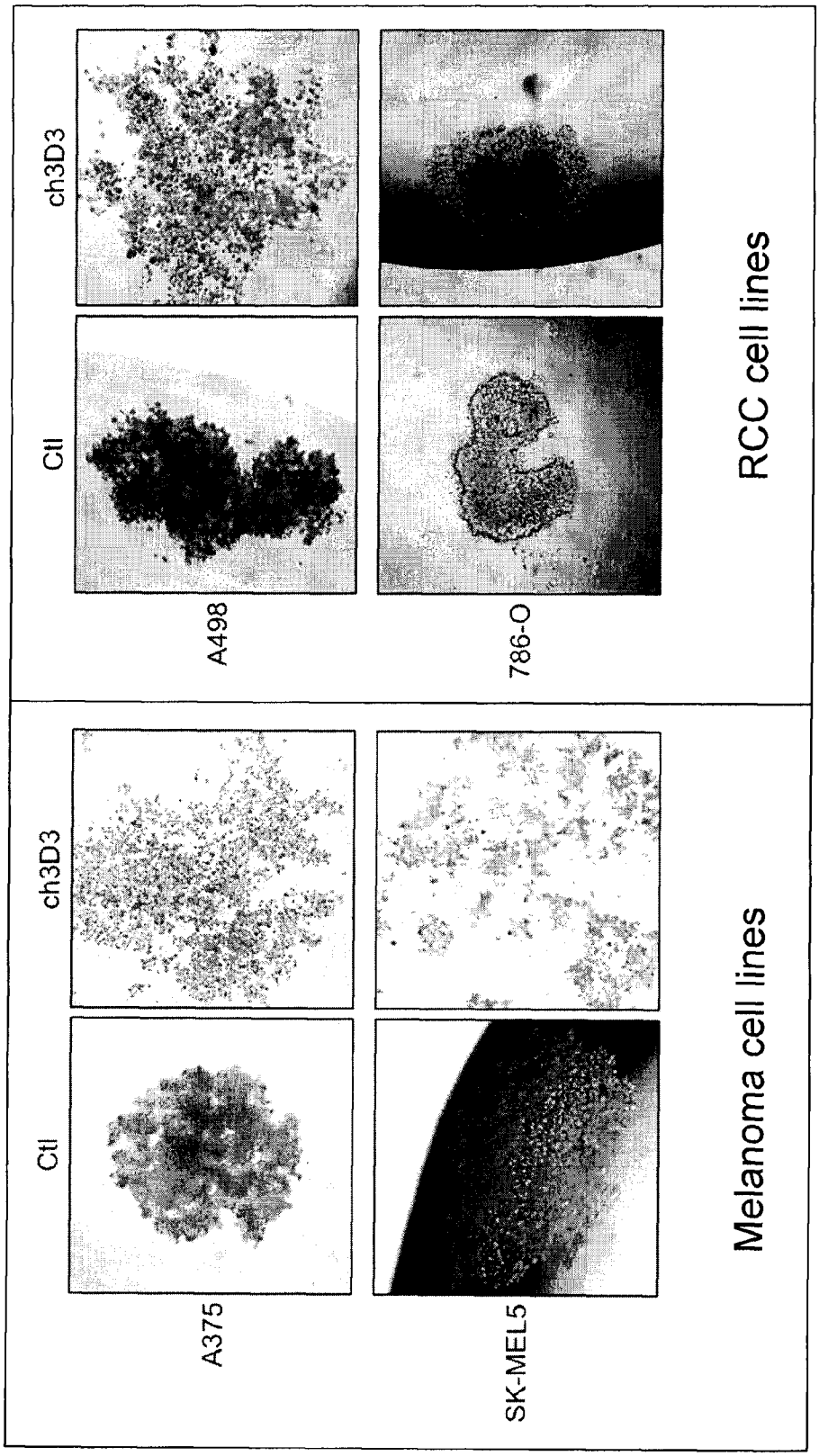
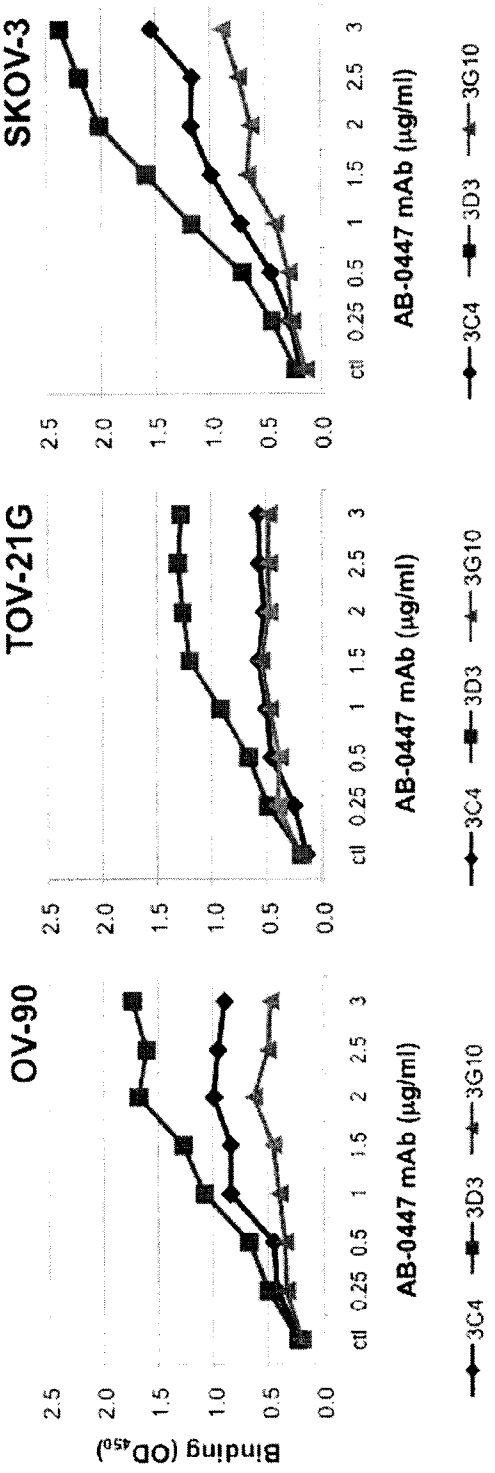

Ctl
ch3D3
A375
SK-MEL5
Melanoma cell lines
A498
786-O
RCC cell lines

FIGURE 17A


OV-90
TOV-21G
SKOV-3
Binding (OD450)
2.5
2.0
1.5
1.0
0.5
0.0
ctl 0.25 0.5 1 1.5 2 2.5 3
AB-0447 mAb (µg/ml)
3C4
3D3
3G10

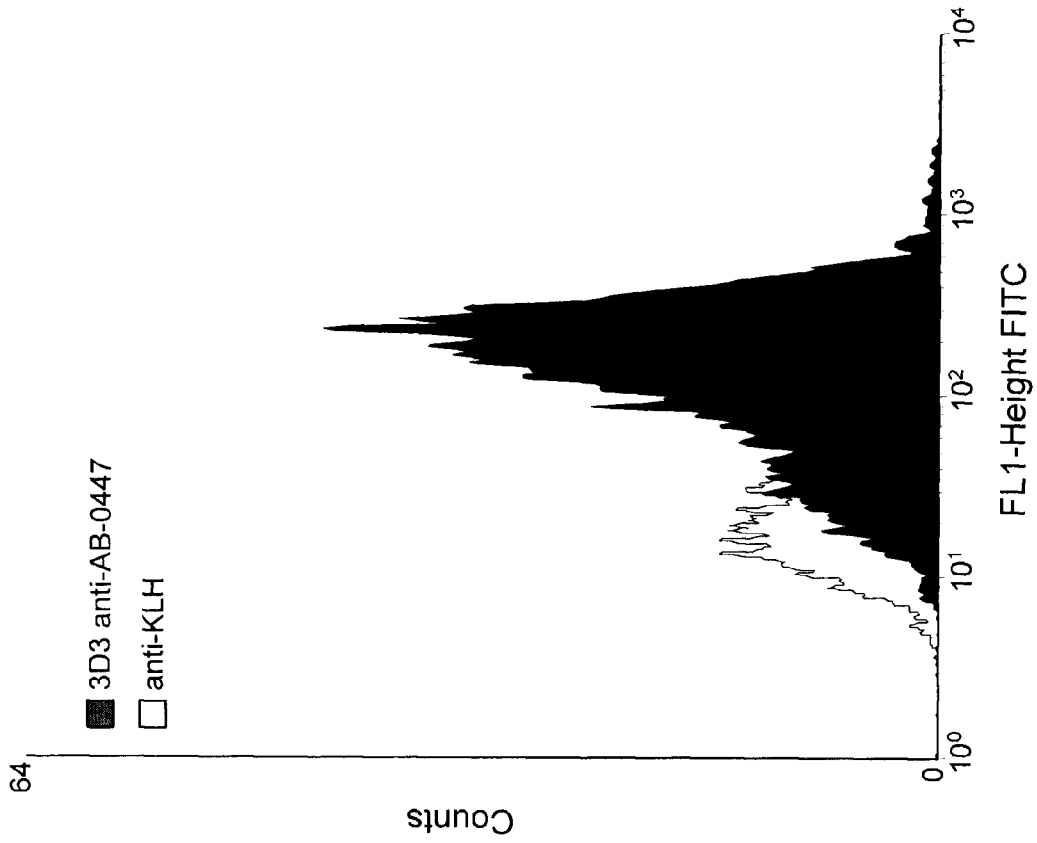

3D3 anti-AB-0447
anti-KLH
64
0
Counts
10^0
10^1
10^2
10^3
10^4
FL1-Height FITC

FIGURE 17B

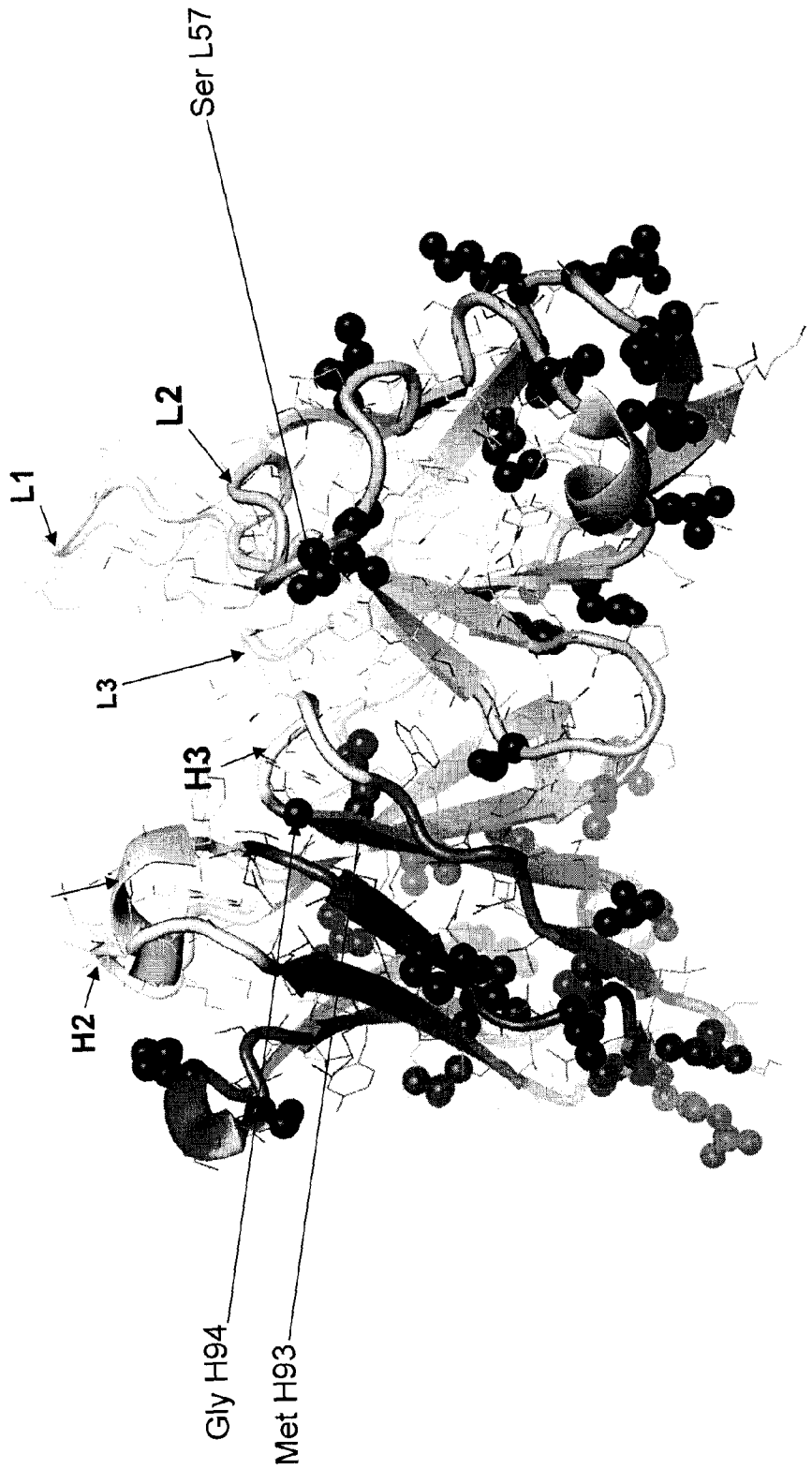


FIGURE 18A

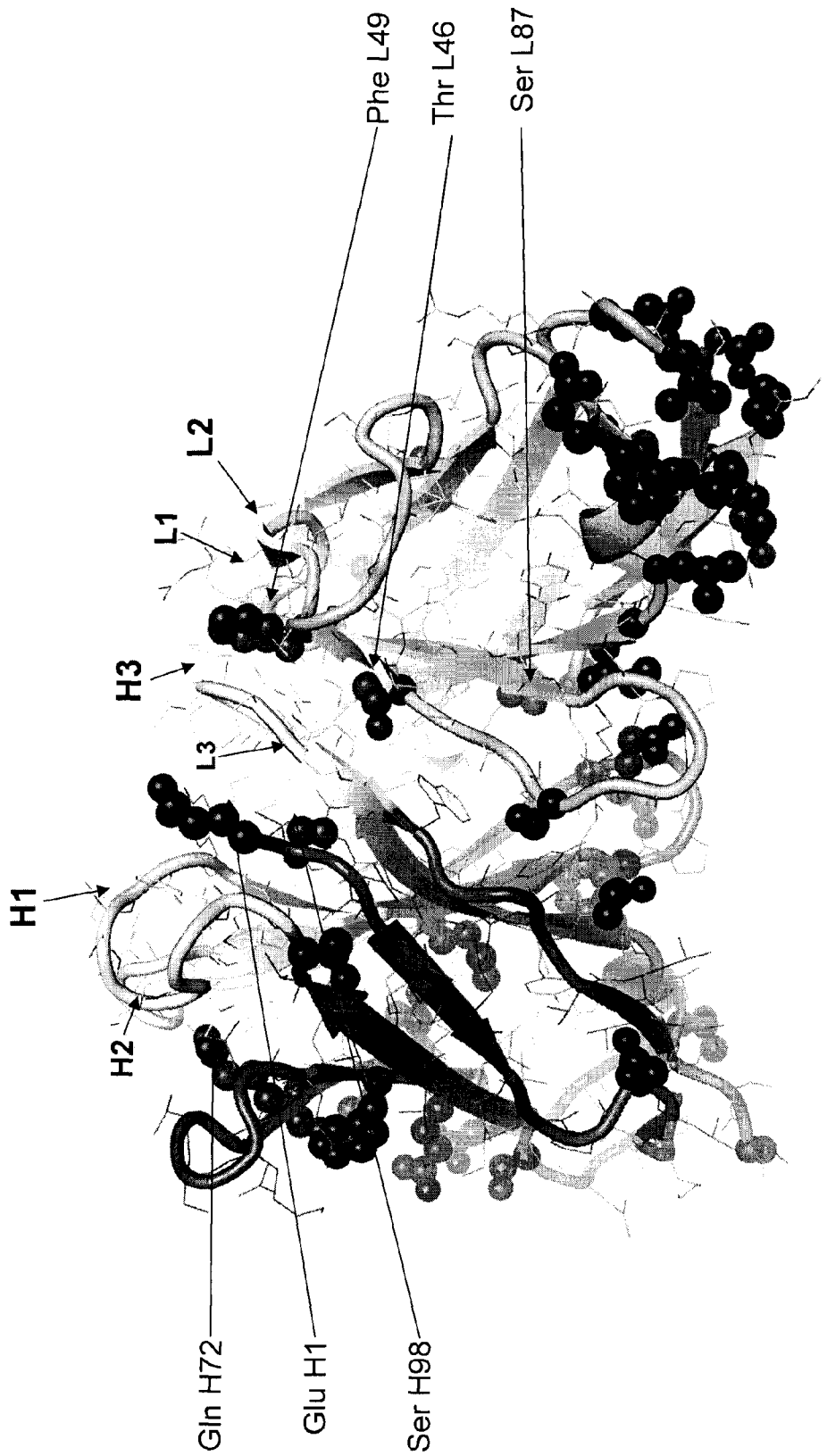
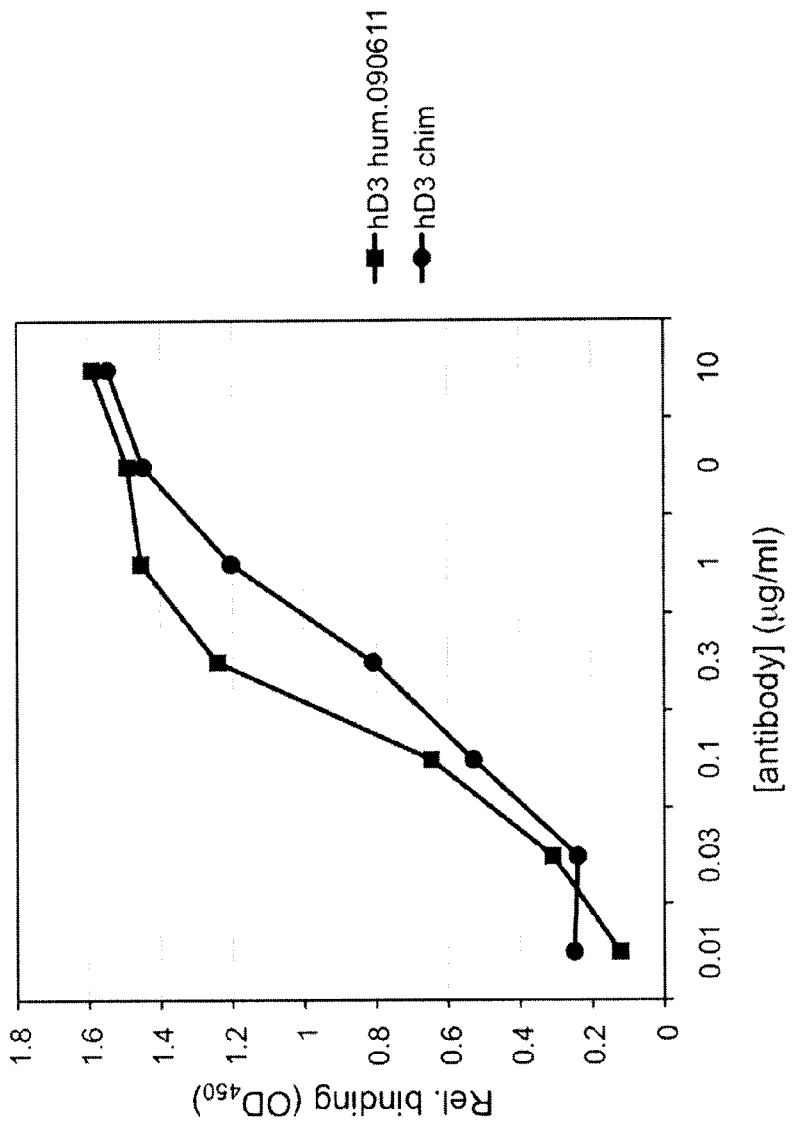


FIGURE 18B

FIGURE 19A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hD3 chim
Rel. binding (OD450)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
0.01
0.03
0.1
0.3
1
0
10
[antibody] (µg/ml)

FIGURE 19B

Antibody	Ka (1/Ms)	Kd (1/s)	K_A (1/M)	K_D (M)	Chi^2
m3D3	2.91×10^6	0.00065	4.5×10^9	2.35×10^{-10}	0.49
CC	1.98×10^6	0.00073	2.71×10^9	3.68×10^{-10}	0.142
HC	2.36×10^6	0.00073	3.24×10^9	3.09×10^{-10}	0.51
CH	2.20×10^6	0.00111	1.98×10^9	5.05×10^{-10}	0.208
HH	2.53×10^6	0.00111	2.28×10^9	4.39×10^{-10}	0.61

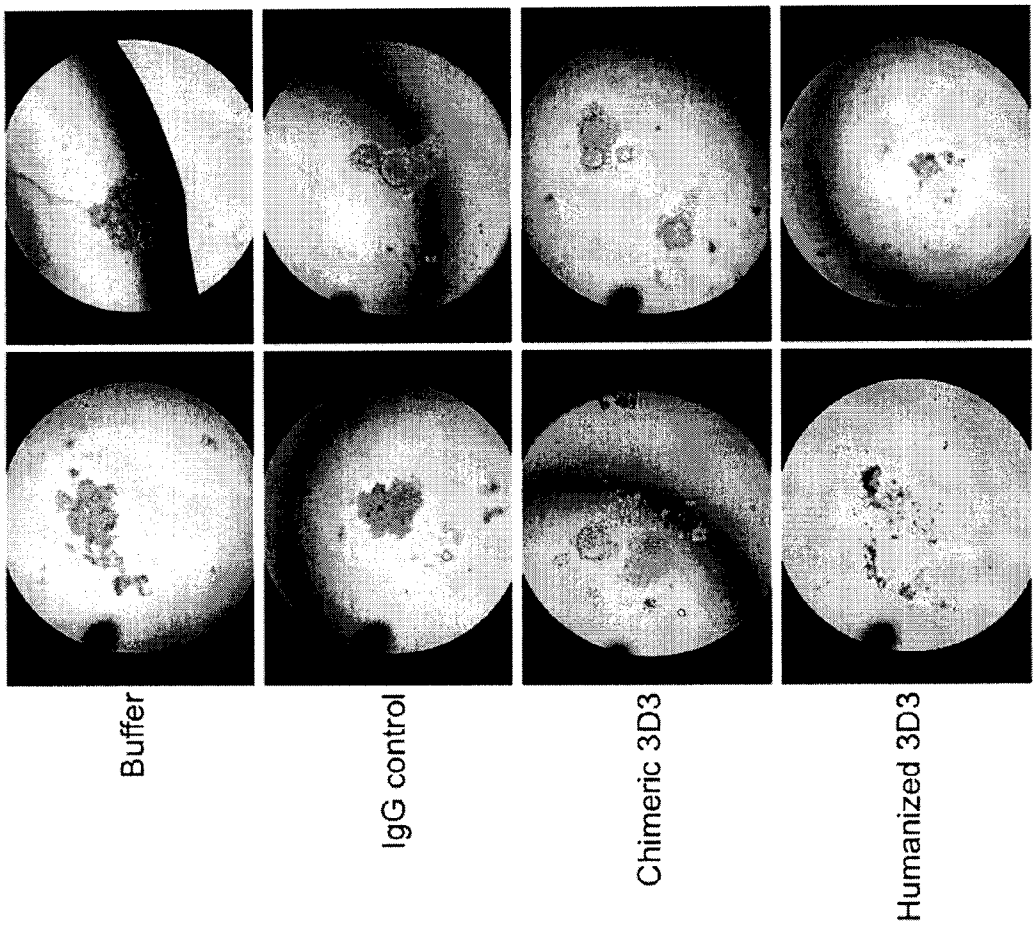

FIGURE 19C

FIGURE 20A

Name	SEQ ID NO.:		
3D3VL	16	DIVMTQSPSSLAVSIGQKVTMNC**KSSQSLLNSNFQKNFLA**WYQQKPGQSPKLLIY**FASTR**	60
		DIVMTQSP SLAVS+G++ T+NC**KSSQSLLNSNFQKNFLA**WYQQKPGQ PKLLIY**FASTR**	
h3D3VL	178	DIVMTQSPDSLAVSLGERATINC**KSSQSLLNSNFQKNFLA**WYQQKPGQPPKLLIY**FASTR**	60
3D3VL	16	**ES**SIPDRFIGSGSGTDFTLTISSVQAEDLADYFC**QQHYSTPLT**FGAGTKLELK	113
		ESS+PDRF GSGSGTDFTLTISS+QAED+A Y+C**QQHYSTPLT**FG GTKLE+K	
h3D3VL	178	**ES**SVPDRFSGSGSGTDFTLTISSLQAEDVAVYYC**QQHYSTPLT**FGQGTKLEIK	113

FIGURE 20B

Name	SEQ ID NO.:		
3D3VH	18	EVQLQQSVAELVRPGASVTLSCKAS**GYIFTDYEIH**WVKQTPVHGLEWIG**VIDPETGNTA**F	60
		EVQL QS AE+ +PGASV +SCKAS**GYIFTDYEIH**WV+Q P GLEW+G**VIDPETGNTA**F	
h3D3VH	179	EVQLVQSGAEVKKPGASVKVSCKAS**GYIFTDYEIH**WVRQAPGQGLEWMG**VIDPETGNTA**F	60
3D3VH	18	NQKFKGKATLTADISSSTAYMELSSLTSEDSAVYYC**MGYSDY**WGQGTTLTVSS	113
		NQKFKG+ T+TAD S+STAYMELSSLTSED+AVYYC**MGYSDY**WGQGT +TVSS	
h3D3VH	179	NQKFKGRVTITADTSTSTAYMELSSLTSEDTAVYYC**MGYSDY**WGQGTLVTVSS	113

FIGURE 21A

Name	SEQ ID NO.:		
3C4VL	24	DIVMSQSPSSMYASLGERVTITC**KASQDIHNFLN**WFQQKPGKSPKTLIF**RANRLVD**GVPS	60
		DIVM+QSPSS+ AS+G+RVTITC**KASQDIHNFLN**WFQQKPGK+PKTLIF**RANRLVD**GVPS	
H3C4VL	182	DIVMTQSPSSLSASVGDRVTITC**KASQDIHNFLN**WFQQKPGKAPKTLIF**RANRLVD**GVPS	60
3C4VL	24	RFSGSGSGQDYSLTISSLEFEDLGIYSC**LQYDEIPLT**FGAGTKLELR	107
		RFSGSGSG DY+LTISSL+ ED YSC**LQYDEIPLT**FG GTKLE++	
H3C4VL	182	RFSGSGSGTDYTLTISSLQPEDFATYSC**LQYDEIPLT**FGQGTKLEIK	107

FIGURE 21B

Name	SEQ ID NO.:		
3C4VH	26	EVQLQESGPDLVKPSQSLSLTCTVT**GFSITSGYGWH**WIRQFPGNKLEWMG**YINYDGHND**Y	60
		EVQLQESGP LVKPSQ+LSLTCTV+**GFSITSGYGWH**WIRQ PG LEW+G**YINYDGHND**Y	
H3C4VH	183	EVQLQESGPGLVKPSQTLSLTCTVS**GFSITSGYGWH**WIRQHPGKGLEWIG**YINYDGHND**Y	60
3C4VH	26	NPSLKSRISITQDTSKNQFFLQLNSVTTEDTATYYC**ASSYDGLFAY**WGQGTLVTVSA	117
		NPSLKSR++I+QDTSKNQF L+L+SVT DTA YYC**ASSYDGLFAY**WGQGTLVTVS	
H3C4VH	183	NPSLKSRVTISQDTSKNQFSLKLSSVTAADTAVYYC**ASSYDGLFAY**WGQGTLVTVS	116

SEQUENCE LISTING

<110> Alethia Biotherapeutics Inc.
TREMBLAY, Gilles Bernard
FILION, Mario
SULEA, Traian

<120> ANTIBODIES THAT SPECIFICALLY BLOCK THE BIOLOGICAL ACTIVITY OF A TUMOR ANTIGEN

<130> 2010008-0008

<140> US13/127,439
<141> 2011-05-03

<150> US61/193,184
<151> 2008-11-03

<150> US61/213,666
<151> 2009-06-30

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<302> A new antigen recognized by cytolytic T lymphocytes on a human kidney tumor results from reverse strand transcription
<303> J. Exp. Med.
<304> 190
<305> 12
<306> 1793-1800
<307> 1999-12-20

<400> 1

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gggatctgca tttcttcata tcaaccccac actatagggc acctaaatgg gtgggcggtg 120

ggggagaccg actcacttga gtttcttgaa ggcttcctgg cctccagcca cgtaattgcc 180

cccgctctgg atctggtcta gcttccggat tcggtggcca gtccgcgggg tgtagatgtt 240

cctgacggcc ccaaagggtg cctgaacgcc gccggtcacc tccttcagga agacttcgaa 300

gctggacacc ttcttctcat ggatgacgac gcggcgcccc gcgtagaagg ggtccccgtt 360

gcggtacaca agcacgctct tcacgacggg ctgagacagg tggctggacc tggcgctgct 420

gccgctcatc ttccccgctg gccgccgcct cagctcgctg cttcgcgtcg ggaggcacct 480

ccgctgtccc agcggcctca ccgcacccag ggcgcgggat cgcctcctga aacgaacgag 540

aaactgacga atccacaggt gaaagagaag taacggccgt gcgcctaggc gtccacccag 600

aggagacact aggagcttgc aggactcgga gtagacgctc aagtttttca ccgtggcgtg 660

cacagccaat caggacccgc agtgcgcgca ccacaccagg ttcacctgct acgggcagaa 720

tcaaggtgga cagcttctga gcaggagccg gaaacgcgcg gggccttcaa acaggcacgc 780

ctagtgaggg caggagagag gaggacgcac acacacacac acacacaaat atggtgaaac 840

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<210> 2
<211> 84
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<213> Homo sapiens

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<302> A new antigen recognized by cytolytic T lymphocytes on a human kidney tumor results from reverse strand transcription
<303> J. Exp. Med.
<304> 190
<305> 12
<306> 1793-1800
<307> 1999-12-20

<400> 2

Met Asp Asp Asp Ala Ala Pro Arg Val Glu Gly Val Pro Val Ala Val
1 5 10 15

His Lys His Ala Leu His Asp Gly Leu Arg Gln Val Ala Gly Pro Gly
20 25 30

Ala Ala Ala Ala His Leu Pro Arg Trp Pro Pro Pro Gln Leu Ala Ala
35 40 45

Ser Arg Arg Glu Ala Pro Pro Leu Ser Gln Arg Pro His Arg Thr Gln
50 55 60

Gly Ala Gly Ser Pro Pro Glu Thr Asn Glu Lys Leu Thr Asn Pro Gln
65 70 75 80

Val Lys Glu Lys

<210> 3
<211> 657
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3D3 antibody light chain

<400> 3
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atgaactgca agtccagtca gagcctttta aatagtaact ttcaaaagaa ctttttggcc 120

tggtaccagc agaaaccagg ccagtctcct aaacttctga tatactttgc atccactcgg 180

gaatctagta tccctgatcg cttcataggc agtggatctg ggacagattt cactcttacc 240

atcagcagtg tgcaggctga agacctggca gattacttct gtcagcaaca ttatagcact 300

ccgctcacgt tcggtgctgg gaccaagctg gagctgaaag ctgtggctgc accatctgtc 360

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg 420

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa 480

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc 540

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa 600

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt 657

<210> 4

<211> 219

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3D3 antibody light chain

<400> 4

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

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

```
Ser Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Ile
    50                  55                  60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
        115                 120                 125

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
    130                 135                 140

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
145                 150                 155                 160

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
                165                 170                 175

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
            180                 185                 190
```

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
195 200 205

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 5
<211> 1329
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3D3 antibody heavy chain

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tcctgcaagg cttcgggcta catatttact gactatgaga tacactgggt gaagcagact 120

cctgtgcatg gcctggaatg gattggggtt attgatcctg aaactggtaa tactgccttc 180

aatcagaagt tcaagggcaa ggccacactg actgcagaca tatcctccag cacagcctac 240

atggaactca gcagtttgac atctgaggac tctgccgtct attactgtat gggttattct 300

gattattggg gccaaggcac cactctcaca gtctcctcag cctcaacgaa gggcccatct 360

gtctttcccc tggcccctc ctccaagagc acctctgggg gcacagcggc cctgggctgc 420

ctggtcaagg actacttccc cgaaccggtg acggtgtcgt ggaactcagg cgccctgacc 480

agcggcgtgc acaccttccc ggctgtccta cagtcctcag gactctactc cctcagcagc 540

gtggtgaccg tgccctccag cagcttgggc acccagacct acatctgcaa cgtgaatcac 600

aagcccagca acaccaaggt ggacaagaaa gttgagccca aatcttgtga attcactcac 660

acatgcccac cgtgcccagc acctgaactc ctgggggggac cgtcagtctt cctcttcccc 720

ccaaaaccca aggacaccct catgatctcc cggacccctg aggtcacatg cgtggtggtg 780

gacgtgagcc acgaagaccc tgaggtcaag ttcaactggt acgtggacgg cgtggaggtg 840

cataatgcca agacaaagcc gcgggaggag cagtacaaca gcacgtaccg tgtggtcagc 900

gtcctcaccg tcctgcacca ggactggctg aatggcaagg agtacaagtg caaggtctcc 960

aacaaagccc tcccagcccc catcgagaaa accatctcca aagccaaagg gcagccccga 1020

gaaccacagg tgtacaccct gcccccatcc cgggatgagc tgaccaagaa ccaggtcagc 1080

ctgacctgcc tggtcaaagg cttctatccc agcgacatcg ccgtggagtg ggagagcaat 1140

gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga cggctccttc 1200

ttcctctaca gcaagctcac cgtggacaag agcaggtggc agcaggggaa cgtcttctca 1260

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cccgggaaa 1329

<210> 6

<211> 443

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3D3 antibody heavy chain

<400> 6

Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
100 105 110

```
Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
        115                 120                 125

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
    130                 135                 140

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
145                 150                 155                 160

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
                165                 170                 175

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
            180                 185                 190

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
        195                 200                 205

Lys Lys Val Glu Pro Lys Ser Cys Glu Phe Thr His Thr Cys Pro Pro
    210                 215                 220

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
225                 230                 235                 240
```

```
Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                245                 250                 255

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
            260                 265                 270

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        275                 280                 285

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    290                 295                 300

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305                 310                 315                 320

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
                325                 330                 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
            340                 345                 350

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        355                 360                 365

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    370                 375                 380
```

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385 390 395 400

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
405 410 415

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
420 425 430

Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440

<210> 7
<211> 654
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3G10 antibody light chain

<400> 7
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atctcttgta gatcgagtca gagcctttta catagtaatg gaaacaccta tttagaatgg 120

tatttgcaga aaccaggcca gcctccaaag gtcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcggagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct 300

ctcacgttcg gtgctgggac caagctggag ctgaaagctg tggctgcacc atctgtcttc 360

atcttcccgc catctgatga gcagttgaaa tctggaactg cctctgttgt gtgcctgctg 420

aataacttct atcccagaga ggccaaagta cagtggaagg tggataacgc cctccaatcg 480

ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 540

agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 600

acccatcagg gcctgagctc gcccgtcaca aagagcttca acaggggaga gtgt 654

<210> 8

<211> 218

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3G10 antibody light chain

<400> 8

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

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

```
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Pro
        35                  40                  45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

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

Ser Gly Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105                 110

Ala Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
        115                 120                 125

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
    130                 135                 140

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
145                 150                 155                 160

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
                165                 170                 175
```

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
180 185 190

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
195 200 205

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
210 215

<210> 9
<211> 1335
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3G10 antibody heavy chain

<400> 9
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tcctgtaagg cttctggata caccttcact gacaactaca tgaactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggagat attaatcctt actatggtac tactacctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctcccg cacagcctac 240

atggagctcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgac 300

tggtttgatt attggggcca agggactctg gtcactgtct ctgcagcctc aacgaagggc 360

ccatctgtct ttcccctggc cccctcctcc aagagcacct ctgggggcac agcggccctg 420

ggctgcctgg tcaaggacta cttccccgaa ccggtgacgg tgtcgtggaa ctcaggcgcc 480

ctgaccagcg gcgtgcacac cttcccggct gtcctacagt cctcaggact ctactccctc 540

agcagcgtgg tgaccgtgcc ctccagcagc ttgggcaccc agacctacat ctgcaacgtg 600

aatcacaagc ccagcaacac caaggtggac aagaaagttg agcccaaatc ttgtgaattc 660

actcacacat gcccaccgtg cccagcacct gaactcctgg ggggaccgtc agtcttcctc 720

ttcccccaa aacccaagga caccctcatg atctcccgga cccctgaggt cacatgcgtg 780

gtggtggacg tgagccacga agaccctgag gtcaagttca actggtacgt ggacggcgtg 840

gaggtgcata atgccaagac aaagccgcgg gaggagcagt acaacagcac gtaccgtgtg 900

gtcagcgtcc tcaccgtcct gcaccaggac tggctgaatg gcaaggagta caagtgcaag 960

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ccccgagaac cacaggtgta caccctgccc ccatcccggg atgagctgac caagaaccag 1080

gtcagcctga cctgcctggt caaaggcttc tatcccagcg acatcgccgt ggagtgggag 1140

agcaatgggc agccggagaa caactacaag accacgcctc ccgtgctgga ctccgacggc 1200

tccttcttcc tctacagcaa gctcaccgtg gacaagagca ggtggcagca ggggaacgtc 1260

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ctgtctcccg ggaaa 1335

<210> 10
<211> 445
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3G10 antibody heavy chain

<400> 10

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1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65 70 75 80

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

```
Ala Arg Asp Asp Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
            100                 105                 110

Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro
        115                 120                 125

Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val
    130                 135                 140

Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala
145                 150                 155                 160

Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly
                165                 170                 175

Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly
            180                 185                 190

Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys
        195                 200                 205

Val Asp Lys Lys Val Glu Pro Lys Ser Cys Glu Phe Thr His Thr Cys
    210                 215                 220
```

```
Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu
225                 230                 235                 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu
                245                 250                 255

Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys
            260                 265                 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys
        275                 280                 285

Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu
    290                 295                 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys
305                 310                 315                 320

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys
                325                 330                 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser
            340                 345                 350

Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys
        355                 360                 365
```

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln
370 375 380

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly
385 390 395 400

Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln
405 410 415

Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn
420 425 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 11
<211> 639
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3C4 antibody light chain

<400> 11
gacatcgtta tgtctcagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattcat aacttttaa actggttcca gcagaaacca 120

ggaaaatctc caaagaccct gatctttcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagttt 240

gaagatttgg gaatttattc ttgtctacag tatgatgaga ttccgctcac gttcggtgct 300

gggaccaagc tggagctgag agctgtggct gcaccatctg tcttcatctt cccgccatct 360

gatgagcagt tgaaatctgg aactgcctct gttgtgtgcc tgctgaataa cttctatccc 420

agagaggcca aagtacagtg gaaggtggat aacgccctcc aatcgggtaa ctcccaggag 480

agtgtcacag agcaggacag caaggacagc acctacagcc tcagcagcac cctgacgctg 540

agcaaagcag actacgagaa acacaaagtc tacgcctgcg aagtcaccca tcagggcctg 600

agctcgcccg tcacaaagag cttcaacagg ggagagtgt 639

<210> 12

<211> 213

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3C4 antibody light chain

<400> 12

Asp Ile Val Met Ser Gln Ser Pro Ser Ser Met Tyr Ala Ser Leu Gly

1 5 10 15

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Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
            20                  25                  30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
        35                  40                  45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

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

Glu Asp Leu Gly Ile Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg Ala Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160
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Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
165 170 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
180 185 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
195 200 205

Asn Arg Gly Glu Cys
210

<210> 13
<211> 1341
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3C4 antibody heavy chain

<400> 13
gaggtgcagc ttcaggagtc aggacctgac ctggtgaaac cttctcagtc actttcactc 60

acctgcactg tcactggctt ctccatcacc agtggttatg gctggcactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataaact acgatggtca caatgactac 180

aacccatctc tcaaaagtcg aatctctatc actcaagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagcagttac 300

gacggcttat ttgcttactg gggccaaggg actctggtca ctgtctctgc agcctcaacg 360

aagggcccat ctgtctttcc cctggccccc tcctccaaga gcacctctgg gggcacagcg 420

gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca 480

ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac 540

tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc 600

aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc caaatcttgt 660

gaattcactc acacatgccc accgtgccca gcacctgaac tcctgggggg accgtcagtc 720

ttcctcttcc ccccaaaacc caaggacacc ctcatgatct cccggacccc tgaggtcaca 780

tgcgtggtgg tggacgtgag ccacgaagac cctgaggtca agttcaactg gtacgtggac 840

ggcgtggagg tgcataatgc caagacaaag ccgcgggagg agcagtacaa cagcacgtac 900

cgtgtggtca gcgtcctcac cgtcctgcac caggactggc tgaatggcaa ggagtacaag 960

tgcaaggtct ccaacaaagc cctcccagcc cccatcgaga aaaccatctc caaagccaaa 1020

gggcagcccc gagaaccaca ggtgtacacc ctgcccccat cccgggatga gctgaccaag 1080

aaccaggtca gcctgacctg cctggtcaaa ggcttctatc ccagcgacat cgccgtggag 1140

tgggagagca atgggcagcc ggagaacaac tacaagacca cgcctcccgt gctggactcc 1200

gacggctcct tcttcctcta cagcaagctc accgtggaca agagcaggtg gcagcagggg 1260

aacgtcttct catgctccgt gatgcatgag gctctgcaca accactacac gcagaagagc 1320

ctctccctgt ctcccgggaa a 1341

<210> 14
<211> 447
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3C4 antibody heavy chain

<400> 14

Glu Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln
1 5 10 15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser Gly
20 25 30

Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
35 40 45

Met Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Ile Ser Ile Thr Gln Asp Thr Ser Lys Asn Gln Phe Phe
65 70 75 80

```
Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu
        115                 120                 125

Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys
    130                 135                 140

Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser
145                 150                 155                 160

Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser
                165                 170                 175

Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser
            180                 185                 190

Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn
        195                 200                 205
```

```
Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Glu Phe Thr His
    210                 215                 220

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
            260                 265                 270

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350
```

Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
355 360 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
370 375 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385 390 395 400

Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg
405 410 415

Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
420 425 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
435 440 445

<210> 15
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3D3 antibody light chain variable region

<400> 15

gacattgtga tgacccagtc tccatcctcc ctggctgtgt caataggaca gaaggtcact 60

atgaactgca agtccagtca gagcctttta aatagtaact ttcaaaagaa ctttttggcc 120

tggtaccagc agaaaccagg ccagtctcct aaacttctga tatactttgc atccactcgg 180

gaatctagta tccctgatcg cttcataggc agtggatctg ggacagattt cactcttacc 240

atcagcagtg tgcaggctga agacctggca gattacttct gtcagcaaca ttatagcact 300

ccgctcacgt tcggtgctgg gaccaagctg gagctgaaa 339

<210> 16

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3D3 antibody light chain variable region

<400> 16

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

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Ile
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 17
<211> 339
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3D3 antibody heavy chain variable region

<400> 17

gaggttcagc tgcagcagtc tgtagctgag ctggtgaggc ctggggcttc agtgacgctg 60

tcctgcaagg cttcgggcta catatttact gactatgaga tacactgggt gaagcagact 120

cctgtgcatg gcctggaatg gattggggtt attgatcctg aaactggtaa tactgccttc 180

aatcagaagt tcaagggcaa ggccacactg actgcagaca tatcctccag cacagcctac 240

atggaactca gcagtttgac atctgaggac tctgccgtct attactgtat gggttattct 300

gattattggg gccaaggcac cactctcaca gtctcctca 339

<210> 18

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3D3 antibody heavy chain variable region

<400> 18

Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly Ala
1 5 10 15

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ala Asp Ile Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser
100 105 110

Ser

<210> 19
<211> 336
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3G10 antibody light chain variable region

<400> 19
gatgttttga tgacccaaac tccacgctcc ctgtctgtca gtcttggaga tcaagcctcc 60

atctcttgta gatcgagtca gagcctttta catagtaatg gaaacaccta tttagaatgg 120

tatttgcaga aaccaggcca gcctccaaag gtcctgatct acaaagtttc caaccgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcggagtgg aggctgagga tctgggagtt tattactgct ttcaaggttc acatgttcct 300

ctcacgttcg gtgctgggac caagctggag ctgaaa 336

<210> 20

<211> 112

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3G10 antibody light chain variable region

<400> 20

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

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

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

Ser Gly Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 21
<211> 345
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3G10 antibody heavy chain variable region

<400> 21
gagatccagc tgcagcagtc tggacctgag ttggtgaagc ctggggcttc agtgaagata 60

tcctgtaagg cttctggata caccttcact gacaactaca tgaactgggt gaagcagagc 120

catggaaaga gccttgagtg gattggagat attaatcctt actatggtac tactacctac 180

aaccagaagt tcaagggcaa ggccacattg actgtagaca agtcctcccg cacagcctac 240

atggagctcc gcggcctgac atctgaggac tctgcagtct attactgtgc aagagatgac 300

tggtttgatt attggggcca agggactctg gtcactgtct ctgca 345

<210> 22
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3G10 antibody heavy chain variable region

<400> 22

Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Asn
20 25 30

Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp Ile
35 40 45

Gly Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Val Asp Lys Ser Ser Arg Thr Ala Tyr
65 70 75 80

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

Ala Arg Asp Asp Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala
115

<210> 23
<211> 321
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3C4 antibody light chain variable region

<400> 23
gacatcgtta tgtctcagtc tccatcttcc atgtatgcat ctctaggaga gagagtcact 60

atcacttgca aggcgagtca ggacattcat aacttttaa actggttcca gcagaaacca 120

ggaaaatctc caaagaccct gatctttcgt gcaaacagat tggtagatgg ggtcccatca 180

aggttcagtg gcagtggatc tgggcaagat tattctctca ccatcagcag cctggagttt 240

gaagatttgg gaatttattc ttgtctacag tatgatgaga ttccgctcac gttcggtgct 300

gggaccaagc tggagctgag a 321

<210> 24
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3C4 antibody light chain variable region

<400> 24

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

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Leu Gly Ile Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
100 105

<210> 25
<211> 351
<212> DNA
<213> Artificial Sequence

<220>
<223> Nucleotide sequence of the 3C4 antibody heavy chain variable region

<400> 25
gaggtgcagc ttcaggagtc aggacctgac ctggtgaaac cttctcagtc actttcactc 60

acctgcactg tcactggctt ctccatcacc agtggttatg gctggcactg gatccggcag 120

tttccaggaa acaaactgga gtggatgggc tacataaact acgatggtca caatgactac 180

aacccatctc tcaaaagtcg aatctctatc actcaagaca catccaagaa ccagttcttc 240

ctgcagttga attctgtgac tactgaggac acagccacat attactgtgc aagcagttac 300

gacggcttat ttgcttactg gggccaaggg actctggtca ctgtctctgc a 351

<210> 26
<211> 117
<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3C4 antibody heavy chain variable region

<400> 26

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Glu Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser Gln
1               5                   10                  15

Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser Gly
            20                  25                  30

Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu Trp
        35                  40                  45

Met Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Ile Ser Ile Thr Gln Asp Thr Ser Lys Asn Gln Phe Phe
65                  70                  75                  80

Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr Cys
                85                  90                  95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
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Val Thr Val Ser Ala
115

<210> 27
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3D3 light chain CDR1

<400> 27

Lys Ser Ser Gln Ser Leu Leu Asn Ser Asn Phe Gln Lys Asn Phe Leu
1 5 10 15

Ala

<210> 28
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3D3 light chain CDR2

<400> 28

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 29
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3D3 light chain CDR3

<400> 29

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 30
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3D3 heavy chain CDR1

<400> 30

Gly Tyr Ile Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 31
<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3D3 heavy chain CDR2

<400> 31

Val Ile Asp Pro Glu Thr Gly Asn Thr Ala
1 5 10

<210> 32

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3D3 heavy chain CDR3

<400> 32

Met Gly Tyr Ser Asp Tyr
1 5

<210> 33

<211> 16

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3G10 light chain CDR1

<400> 33

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> 34
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3G10 light chain CDR2

<400> 34

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 35
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3G10 light chain CDR3

<400> 35

Phe Gln Gly Ser His Val Pro Leu Thr
1 5

<210> 36
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3G10 heavy chain CDR1

<400> 36

Gly Tyr Thr Phe Thr Asp Asn Tyr Met Asn
1 5 10

<210> 37
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3G10 heavy chain CDR2

<400> 37

Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr
1 5 10

<210> 38
<211> 8
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3G10 heavy chain CDR3

<400> 38

Ala Arg Asp Asp Trp Phe Asp Tyr
1 5

<210> 39
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3C4 light chain CDR1

<400> 39

Lys Ala Ser Gln Asp Ile His Asn Phe Leu Asn
1 5 10

<210> 40
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3C4 light chain CDR2

<400> 40

Arg Ala Asn Arg Leu Val Asp
1 5

<210> 41
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3C4 light chain CDR3

<400> 41

Leu Gln Tyr Asp Glu Ile Pro Leu Thr
1 5

<210> 42
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3C4 heavy chain CDR1

<400> 42

Gly Phe Ser Ile Thr Ser Gly Tyr Gly Trp His
1 5 10

<210> 43
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3C4 heavy chain CDR2

<400> 43

Tyr Ile Asn Tyr Asp Gly His Asn Asp
1 5

<210> 44

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3C4 heavy chain CDR3

<400> 44

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr
1 5 10

<210> 45

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> Primer to amplify KAAG1 mRNA sequence

<400> 45

gaggggcatc aatcacaccg agaa 24

<210> 46
<211> 22
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer to amplify KAAG1 mRNA sequence

<400> 46
ccccaccgcc cacccattta gg 22

<210> 47
<211> 26
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer to amplify GAPDH gene

<400> 47
tgaaggtcgg agtcaacgga tttggt 26

<210> 48
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer to amplify GAPDH gene

<400> 48
catgtgggcc atgaggtcca ccac 24

<210> 49
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> 19-mer used to generate KAAG1-specific shRNA

<400> 49
ggcctccagc cacgtaatt 19

<210> 50
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> 19-mer used to generate KAAG1-specific shRNA

<400> 50
ggcgctgctg ccgctcatc 19

<210> 51
<211> 4455
<212> DNA
<213> Artificial Sequence

<220>

<223> pSilencer 2.0 plasmid

<400> 51

tcgcgcgttt cggtgatgac ggtgaaaacc tctgacacat gcagctcccg gagacggtca 60

cagcttgtct gtaagcggat gccgggagca gacaagcccg tcagggcgcg tcagcgggtg 120

ttggcgggtg tcggggctgg cttaactatg cggcatcaga gcagattgta ctgagagtgc 180

accatatgcg gtgtgaaata ccgcacagat gcgtaaggag aaaataccgc atcaggcgcc 240

attcgccatt caggctgcgc aactgttggg aagggcgatc ggtgcgggcc tcttcgctat 300

tacgccagct ggcgaaaggg ggatgtgctg caaggcgatt aagttgggta acgccagggt 360

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<213> Artificial Sequence

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<210> 63
<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer specific for the light chain variable region of the 3G10 antibody

<400> 63
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<210> 64
<211> 43

<212> DNA

<213> Artificial Sequence

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<223> Primer specific for the light chain variable region of the 3C4 antibody

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<212> DNA

<213> Artificial Sequence

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<223> OGS1769 primer

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<210> 69

<211> 103

<212> PRT

<213> Homo sapiens

<400> 69

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        35                  40                  45

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
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<223> pYD15 plasmid

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<210> 72

<211> 43
<212> DNA
<213> Artificial Sequence

<220>
<223> Primer specific for the heavy chain variable region of the 3C4 antibody

<400> 72
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<210> 73
<211> 38
<212> DNA
<213> Artificial Sequence

<220>
<223> reverse primer to amplify the 3D3, 3G10 and 3C4 antibody heavy chains

<400> 73
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<210> 74
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<213> Artificial Sequence

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<220>
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<220>
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<223> Xaa is absent, Ser or Asn

<220>
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<222> (11)..(11)
<223> Xaa is Asp, Phe or Asn

<220>
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<223> Xaa is Gly or Gln

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<222> (13)..(13)
<223> Xaa is Lys, Leu or Asn

<220>
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<223> Xaa is Thr or Asn

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<222> (15)..(15)
<223> Xaa is an aromatic amino acid

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<221> MISC_FEATURE
<222> (17)..(17)
<223> Xaa is Ala, Asn, Glu or Tyr

<400> 74

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Xaa

<210> 75
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<223> Xaa is an hydrophobic amino acid

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<222> (7)..(7)

<223> Xaa is Gly or His

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> Xaa is Thr, Asn or Arg

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<221> MISC_FEATURE

<222> (9)..(9)

<223> Xaa is Phe, Tyr or Ala

<220>

<221> MISC_FEATURE

<222> (10)..(10)

<223> Xaa is an hydrophobic amino acid

<220>

<221> MISC_FEATURE

<222> (11)..(11)

<223> Xaa is Asn or Ala

<400> 75

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<210> 76
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<223> Xaa is Arg or Thr

<220>
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<223> Xaa is Glu, Lys or Ala

<400> 76

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<223> Xaa is Asp or Phe

<400> 77

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<400> 78

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<222> (3)..(3)
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<220>
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<222> (5)..(5)
<223> Xaa is Glu, Ala, Asn or Ser

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is Ile, Phe or Thr

<400> 79

Xaa Gln Xaa Xaa Xaa Xaa Pro Leu Thr
1 5

<210> 80
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> light chain CDR3 consensus version 2

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is an aromatic amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Asn or Ser

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is Ile or Thr

<400> 80

Gln Gln His Xaa Xaa Xaa Pro Leu Thr
1 5

<210> 81
<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> light chain CDR3 consensus version 3

<220>

<221> MISC_FEATURE

<222> (1)..(1)

<223> Xaa is an aromatic amino acid

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Xaa is a neutral hydrophilic amino acid

<220>

<221> MISC_FEATURE

<222> (6)..(6)

<223> Xaa is Phe or Val

<220>

<221> MISC_FEATURE

<222> (8)..(8)

<223> Xaa is Arg or Leu

<400> 81

Xaa Gln Gly Xaa His Xaa Pro Xaa Thr

1 5

<210> 82

<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR1 consensus

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Thr, Ile or Lys

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is a neutral hydrophilic amino acid

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is an acidic amino acid

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Glu, Asn or Asp

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is an hydrophobic amino acid

<400> 82

Gly Tyr Xaa Phe Xaa Xaa Tyr Xaa Xaa His
1 5 10

<210> 83
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 consensus version 1

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is Val or Gly

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is an hydrophobic amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Ala, Gly or Glu

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Arg, Gly, Asp, Ala, Ser, Asn or Val

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is an hydrophobic amino acid

<400> 83

Xaa Xaa Asp Pro Xaa Thr Gly Xaa Thr Xaa
1 5 10

<210> 84
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 consensus version 2

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is an hydrophobic amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Ala, Glu or Gly

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Arg, Gly, Ala, Ser, Asn, Val or Asp

<400> 84

Val Xaa Asp Pro Xaa Thr Gly Xaa Thr Ala
1 5 10

<210> 85
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 consensus version 3

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Ser or Asn

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is an aromatic amino acid

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Asp, Glu or Asn

<220>
<221> MISC_FEATURE
<222> (7)..(7)

<223> Xaa is Asp or His

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Tyr, Ser or Asn

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Asp, Glu or Asn

<400> 85

Tyr Ile Xaa Xaa Xaa Gly Xaa Xaa Xaa
1 5

<210> 86
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 consensus version 4

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is Asn or Tyr

<220>
<221> MISC_FEATURE

<222> (7)..(7)
<223> Xaa is Glu, Asp or Asn

<400> 86

Xaa Ile Asn Pro Tyr Asn Xaa Val Thr Glu
1 5 10

<210> 87
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR2 consensus version 5

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Asn or Tyr

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Gly or Thr

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Ile or Thr

<400> 87

Asp Ile Asn Pro Xaa Tyr Gly Xaa Xaa Thr
1 5 10

<210> 88
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 consensus version 1

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Gly or Ser

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Tyr or His

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is Ala or Ser

<400> 88

Met Xaa Xaa Xaa Asp Tyr
1 5

<210> 89
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 consensus version 2

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Gly or Ser

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is absent or Met

<400> 89

Ile Xaa Tyr Ala Xaa Asp Tyr
1 5

<210> 90
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> heavy chain CDR3 consensus version 3

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Arg or Trp

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is an aromatic amino acid

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is a basic amino acid

<400> 90

Ala Xaa Xaa Gly Leu Arg Xaa
1 5

<210> 91
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a light chain CDR1

<220>
<221> MISC_FEATURE
<222> (8)..(8)

<223> Xaa is Asn or His

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Ser or Thr

<220>
<221> MISC_FEATURE
<222> (10)..(10)
<223> Xaa is Ser, Asn or Asp

<220>
<221> MISC_FEATURE
<222> (11)..(11)
<223> Xaa is Asn or Gly

<220>
<221> MISC_FEATURE
<222> (12)..(12)
<223> Xaa is Gln, Asn or Lys

<220>
<221> MISC_FEATURE
<222> (13)..(13)
<223> Xaa is Lys or Leu

<400> 91

Lys Ser Ser Gln Ser Leu Leu Xaa Xaa Xaa Xaa Xaa Xaa Asn Tyr Leu
1 5 10 15

Ala

<210> 92
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a light chain CDR1

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Asn or Thr

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Tyr or Phe

<400> 92

Lys Ala Ser Gln Asp Ile His Xaa Xaa Leu Asn
1 5 10

<210> 93
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> Exemplary embodiment of a light chain CDR2

<400> 93

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 94
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a light chain CDR2

<400> 94

Leu Val Ser Lys Leu Asp Ser
1 5

<210> 95
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a light chain CDR2

<400> 95

Arg Ala Asn Arg Leu Val Asp
1 5

<210> 96
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a light chain CDR3

<400> 96

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 97
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a light chain CDR3

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is Trp or Leu

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Tyr or Gly

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is Asp or Thr

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Ala, Glu or His

<400> 97

Xaa Gln Xaa Xaa Xaa Phe Pro Arg Thr
1 5

<210> 98
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a heavy chain CDR1

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is The or Ile

<220>
<221> MISC_FEATURE
<222> (6)..(6)

<223> Xaa is Asp or Glu

<220>
<221> MISC_FEATURE
<222> (8)..(8)
<223> Xaa is Glu or Asn

<220>
<221> MISC_FEATURE
<222> (9)..(9)
<223> Xaa is Met, Ile or Val

<400> 98

Gly Tyr Xaa Phe Thr Xaa Tyr Xaa Xaa His
1 5 10

<210> 99
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a heavy chain CDR1

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Thr or Ser

<400> 99

Gly Phe Xaa Ile Thr Ser Gly Tyr Gly Trp His
1 5 10

<210> 100
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a heavy chain CDR2

<220>
<221> MISC_FEATURE
<222> (1)..(1)
<223> Xaa is Val, Asn or Gly

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Ile or Leu

<220>
<221> MISC_FEATURE
<222> (5)..(5)
<223> Xaa is Glu, Ala or Gly

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> Xaa is Thr or Tyr

<220>

<221> misc_feature

<222> (8)..(8)

<223> Xaa can be any naturally occurring amino acid

<400> 100

Xaa Xaa Asp Pro Xaa Xaa Gly Xaa Thr Ala
1 5 10

<210> 101

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> Exemplary embodiment of a heavy chain CDR2

<220>

<221> MISC_FEATURE

<222> (3)..(3)

<223> Xaa is Asn or Ser

<220>

<221> MISC_FEATURE

<222> (4)..(4)

<223> Xaa is Phe or Tyr

<220>

<221> MISC_FEATURE

<222> (5)..(5)

<223> Xaa is Asn or Asp

<400> 101

Tyr Ile Xaa Xaa Xaa Gly
1 5

<210> 102
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a heavy chain CDR3

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> Xaa is Ser or Ala

<400> 102

Met Gly Tyr Xaa Asp Tyr
1 5

<210> 103
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a heavy chain CDR3

<400> 103

Ala Ser Ser Tyr Asp Gly Phe Leu Ala Tyr
1 5 10

<210> 104
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Exemplary embodiment of a heavy chain CDR3

<220>
<221> MISC_FEATURE
<222> (2)..(2)
<223> Xaa is Arg or Trp

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> Xaa is Trp or Phe

<220>
<221> MISC_FEATURE
<222> (7)..(7)
<223> Xaa is Gln or Asn

<400> 104

Ala Xaa Xaa Gly Leu Arg Xaa
1 5

<210> 105
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1A02 light chain

<400> 105

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

Gln Pro Ala Ser Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
20 25 30

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

Pro Lys Arg Leu Ile Ser Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Phe Pro Arg Thr Phe Ala Gly Gly Thr Asn Leu Glu Ile Lys
100 105 110

<210> 106
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F06 light chain

<400> 106

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

Gln Pro Ala Ser Ile Thr Cys Lys Ser Ser Gln Ser Leu Leu Tyr Ser
20 25 30

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

Pro Lys Arg Leu Ile Ser Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 107
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E08 light chain

<400> 107

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

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Leu Leu His Ser
20 25 30

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

Pro Lys Arg Leu Ile Tyr Leu Val Ser Lys Leu Asp Ser Gly Val Pro
50 55 60

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

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

Thr His Phe Pro Arg Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 108
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G10 light chain

<400> 108

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

Asp Gln Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Pro
35 40 45

Pro Lys Val Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

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

Ser Gly Val Glu Ala Glu Asp Leu Gly Val Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser His Val Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105 110

<210> 109
<211> 112
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E10 light chain

<400> 109

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

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

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

Leu Glu Tyr Pro Tyr Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> 110
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1A09 light chain

<400> 110

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

```
Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

Asn Asn Gln Leu Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

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

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

Ile Thr Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Phe Asn Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys
```

<210> 111
<211> 113
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1B01 light chain

<400> 111

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

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

Ser Pro Lys Leu Leu Val Phe Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110
```

Lys

<210> 112
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G05 light chain

<400> 112

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Val Phe Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Thr Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ser Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 113
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1B02 light chain

<400> 113

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 114
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1B08 light chain

<400> 114

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 115
<211> 113
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1G08 light chain

<400> 115

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

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

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys
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<210> 116
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F07 light chain

<400> 116

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 117
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E09 light chain

<400> 117

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Thr Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 118
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1C03 light chain

<400> 118

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Val Tyr Phe Gly Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Gly Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 119
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E12 light chain

<400> 119

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

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Arg
20 25 30

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

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Ile Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 120

<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 4z1A02 light chain

<400> 120

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

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Asn
            20                  25                  30

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

Ser Pro Lys Leu Leu Leu Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95
```

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Asp Leu
100 105 110

Lys

<210> 121
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F10 light chain

<400> 121

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Thr
20 25 30

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

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Thr Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 122
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F04 light chain

<400> 122

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Thr
20 25 30

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

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

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 123
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1B11 light chain

<400> 123

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

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

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
                85                  90                  95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
            100                 105                 110

Lys
```

<210> 124
<211> 113

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1D03 ight chain

<400> 124

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

Gln Lys Val Thr Met Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Ser Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Ile
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 125
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1C03 light chain

<400> 125

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

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Ser Pro Lys Leu Leu Val Tyr Phe Gly Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Gly Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu
100 105 110

Lys

<210> 126
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G12 light chain

<400> 126

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

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

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Glu Leu Leu Ile
35 40 45

Tyr Trp Thr Ser Thr Arg His Thr Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val Gln Ala
65 70 75 80

Glu Asp Leu Ala Asp Tyr Phe Cys Gln Gln His Tyr Ser Ile Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
100 105

<210> 127
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1C04 light chain

<400> 127

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

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Asn Phe
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Leu Gly Ile Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Arg
100 105

<210> 128
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1D01 light chain

<400> 128

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

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Thr Tyr
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Glu Thr Leu Ile
35 40 45

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

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Met Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Glu Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 129
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1C02 light chain

<400> 129

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

Glu Arg Val Thr Leu Thr Cys Lys Ala Ser Gln Asp Ile His Asn Tyr
20 25 30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
35 40 45

His Arg Ala Asn Arg Leu Val Ala Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65 70 75 80

Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Ala Phe Pro Leu
85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 130
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1E06 light chain

<400> 130

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

Glu Arg Val Thr Leu Thr Cys Lys Ala Ser Gln Asp Ile His Asn Tyr
            20                  25                  30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
        35                  40                  45

His Arg Ala Asn Arg Leu Val Ala Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Gln Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65                  70                  75                  80

Glu Asp Leu Gly Ile Tyr Tyr Cys Leu Gln Tyr Asp Ala Phe Pro Leu
                85                  90                  95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
            100                 105
```

<210> 131

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1H03 light chain

<400> 131

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

Glu Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Ile His Arg Phe
            20                  25                  30

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ser Pro Lys Thr Leu Ile
        35                  40                  45

Phe His Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Leu Asp Tyr Ser Leu Thr Ile Ser Ser Leu Glu Tyr
65                  70                  75                  80

Glu Asp Met Gly Ile Tyr Phe Cys Leu Gln Tyr Asp Ala Phe Pro Leu
                85                  90                  95
```

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys
100 105

<210> 132
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1A02 heavy chain

<400> 132

His Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
1 5 10 15

Ala Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Asn Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Asn Pro Tyr Asn Asp Val Thr Glu Tyr Asn Glu Lys
50 55 60

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

Tyr Met Asp Leu Ser Ser Leu Thr Ser Asp Asp Ser Ala Val Tyr Phe
85 90 95

Cys Ala Trp Phe Gly Leu Arg Gln Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Thr
115

<210> 133
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F06 heavy chain

<400> 133

His Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
1 5 10 15

Ala Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Glu
20 25 30

Tyr Asn Ile His Trp Val Lys Gln Lys Pro Gly Gln Gly Pro Glu Trp
35 40 45

Ile Gly Asn Ile Asn Pro Tyr Asn Asp Val Thr Glu Tyr Asn Glu Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ala Ser Ser Thr Ala
65 70 75 80

Tyr Met Asp Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Trp Gly Leu Arg Asn Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala
115

<210> 134
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E08 heavy chain

<400> 134

His Glu Val Gln Leu Gln Gln Ser Val Pro Glu Leu Val Lys Pro Gly
1 5 10 15

Ala Ser Val Lys Met Ser Cys Lys Thr Ser Gly Tyr Thr Phe Thr Glu
20 25 30

Tyr Asn Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Pro Glu Trp
35 40 45

Ile Gly Asn Ile Asn Pro Tyr Asn Asn Val Thr Glu Tyr Asn Glu Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Leu Asp Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Trp Gly Leu Arg Asn Trp Gly Gln Gly Thr Leu Val Thr
100 105 110

Val Ser Ala
115

<210> 135
<211> 114
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1A09 heavy chain

<400> 135

```
His Gln Val Gln Val Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp
            20                  25                  30

Tyr Glu Val His Trp Val Arg Gln Arg Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ala Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Ile Gly Tyr Ala Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser
```

<210> 136
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1B01 heavy chain

<400> 136

```
His Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly
1               5                  10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95
```

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 137
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1B02 heavy chain

<400> 137

His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 138
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F04 heavy chain

<400> 138

His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ser Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ala Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 139
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E09 heavy chain

<400> 139

```
His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1               5                  10                  15

Ala Ser Ala Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ser Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly Tyr Ala Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser
```

<210> 140

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1B08 heavy chain

<400> 140

```
His Glu Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1               5                  10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Asn
    50                  55                  60

Phe Thr Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95
```

Cys Met Gly Tyr Ala Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 141
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G08 heavy chain

<400> 141

His Gln Val Gln Leu Lys Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Val His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Ala Thr Gly Asp Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Val Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 142
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F07 heavy chain

<400> 142

His Gln Ala Tyr Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Asp Lys Ala Thr Leu Thr Ala Asp Lys Ala Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 143
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E12 heavy chain

<400> 143

```
His Gln Val Gln Leu Gln Gln Ser Glu Ala Glu Leu Val Lys Pro Gly
1               5                   10                  15

Ala Ser Val Lys Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asp Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly His Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110

Ser Ser
```

<210> 144
<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1D03 heavy chain

<400> 144

```
His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys
    50                  55                  60

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

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110
```

Ser Ser

<210> 145
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G12 heavy chain

<400> 145

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp
20 25 30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Ala His Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys
50 55 60

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

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 146
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1F10 heavy chain

<400> 146

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Pro Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Val His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Glu Thr Gly Ala Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Ala Ala
65 70 75 80

Tyr Met Glu Leu Ser Arg Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Ser Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 147
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1C03 heavy chain

<400> 147

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Val Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Glu Thr Gly Val Thr Ala Tyr Asn Gln Arg
50 55 60

Phe Arg Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 148
<211> 114
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1C03 heavy chain

<400> 148

```
His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Val Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Ile Asp Pro Glu Thr Gly Val Thr Ala Tyr Asn Gln Arg
    50                  55                  60

Phe Arg Asp Lys Ala Thr Leu Thr Thr Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe
                85                  90                  95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
            100                 105                 110
```

Ser Ser

<210> 149

<211> 114

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1G05 heavy chain

<400> 149

```
His Gln Val Gln Leu Gln Gln Pro Gly Ala Glu Leu Val Arg Pro Gly
1               5                  10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
            20                  25                  30

Tyr Glu Ile His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Val Leu Asp Pro Gly Thr Gly Arg Thr Ala Tyr Asn Gln Lys
    50                  55                  60

Phe Lys Asp Lys Ala Thr Leu Ser Ala Asp Lys Ser Ser Ser Thr Ala
65                  70                  75                  80
```

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Ser Tyr Ser Asp Tyr Trp Gly Pro Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 150
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1B11 heavy chain

<400> 150

His Glu Val Gln Leu Gln Gln Ser Val Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val Arg Gly Leu Glu Trp
35 40 45

Ile Gly Val Ile Asp Pro Ala Thr Gly Asp Thr Ala Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Ala Ala
65 70 75 80

Phe Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val
100 105 110

Ser Ser

<210> 151
<211> 115
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E06 heavy chain

<400> 151

His Gln Val Gln Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly
1 5 10 15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Thr Phe Ser Asp
20 25 30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
35 40 45

Ile Gly Gly Ile Asp Pro Glu Thr Gly Asp Thr Val Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Ile Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
100 105 110

Val Ser Ser
115

<210> 152
<211> 115
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 4z1A02 heavy chain

<400> 152

```
His Gln Val Lys Leu Gln Gln Ser Gly Thr Glu Leu Val Arg Pro Gly
1               5                   10                  15

Ala Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Lys Phe Thr Asp
            20                  25                  30

Tyr Glu Met His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp
        35                  40                  45

Ile Gly Gly Ile Asp Pro Glu Thr Gly Gly Thr Ala Tyr Asn Gln Lys
    50                  55                  60

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

Tyr Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
                85                  90                  95

Cys Ile Ser Tyr Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser Val Thr
            100                 105                 110

Val Ser Ser
        115
```

<210> 153
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E10 heavy chain

<400> 153

His Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
1 5 10 15

Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Asp
20 25 30

Tyr Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp
35 40 45

Ile Gly Asp Ile Asn Pro Asn Tyr Gly Gly Ile Thr Tyr Asn Gln Lys
50 55 60

Phe Lys Gly Lys Ala Thr Leu Thr Val Asp Thr Ser Ser Ser Thr Ala
65 70 75 80

Tyr Met Glu Leu Arg Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Gln Ala Tyr Tyr Arg Asn Ser Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Leu Thr Val Ser Ser
115

<210> 154
<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G10 heavy chain

<400> 154

His Glu Ile Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly
1 5 10 15

Ala Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp
20 25 30

Asn Tyr Met Asn Trp Val Lys Gln Ser His Gly Lys Ser Leu Glu Trp
35 40 45

Ile Gly Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr Tyr Asn Gln Lys
50 55 60

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

Tyr Met Glu Leu Arg Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Asp Trp Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ala
115

<210> 155
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1D01 heavy chain

<400> 155

His Glu Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser
1 5 10 15

Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser
20 25 30

Gly Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asp Lys Leu Glu
35 40 45

Trp Met Gly Tyr Ile Ser Phe Asn Gly Asp Tyr Asn Tyr Asn Pro Ser
50 55 60

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

Phe Leu Gln Leu Ser Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 156
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1C02 heavy chain

<400> 156

```
His Asp Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser
1               5                  10                  15

Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser
            20                  25                  30

Gly Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu
        35                  40                  45

Trp Met Gly Tyr Ile Ser Phe Asn Gly Asp Ser Asn Tyr Asn Pro Ser
    50                  55                  60

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

Phe Leu Gln Leu Asn Ser Val Thr Ser Glu Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Pro
            100                 105                 110

Leu Val Thr Val Ser Ala
        115
```

<210> 157

<211> 118

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1C04 heavy chain

<400> 157

```
His Glu Val Gln Leu Gln Glu Ser Gly Pro Asp Leu Val Lys Pro Ser
1               5                  10                  15

Gln Ser Leu Ser Leu Thr Cys Thr Val Thr Gly Phe Ser Ile Thr Ser
            20                  25                  30

Gly Tyr Gly Trp His Trp Ile Arg Gln Phe Pro Gly Asn Lys Leu Glu
        35                  40                  45

Trp Met Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser
    50                  55                  60

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

Phe Leu Gln Leu Asn Ser Val Thr Thr Glu Asp Thr Ala Thr Tyr Tyr
                85                  90                  95
```

Cys Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ala
115

<210> 158
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1A02 light chain CDR1

<400> 158

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15

<210> 159
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1A02 light chain CDR2

<400> 159

Leu Val Ser Lys Leu Asp Ser
1 5

<210> 160
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1A02 light chain CDR3

<400> 160

Trp Gln Gly Thr His Phe Pro Arg Thr
1 5

<210> 161
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1A02 heavy chain CDR1

<400> 161

Gly Tyr Thr Phe Thr Asp Tyr Asn Met His
1 5 10

<210> 162
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1A02 heavy chain CDR2

<400> 162

Tyr Ile Asn Pro Tyr Asn Asp Val Thr Glu
1 5 10

<210> 163
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1A02 heavy chain CDR3

<400> 163

Ala Trp Phe Gly Leu Arg Gln
1 5

<210> 164
<211> 16
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1E10 light chain CDR1

<400> 164

Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr
1 5 10 15

<210> 165
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E10 light chain CDR2

<400> 165

Arg Met Ser Asn Leu Ala Ser
1 5

<210> 166
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1E10 light chain CDR3

<400> 166

Met Gln His Leu Glu Tyr Pro Tyr Thr
1 5

<210> 167
<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1E10 heavy chain CDR1

<400> 167

Gly Asp Thr Phe Thr Asp Tyr Tyr Met Asn
1 5 10

<210> 168

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1E10 heavy chain CDR2

<400> 168

Asp Ile Asn Pro Asn Tyr Gly Gly Ile Thr
1 5 10

<210> 169

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1E10 heavy chain CDR3

<400> 169

Gln Ala Tyr Tyr Arg Asn Ser Asp Tyr
1 5

<210> 170
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G12 light chain CDR1

<400> 170

Lys Ala Ser Gln Asp Val Gly Thr Ala Val Ala
1 5 10

<210> 171
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G12 light chain CDR2

<400> 171

Trp Thr Ser Thr Arg His Thr
1 5

<210> 172
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G12 light chain CDR3

<400> 172

Gln Gln His Tyr Ser Ile Pro Leu Thr
1 5

<210> 173
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G12 heavy chain CDR1

<400> 173

Gly Tyr Ile Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 174
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> Amino acid sequence of the 3z1G12 heavy chain CDR2

<400> 174

Val Ile Asp Pro Glu Thr Gly Asn Thr Ala
1 5 10

<210> 175
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Amino acid sequence of the 3z1G12 heavy chain CDR3

<400> 175

Met Gly Tyr Ser Asp Tyr
1 5

<210> 176
<211> 240
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized 3D3 antibody light chain

<400> 176

Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1 5 10 15

```
Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala
            20                  25                  30

Val Ser Leu Gly Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser
        35                  40                  45

Leu Leu Asn Ser Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln
    50                  55                  60

Lys Pro Gly Gln Pro Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg
65                  70                  75                  80

Glu Ser Ser Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp
                85                  90                  95

Phe Thr Leu Thr Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr
            100                 105                 110

Tyr Cys Gln Gln His Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr
        115                 120                 125

Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe
    130                 135                 140
```

```
Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys
145                 150                 155                 160

Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val
                165                 170                 175

Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln
            180                 185                 190

Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser
        195                 200                 205

Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His
    210                 215                 220

Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230                 235                 240
```

<210> 177
<211> 462
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized 3D3 antibody heavy chain

<400> 177

```
Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1               5                  10                  15

Thr His Ala Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
            20                  25                  30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe
        35                  40                  45

Thr Asp Tyr Glu Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
    50                  55                  60

Glu Trp Met Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn
65                  70                  75                  80

Gln Lys Phe Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser
                85                  90                  95

Thr Ala Tyr Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Leu Val
        115                 120                 125

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
    130                 135                 140
```

```
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
145                 150                 155                 160

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
                165                 170                 175

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
            180                 185                 190

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
        195                 200                 205

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
    210                 215                 220

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
225                 230                 235                 240

Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
                245                 250                 255

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
            260                 265                 270
```

```
Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
        275                 280                 285

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
    290                 295                 300

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
305                 310                 315                 320

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
                325                 330                 335

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
            340                 345                 350

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
        355                 360                 365

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
    370                 375                 380

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
385                 390                 395                 400

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
                405                 410                 415
```

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
420 425 430

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
435 440 445

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
450 455 460

<210> 178
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized 3D3 antibody light chain variable region

<400> 178

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

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Asn Phe Gln Lys Asn Phe Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Phe Ala Ser Thr Arg Glu Ser Ser Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

His Tyr Ser Thr Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile
100 105 110

Lys

<210> 179
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized 3D3 antibody heavy chain variable region

<400> 179

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
20 25 30

Glu Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asp Pro Glu Thr Gly Asn Thr Ala Phe Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Met Gly Tyr Ser Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser
100 105 110

Ser

<210> 180
<211> 234
<212> PRT
<213> Artificial Sequence

<220>

<223> Humanized 3C4 antibody light chain

<400> 180

```
Met Val Leu Gln Thr Gln Val Phe Ile Ser Leu Leu Leu Trp Ile Ser
1               5                  10                  15

Gly Ala Tyr Gly Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ser
            20                  25                  30

Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp
        35                  40                  45

Ile His Asn Phe Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro
    50                  55                  60

Lys Thr Leu Ile Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser
65                  70                  75                  80

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser
                85                  90                  95

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Ser Cys Leu Gln Tyr Asp
            100                 105                 110
```

```
Glu Ile Pro Leu Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
        115                 120                 125

Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln
    130                 135                 140

Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr
145                 150                 155                 160

Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser
                165                 170                 175

Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr
            180                 185                 190

Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys
        195                 200                 205

His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro
    210                 215                 220

Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225                 230
```

<210> 181
<211> 466

<212> PRT

<213> Artificial Sequence

<220>

<223> Humanized 3C4 antibody heavy chain

<400> 181

Met Asp Trp Thr Trp Arg Ile Leu Phe Leu Val Ala Ala Ala Thr Gly
1 5 10 15

Thr His Ala Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys
20 25 30

Pro Ser Gln Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile
35 40 45

Thr Ser Gly Tyr Gly Trp His Trp Ile Arg Gln His Pro Gly Lys Gly
50 55 60

Leu Glu Trp Ile Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn
65 70 75 80

Pro Ser Leu Lys Ser Arg Val Thr Ile Ser Gln Asp Thr Ser Lys Asn
85 90 95

Gln Phe Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val
100 105 110

```
Tyr Tyr Cys Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln
        115                 120                 125

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
    130                 135                 140

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
145                 150                 155                 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
                165                 170                 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
            180                 185                 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
        195                 200                 205

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
    210                 215                 220

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
225                 230                 235                 240
```

```
Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
                245                 250                 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
            260                 265                 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
        275                 280                 285

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
    370                 375                 380
```

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385 390 395 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
405 410 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
420 425 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
435 440 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
450 455 460

Gly Lys
465

<210> 182
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Humanized 3C4 antibody light chain variable region

<400> 182

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

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

Leu Asn Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Lys Thr Leu Ile
35 40 45

Phe Arg Ala Asn Arg Leu Val Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Ser Cys Leu Gln Tyr Asp Glu Ile Pro Leu
85 90 95

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

<210> 183
<211> 116
<212> PRT
<213> Artificial Sequence

<220>

<223> Humanized 3C4 antibody heavy chain variable region

<400> 183

```
Glu Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                  10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Phe Ser Ile Thr Ser Gly
            20                  25                  30

Tyr Gly Trp His Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu Trp
        35                  40                  45

Ile Gly Tyr Ile Asn Tyr Asp Gly His Asn Asp Tyr Asn Pro Ser Leu
    50                  55                  60

Lys Ser Arg Val Thr Ile Ser Gln Asp Thr Ser Lys Asn Gln Phe Ser
65                  70                  75                  80

Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr Trp Gly Gln Gly Thr Leu
            100                 105                 110
```

Val Thr Val Ser
115

<210> 184
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.111

<400> 184

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 185
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.112

<400> 185

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 186
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to resid3es 24-40 of SEQ ID NO.113

<400> 186

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 187
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.114

<400> 187

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 188
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.115

<400> 188

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 189
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.116

<400> 189

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 190
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.117

<400> 190

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 191
<211> 17
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.118

<400> 191

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 192
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.123

<400> 192

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 193
<211> 17
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.125

<400> 193

Lys Ser Ser Gln Ser Leu Leu Asn Ser Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 194

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.119

<400> 194

Lys Ser Ser Gln Ser Leu Leu Asn Arg Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 195

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.120

<400> 195

Lys Ser Ser Gln Ser Leu Leu Asn Asn Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 196

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.121

<400> 196

Lys Ser Ser Gln Ser Leu Leu Asn Thr Ser Asn Gln Leu Asn Tyr Leu
1 5 10 15

Ala

<210> 197
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.122

<400> 197

Lys Ser Ser Gln Ser Leu Leu Asn Thr Ser Asn Gln Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 198
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.110

<400> 198

Lys Ser Ser Gln Ser Leu Leu Asn Ser Asn Asn Gln Leu Asn Tyr Leu
1 5 10 15

Ala

<210> 199
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-40 of SEQ ID NO.124

<400> 199

Lys Ser Ser Gln Ser Leu Leu Asn Ser Asn Phe Gln Lys Asn Phe Leu
1 5 10 15

Ala

<210> 200
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-39 of SEQ ID NO.105

<400> 200

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15

<210> 201
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-39 of SEQ ID NO.107

<400> 201

Lys Ser Ser Gln Ser Leu Leu His Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15

<210> 202
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-39 of SEQ ID NO.106

<400> 202

Lys Ser Ser Gln Ser Leu Leu Tyr Ser Asp Gly Lys Thr Tyr Leu Asn
1 5 10 15

<210> 203
<211> 16
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRL1 corresponding to residues 24-39 of SEQ ID NO.108

<400> 203

Arg Ser Ser Gln Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> 204
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-39 of SEQ ID NO.109

<400> 204

Arg Ser Ser Lys Ser Leu Leu His Ser Asn Gly Asn Thr Tyr Leu Tyr
1 5 10 15

<210> 205
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-34 of SEQ ID NO.:127

<400> 205

Lys Ala Ser Gln Asp Ile His Asn Phe Leu Asn
1 5 10

<210> 206
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-34 of SEQ ID NO.:131

<400> 206

Lys Ala Ser Gln Asp Ile His Arg Phe Leu Asn
1 5 10

<210> 207
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
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<400> 207

Lys Ala Ser Gln Asp Ile His Asn Tyr Leu Asn
1 5 10

<210> 208
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-34 of SEQ ID NO.:130

<400> 208

Lys Ala Ser Gln Asp Ile His Asn Tyr Leu Asn
1 5 10

<210> 209
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL1 corresponding to residues 24-34 of SEQ ID NO.:128

<400> 209

Lys Ala Ser Gln Asp Ile His Thr Tyr Leu Asn
1 5 10

<210> 210
<211> 11
<212> PRT
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<220>
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<400> 210

Lys Ala Ser Gln Asp Val Gly Thr Ala Val Ala
1 5 10

<210> 211
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:111

<400> 211

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 212
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:112

<400> 212

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 213
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:121

<400> 213

Phe Ala Ser Thr Thr Glu Ser
1 5

<210> 214
<211> 7
<212> PRT
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<220>
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<400> 214

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 215
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:114

<400> 215

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 216
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 216

Phe Gly Ser Thr Arg Glu Ser
1 5

<210> 217
<211> 7
<212> PRT
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<220>
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<400> 217

Phe Gly Ser Thr Arg Glu Ser
1 5

<210> 218
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:115

<400> 218

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 219
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:116

<400> 219

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 220
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:117

<400> 220

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 221
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:119

<400> 221

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 222
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:120

<400> 222

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 223
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:123

<400> 223

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 224
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:124

<400> 224

Phe Ala Ser Thr Arg Glu Ser
1 5

<210> 225
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 225

Phe Ala Ser Thr Arg Lys Ser
1 5

<210> 226
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 56-62 of SEQ ID NO.:122

<400> 226

Phe Ala Ser Thr Arg Ala Ser
1 5

<210> 227
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 227

Leu Val Ser Lys Leu Asp Ser
1 5

<210> 228
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 55-61 of SEQ ID NO.:106

<400> 228

Leu Val Ser Lys Leu Asp Ser
1 5

<210> 229
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 55-61 of SEQ ID NO.:107

<400> 229

Leu Val Ser Lys Leu Asp Ser
1 5

<210> 230
<211> 7

<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 55-61 of SEQ ID NO.:108

<400> 230

Lys Val Ser Asn Arg Phe Ser
1 5

<210> 231
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 50-56 of SEQ ID NO.:127

<400> 231

Arg Ala Asn Arg Leu Val Asp
1 5

<210> 232
<211> 7
<212> PRT
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<220>
<223> CDRL2 corresponding to residues 50-56 of SEQ ID NO.:128

<400> 232

Arg Ala Asn Arg Leu Val Asp
1 5

<210> 233
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL2 corresponding to residues 50-56 of SEQ ID NO.:131

<400> 233

His Ala Asn Arg Leu Val Asp
1 5

<210> 234
<211> 7
<212> PRT
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<220>
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<400> 234

Arg Ala Asn Arg Leu Val Ala
1 5

<210> 235
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
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<400> 235

Arg Ala Asn Arg Leu Val Ala
1 5

<210> 236
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 236

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 237
<211> 9
<212> PRT
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<220>

<223> CDRL3 corresponding to residues 95-103 of SEQ ID NO.:115

<400> 237

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 238
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<212> PRT
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<220>
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<400> 238

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 239
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<212> PRT
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<400> 239

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 240
<211> 9
<212> PRT
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<220>
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<400> 240

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 241
<211> 9
<212> PRT
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<220>
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<400> 241

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 242
<211> 9
<212> PRT
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<220>
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<400> 242

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 243
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<220>
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<400> 243

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 244
<211> 9
<212> PRT
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<220>
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<400> 244

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 245
<211> 9
<212> PRT
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<220>
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<400> 245

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 246
<211> 9
<212> PRT
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<220>
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<400> 246

Gln Gln His Tyr Ser Thr Pro Leu Thr
1 5

<210> 247
<211> 9

<212> PRT
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<220>
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<400> 247

Gln Gln His Tyr Ser Ile Pro Leu Thr
1 5

<210> 248
<211> 9
<212> PRT
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<220>
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<400> 248

Gln Gln His Tyr Ser Ile Pro Leu Thr
1 5

<210> 249
<211> 9
<212> PRT
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<220>
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<400> 249

Gln Gln His Tyr Ser Ile Pro Leu Thr
1 5

<210> 250
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<212> PRT
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<220>
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<400> 250

Gln Gln His Tyr Ser Ile Pro Leu Thr
1 5

<210> 251
<211> 9
<212> PRT
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<220>
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<400> 251

Gln Gln His Tyr Ser Ile Pro Leu Thr
1 5

<210> 252
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
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<400> 252

Gln Gln His Phe Asn Thr Pro Leu Thr
1 5

<210> 253
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRL3 corresponding to residues 89-97 of SEQ ID NO.:129

<400> 253

Leu Gln Tyr Asp Ala Phe Pro Leu Thr
1 5

<210> 254
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRL3 corresponding to residues 89-97 of SEQ ID NO.:130

<400> 254

Leu Gln Tyr Asp Ala Phe Pro Leu Thr
1 5

<210> 255
<211> 9
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<220>
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<400> 255

Leu Gln Tyr Asp Ala Phe Pro Leu Thr
1 5

<210> 256
<211> 9
<212> PRT
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<220>
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<400> 256

Leu Gln Tyr Asp Glu Phe Pro Leu Thr
1 5

<210> 257
<211> 9
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<220>
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<400> 257

Leu Gln Tyr Asp Glu Ile Pro Leu Thr
1 5

<210> 258
<211> 9
<212> PRT
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<220>
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<400> 258

Trp Gln Gly Thr His Phe Pro Arg Thr
1 5

<210> 259
<211> 9
<212> PRT
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<220>

<223> CDRL3 corresponding to residues 94-102 of SEQ ID NO.:106

<400> 259

Trp Gln Gly Thr His Phe Pro Arg Thr
1 5

<210> 260

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 corresponding to residues 94-102 of SEQ ID NO.:107

<400> 260

Trp Gln Gly Thr His Phe Pro Arg Thr
1 5

<210> 261

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRL3 corresponding to residues 94-102 of SEQ ID NO.:108

<400> 261

Phe Gln Gly Ser His Val Pro Leu Thr
1 5

<210> 262
<211> 10
<212> PRT
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<220>
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<400> 262

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 263
<211> 10
<212> PRT
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<220>
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<400> 263

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 264
<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:138

<400> 264

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 265

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:140

<400> 265

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 266

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:142

<400> 266

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 267
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:143

<400> 267

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 268
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:147

<400> 268

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 269
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:148

<400> 269

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 270
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:149

<400> 270

Gly Tyr Thr Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 271
<211> 10
<212> PRT
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<220>

<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:144

<400> 271

Gly Tyr Ile Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 272
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:145

<400> 272

Gly Tyr Ile Phe Thr Asp Tyr Glu Ile His
1 5 10

<210> 273
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:135

<400> 273

Gly Tyr Ile Phe Thr Asp Tyr Glu Val His
1 5 10

<210> 274
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:141

<400> 274

Gly Tyr Thr Phe Thr Asp Tyr Glu Val His
1 5 10

<210> 275
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:146

<400> 275

Gly Tyr Thr Phe Thr Asp Tyr Glu Val His
1 5 10

<210> 276
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:139

<400> 276

Gly Tyr Thr Phe Thr Asp Tyr Glu Met His
1 5 10

<210> 277
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:151

<400> 277

Gly Tyr Thr Phe Ser Asp Tyr Glu Met His
1 5 10

<210> 278
<211> 10
<212> PRT
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<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:150

<400> 278

Gly Tyr Thr Phe Thr Asp Tyr Glu Met His
1 5 10

<210> 279
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH1 corresponding to residues 27-36 of SEQ ID NO.:152

<400> 279

Gly Tyr Lys Phe Thr Asp Tyr Glu Met His
1 5 10

<210> 280
<211> 10
<212> PRT
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<220>
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<400> 280

Gly Tyr Thr Phe Thr Asp Tyr Asn Met His
1 5 10

<210> 281
<211> 10

<212> PRT
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<220>
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<400> 281

Gly Tyr Ile Phe Thr Glu Tyr Asn Ile His
1 5 10

<210> 282
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
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<400> 282

Gly Tyr Thr Phe Thr Glu Tyr Asn Met His
1 5 10

<210> 283
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH1 corresponding to residues 27-37 of SEQ ID NO.:155

<400> 283

Gly Phe Ser Ile Thr Ser Gly Tyr Gly Trp His
1 5 10

<210> 284
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH1 corresponding to residues 27-37 of SEQ ID NO.:156

<400> 284

Gly Phe Ser Ile Thr Ser Gly Tyr Gly Trp His
1 5 10

<210> 285
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> CDRH2 corresponding to residues 51-60 of SEQ ID NO.:141

<400> 285

Val Ile Asp Pro Ala Thr Gly Asp Thr Ala
1 5 10

<210> 286
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<212> PRT
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<220>
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<400> 286

Val Ile Asp Pro Ala Thr Gly Asp Thr Ala
1 5 10

<210> 287
<211> 10
<212> PRT
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<220>
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<400> 287

Val Ile Asp Pro Glu Thr Gly Asp Thr Ala
1 5 10

<210> 288
<211> 10
<212> PRT
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<220>

<223> CDRH2 corresponding to residues 51-60 of SEQ ID NO.:142

<400> 288

Val Ile Asp Pro Glu Thr Gly Asp Thr Ala
1 5 10

<210> 289
<211> 10
<212> PRT
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<220>
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<400> 289

Val Ile Asp Pro Glu Thr Gly Asp Thr Ala
1 5 10

<210> 290
<211> 10
<212> PRT
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<220>
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<400> 290

Val Ile Asp Pro Glu Thr Gly Asp Thr Ala
1 5 10

<210> 291
<211> 10
<212> PRT
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<220>
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<400> 291

Val Ile Asp Pro Glu Thr Gly Val Thr Ala
1 5 10

<210> 292
<211> 10
<212> PRT
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<220>
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<400> 292

Val Ile Asp Pro Glu Thr Gly Val Thr Ala
1 5 10

<210> 293
<211> 10
<212> PRT
<213> Artificial Sequence

<220>

<223> CDRH2 corresponding to residues 51-60 of SEQ ID NO.:144

<400> 293

Val Ile Asp Pro Glu Thr Gly Asn Thr Ala
1 5 10

<210> 294

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH2 corresponding to residues 51-60 of SEQ ID NO.:145

<400> 294

Val Ile Asp Pro Glu Thr Gly Asn Thr Ala
1 5 10

<210> 295

<211> 10

<212> PRT

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<400> 295

Val Ile Asp Pro Glu Thr Gly Ser Thr Ala
1 5 10

<210> 296
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<400> 296

Val Ile Asp Pro Glu Thr Gly Ser Thr Ala
1 5 10

<210> 297
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<400> 297

Val Ile Asp Pro Glu Thr Gly Ala Thr Ala
1 5 10

<210> 298
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<212> PRT

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<220>

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<400> 298

Val Ile Asp Pro Glu Thr Gly Ala Thr Ala
1 5 10

<210> 299

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

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<400> 299

Gly Ile Asp Pro Glu Thr Gly Asp Thr Val
1 5 10

<210> 300

<211> 10

<212> PRT

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Gly Ile Asp Pro Glu Thr Gly Gly Thr Ala
1 5 10

<210> 301
<211> 10
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<400> 301

Val Ile Asp Pro Glu Thr Gly Gly Thr Ala
1 5 10

<210> 302
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<400> 302

Val Leu Asp Pro Gly Thr Gly Arg Thr Ala
1 5 10

<210> 303
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<400> 303

Tyr Ile Ser Phe Asn Gly Asp Tyr Asn
1 5

<210> 304
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<212> PRT
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<400> 304

Tyr Ile Ser Phe Asn Gly Asp Ser Asn
1 5

<210> 305
<211> 9
<212> PRT
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<220>

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<400> 305

Tyr Ile Asn Tyr Asp Gly His Asn Asp
1 5

<210> 306
<211> 10
<212> PRT
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<400> 306

Asn Ile Asn Pro Tyr Asn Asp Val Thr Glu
1 5 10

<210> 307
<211> 10
<212> PRT
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<400> 307

Asn Ile Asn Pro Tyr Asn Asn Val Thr Glu
1 5 10

<210> 308
<211> 10
<212> PRT
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<220>
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<400> 308

Tyr Ile Asn Pro Tyr Asn Asp Val Thr Glu
1 5 10

<210> 309
<211> 10
<212> PRT
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<220>
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<400> 309

Asp Ile Asn Pro Asn Tyr Gly Gly Ile Thr
1 5 10

<210> 310
<211> 10
<212> PRT
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<400> 310

Asp Ile Asn Pro Tyr Tyr Gly Thr Thr Thr
1 5 10

<210> 311

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

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<400> 311

Met Ser Tyr Ser Asp Tyr
1 5

<210> 312

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

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<400> 312

Met Ser Tyr Ser Asp Tyr
1 5

<210> 313
<211> 6
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<400> 313

Met Gly Tyr Ser Asp Tyr
1 5

<210> 314
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<400> 314

Met Gly Tyr Ser Asp Tyr
1 5

<210> 315
<211> 6

<212> PRT
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<220>
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<400> 315

Met Gly Tyr Ser Asp Tyr
1 5

<210> 316
<211> 6
<212> PRT
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<220>
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<400> 316

Met Gly Tyr Ser Asp Tyr
1 5

<210> 317
<211> 6
<212> PRT
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<400> 317

Met Gly Tyr Ser Asp Tyr
1 5

<210> 318
<211> 6
<212> PRT
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<220>
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<400> 318

Met Gly His Ser Asp Tyr
1 5

<210> 319
<211> 6
<212> PRT
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<400> 319

Met Gly Tyr Ser Asp Tyr
1 5

<210> 320
<211> 6
<212> PRT
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<400> 320

Met Gly Tyr Ser Asp Tyr
1 5

<210> 321
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<400> 321

Met Gly Tyr Ser Asp Tyr
1 5

<210> 322
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<212> PRT
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<400> 322

Met Gly Tyr Ser Asp Tyr
1 5

<210> 323
<211> 6
<212> PRT
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<220>
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<400> 323

Met Gly Tyr Ser Asp Tyr
1 5

<210> 324
<211> 6
<212> PRT
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<400> 324

Met Gly Tyr Ala Asp Tyr
1 5

<210> 325
<211> 6
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<400> 325

Met Gly Tyr Ala Asp Tyr
1 5

<210> 326
<211> 7
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<400> 326

Ile Ser Tyr Ala Met Asp Tyr
1 5

<210> 327
<211> 7
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<400> 327

Ile Ser Tyr Ala Met Asp Tyr
1 5

<210> 328

<211> 6

<212> PRT

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<400> 328

Ile Gly Tyr Ala Asp Tyr
1 5

<210> 329

<211> 7

<212> PRT

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<400> 329

Ala Arg Trp Gly Leu Arg Asn
1 5

<210> 330
<211> 7
<212> PRT
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<400> 330

Ala Arg Trp Gly Leu Arg Asn
1 5

<210> 331
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<400> 331

Ala Trp Phe Gly Leu Arg Gln
1 5

<210> 332
<211> 10

<212> PRT

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<400> 332

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr
1 5 10

<210> 333

<211> 10

<212> PRT

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<220>

<223> CDRH3 corresponding to residues 98-107 of SEQ ID NO.:156

<400> 333

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr
1 5 10

<210> 334

<211> 10

<212> PRT

<213> Artificial Sequence

<220>

<223> CDRH3 corresponding to residues 98-107 of SEQ ID NO.:157

<400> 334

Ala Ser Ser Tyr Asp Gly Leu Phe Ala Tyr
1 5 10